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Review Article

Surgical prevention strategies in ovarian cancer

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HIGHLIGHTS

- Understanding of the etiology and pathogenesis of ovarian cancer has significantly evolved over the past two decades.
- Surgical prophylactic surgery has saved lives in high-risk populations of women.
- Although the evidence-base is limited, surgical risk-reduction methods have increasingly been applied to average-risk women.
- There are different side effect profiles associated with various types of surgical prevention strategies.
- Current prospective trials may offer evidence for less toxic alternative prophylactic surgical options in the future.

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ABSTRACT

Given the current lack of effective screening for ovarian cancer, surgical removal of at-risk tissue is the most successful strategy to decrease risk of cancer development. However, the optimal timing of surgery and tissues to remove, as well as the appropriate patients to undergo preventive procedures are poorly understood. In this review, we first discuss the origin and precursors of ovarian epithelial carcinomas, focusing on high-grade serous carcinomas and endometriosis-associated carcinomas, which cause the majority of the mortality and incidence of ovarian cancer. In addition, we summarize the implications of current understanding of specific pathogenic origins for surgical prevention and remaining gaps in knowledge. Secondly, we review evidence from the epidemiologic literature on the associations of various surgical prevention strategies, including endometriosis excision, tubal procedures, and bilateral salpingo-oophorectomy, with risk of future ovarian cancer development, as well as the short- and long-term consequences of these strategies on women's health and quality and life. We conclude with recommendations for surgical prevention in women with high-risk genetic mutations and average-risk women, and a brief discussion of ongoing research that will help clarify optimal surgical approaches that balance risk-reduction with maintenance of women's quality of life.

Contents

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1. Introduction

The decision that many women face about their opportunities to reduce the risk of ovarian, fallopian and peritoneal cancer is difficult and influenced by genetic risk, age, fertility considerations, surgical risks, and evolving data. The lack of effective screening forces women to make a decision that places many of those factors at odds. To date, surgical removal of at risk tissue represents our best success at decreasing risk of developing ovarian cancer and overall mortality. Still, the optimal timing of surgery and tissues to remove, as well as the appropriate patients to undergo preventive procedures are poorly understood. In this review, we discuss current understanding of the origin and precursors of ovarian carcinomas, and implications of pathogenesis for surgical prevention. In addition, we highlight the epidemiologic evidence on various surgical prevention strategies and future risk of ovarian cancer, as well as short- and long-term consequences of these strategies on women's overall health and quality of life. Finally, we review recommendations for surgical prevention of ovarian cancer in women with high-risk genetic mutations and average risk women, and ongoing research that will provide further insight into optimal prevention approaches.

2. Biology of ovarian cancer development in relation to preventive strategies

Epithelial ovarian cancer comprises a spectrum of malignancies linked to several potential cell types. For this review we focus on two pathways historically termed Type I and Type II. This division is simplistic, but the Type I tumors are those that arise predominantly from the ovary and include lower grade endometrioid adenocarcinomas, clear cell carcinomas, mucinous adenocarcinomas, and low-grade serous carcinomas. All of the tumors in this group can be associated with benign or borderline tumors bearing the same name. Type II tumors consist of those for which an origin in the ovary is unclear, while a well-described carcinogenic sequence has been described for many in the distal fallopian tube. This group includes the high-grade serous carcinomas, many of which can be traced to an intraepithelial carcinoma of the fallopian tube. Many tumors previously classified as high grade endometrioid carcinomas, transitional carcinomas or poorly differentiated carcinomas (not otherwise specified) fall into this category and virtually all contain a mutation in the tumor suppressor *TP53* [1].

Most ovarian carcinomas are sporadic, but a hereditary component has been suggested in around 20% of cases [2]. The more common hereditary breast and ovarian cancer syndrome (HBOC, linked to *BRCA* mutations), and less common Lynch syndrome (i.e., heritable non-polyposis colorectal cancer syndrome (HNPCC) linked to DNA mismatch repair mutations) are the two main syndromes accounting for most familial ovarian cancers [2]. Several other tumor oncogenes and suppressor genes (e.g., *TP53*, *BARD1*, *CHEK2*, *RAD51*, *PALB2*) have also been associated with hereditary ovarian cancer [3].

Understanding the precursors and hereditary predisposition for these ovarian cancer subtypes is critical to optimize the type and timing of preventive surgical strategies and the selection of appropriate patients. Identification of precursor lesions in surgical specimens from asymptomatic, high-risk women provides information about risk of developing an ovarian malignancy. Among women with symptomatic ovarian cancer, detection of precursor lesions may provide insight into tumor origin and, depending on the tumor subtype, patients may need to undergo genetic testing for risk assessment and counseling.

In the following sections, the origin and precursors of ovarian epithelial carcinoma will be discussed, focusing on high-grade serous carcinomas and endometriosis-associated carcinomas as the prototypes of type I and type II carcinomas, which cause the majority of the mortality and incidence of ovarian cancer.

2.1. High-grade serous carcinomas (HGSCs)

HGSCs, including variants, constitute the most common subtype (~70%) of epithelial ovarian carcinomas. Women having germ-line *BRCA* 1/2 mutations are at increased risk for developing these cancers, with about 10–40% of *BRCA* mutation carriers developing ovarian malignancies by the age of 70 [4].

By the time of diagnosis most HGSCs are already at an advanced stage (≥FIGO stage 3) with metastatic disease. Often, both the fallopian tubes and ovaries are extensively involved by tumor, obscuring the early stage of carcinogenesis or pre-existing precursor lesions. In a subset of HGSCs, the bulk of tumor is found primarily in the peritoneum with minimal or no ovarian involvement, and historically these have been classified as “primary peritoneal carcinomas.”

2.1.1. Theories on tumor precursors

As involvement of ovarian cortex and/or surface is common among HGSCs, these tumors had traditionally been theorized to arise from the peritoneal-ovarian surface epithelium (POSE). This theory is supported by experimental models suggesting presence of a cancer-prone OSE stem cell niche at the ovarian hilum [5] and the ability of OSE to acquire phenotypes reminiscent of ovarian carcinoma via inactivation of p53 and Ras pathway in conjunction with Akt and c-myc transduction

in in vitro models [6]. Nonetheless, convincing precursor lesions for HGSCs have not been identified on OSE [1,7] and Stage I ovarian HGSCs are decidedly uncommon.

Following observations of early HGSCs in the distal fallopian tubes of *BRCA* 1/2 mutation carriers, adoption of the SEE-FIM protocol permitted widespread recognition of the fimbria as the dominant site of early HGSC in the form of serous tubal intraepithelial carcinoma (STIC) [8,9]. Moreover, shared sequence specific *TP53* mutations by STICs and metastatic HGSCs supported a shared lineage between the two [8,10]. This was supported further by molecular profiling that linked HGSC to the fallopian tube, [11] regardless of presence or absence of concurrent STIC [12].

It is estimated that at least one epithelial focus with a clonal *TP53* mutation is identified in about half of distal fallopian tubes in women with no disease [13]. Lesions termed "p53 signature" have been described as a latent non-malignant precursor which consists of benign-appearing tubal epithelium having a secretory phenotype and low proliferative activity in contrast to STICs. Similar to STICs, p53 signatures are often located in the fimbriae and show *TP53* mutations which are often identical to those seen in concurrent STICs and HGSCs [10,14,15]. Multiple p53 signatures are less common, except in cases of Li Fraumeni syndrome (LFS) having germ-line *TP53* mutation [16]. LFS by itself, however, is not associated with an increased risk for HGSCs, implicating that *TP53* mutation alone is insufficient to trigger carcinogenesis.

2.1.2. Challenges in completing the model for high-grade serous carcinogenesis

A precise understanding of HGSC prevention is hampered by unanswered questions from the pathologic perspective. For one, it remains controversial whether the fallopian tubes represent the sole origin of HGSCs. STICs have been designated as the prime launching point for disseminated HGSC. They are found in approximately 5% of risk reducing salpingo-oophorectomies (RRSOs) and another source of early HGSC has not emerged in these patients. Around 5–10% of these women or more will later develop a HGSC [17]. However, in consecutively accessioned HGSCs, STICs are found in a wide range of frequencies, from 10 to 60% [18], and the percentage is not dramatically changed by extensive sectioning of the tubes [19–21]. Moreover whole exome sequencing has suggested that some STICs are actually metastases [22].

An emerging hypothesis of "precursor escape" has been proposed for HGSCs, in which tubal epithelial cells from earlier serous cancer precursors containing a *TP53* mutation could exfoliate and eventually give rise to tumor elsewhere, obscuring the role of the fallopian tube [21]. This hypothesis is similar to the model suggested for endometriosis and endometrioid adenocarcinoma [23], which will be discussed in later section.

One view of HGSC pathogenesis links the fallopian tube to development of HGSCs via exposure of tubal epithelial cells to follicular fluid, leading to genotoxic damage, *TP53* mutations, and other genetic perturbations [24,25]. Incessant ovulation has long been recognized as an ovarian cancer risk factor, suggested by epidemiologic studies that showed a positive association between number of ovulatory cycles and ovarian cancer, and apparent protective effects of factors suppressing ovulation or inflammation including oral contraceptive use, parity [26–28] as well as use of non-steroidal inflammatory drugs (NSAIDs) in women at average risk and *BRCA1/2* carriers [29,30].

Ovulation is believed to promote ovarian carcinogenesis by instigating a proinflammatory microenvironment for the distal fallopian tube. Other local environmental exposures, such as perinatal talc use and retrograde menstruation, have also been suggested by epidemiologic studies to increase risk of ovarian cancer [25,31], although the contributory role of retrograde menstruation is better seen with cancer histotypes other than HGSCs. The exact underlying mechanisms and potential ways to manipulate these host risk factors remain poorly understood.

2.1.3. Pathogenesis informs prevention

Knowledge of the steps involved in HGSC pathogenesis is critical to inform surgical prevention strategies. For example, if every HGSC must be launched from a STIC, a certain expectation can be assumed regarding the value of certain surgical procedures. However, the uncertainties on both the origin and pathogenesis of HGSCs based on the current data raise multiple issues and questions that need to be considered in prevention of HGSCs:

(i) Timing of surgical intervention: If the concept of "precursor escape" from the fallopian tubes is corroborated by additional studies, what is the rate of malignant transformation; how early should surgical intervention be performed; and can there be other medical measures arresting precursor dissemination and progression into malignancy?
(ii) Risk conferred by precursors in *BRCA* mutation carriers: Is oophorectomy essential in reducing risk of HGSCs and how would estrogen stimulation be related to the involution, or progression of precursor lesions to malignancy in *BRCA* carriers versus the general population?
(iii) Adjuvant treatment along with surgical intervention: If a proinflammatory microenvironment promotes mutagenesis and carcinogenesis, can anti-inflammatory therapies be effective in reducing malignant transformation of precursors, and decreasing the need of surgical intervention and removal of ovaries?
(iv) Regardless of the type of intervention, the benefit-to-risk ratios need to be further studied in high-risk as well as the general population.

2.2. Endometriosis-associated ovarian carcinomas: endometrioid adenocarcinoma and clear cell carcinoma

Endometrioid adenocarcinomas (EC) and clear cell carcinomas (CCC) are the main ovarian cancer subtypes associated with endometriosis [32–34]. They account for approximately 15% and 5–10% of all epithelial ovarian carcinomas, respectively. A minority (≤5%) of these cases are hereditary by nature, and are mostly seen in patients with Lynch syndrome who have increased lifetime risk (8%) for ovarian carcinomas [35] with endometrioid followed by mixed carcinomas with endometrioid component and clear cell carcinoma being the common subtypes [36].

Most ovarian ECs and CCCs present as low-stage disease with good prognosis. Concurrent endometriosis, either isolated or adjacent to the invasive carcinoma, has been reported in at least 20% of CCCs and 25% of ECs, versus <10% in other histotypes such as serous and mucinous carcinomas [37,38], suggesting that ovarian cancers associated with endometriosis may have more favorable biologic behavior than malignancies that are not associated with endometriosis [34].

2.2.1. Endometriosis, and model on dissemination and malignant transformation

Endometriosis refers to the presence of ectopic endometrial glands and stroma outside of the uterus, and is believed to be a hormone-dependent inflammatory lesion. This benign condition has been reported in about 5–15% of women at reproductive age and ≤5% of postmenopausal women [34]. Endometriosis in the pelvis can be present superficially on organ parts or deeply infiltrating into non-ovarian tissue. The exact etiologic and developmental mechanisms of these lesions are still not well defined, but at least 3 pathways have been suggested to give rise to endometriosis of which the origin is likely multifactorial: (i) retrograde menstruation with refluxed cells flowing through the fallopian tubes and out into the pelvis, followed by persistence at permissive sites with suitable microenvironment; (ii) direct metaplasia among sites with a shared embryological lineage, or (iii) hematologic or lymphatic spread from uterus to other places [23,34].

Epidemiologic data on endometriosis as an ovarian cancer risk factor have been somewhat conflicting, [39] likely due to inconsistent consideration of heterogeneity in associations across histotypes in previous analyses and misclassification based on self-reported endometriosis status [39]. However, findings from studies that examined associations by histotype found two- to three-fold increased risks of developing type 1 tumors [40,41].

The model of progression from endometriosis to malignancy was first introduced in 1925 [42], with recognition of atypical endometriosis as likely an intermediate precursor in subsequent years [43]. Investigations have revealed that intrinsic hormonal and immuno-regulation are involved not only in the development of endometriosis but may also play a role in their acquiring mutations conducive to malignant transformation [44]. A portion of benign and/or atypical endometriosis have been shown to harbor cancer driver mutations seen in ECs and CCCs, including *PTEN*, *ARID1A*, *PIK3CA*, *KRAS*, *and PPP2R1A*, either associated with concurrent cancers or in settings where no invasive cancer is present [23,45–47]. In addition, clonality is also demonstrated across the epithelial compartments in multifocal endometriotic lesions in some cases [45], suggesting that a portion of endometriotic lesions can be capable of precursor "metastasis" across pelvic sites as seeds for subsequent malignancy development. This model of "precursor escape" is also supported by the observation of clonality between synchronous ovarian and endometrial endometrioid carcinomas suggesting a common ancestral proliferation giving rise to tumors at different anatomic locations [48].

2.2.2. Implications for prevention

As it is now generally accepted that endometriosis can serve as a precursor for ECs and CCCs, identification of risk factors for endometriosis and its potential dissemination and malignant transformation is essential for devising preventive strategies. Various risk factors have been noted to associate with endometriosis, including factors predisposing to hyperestrogenism such as early menarche and nulliparity, anatomic anomalies promoting retrograde menstruation, Caucasian and Asian lineages, as well as genetic loci that have been suggested to correlate with increased risk of endometriosis in single-gene association and genome-wide association studies (GWAS) [45]. Local immune influences [49], such as macrophage infiltration, have also been proposed to induce a pro-oncogenic microenvironment at sites of endometriosis [50,51]. How these factors would interact and translate to the risk of subsequent malignancy development from endometriosis remains elusive. Other relevant questions that are in need for additional study data are also raised by our current understanding of endometriosis in relation to prevention of ovarian cancers:

(i) Target of intervention and risk stratification of endometriotic lesions: As endometriosis can be multifocal and only a portion of them harbor cancer driver mutations, is it possible to classify lesions that are at high risk for malignant transformation to facilitate screening, monitoring or treatment?
(ii) If targetable driver mutations are present, e.g. *PIK3CA*-activating changes, are they sufficient to define risk of malignant transformation?
(iii) What should be the indication(s) for "targeted" surgical and/or non-surgical treatment in reducing risk of ECs and CCCs, in the era of precision medicine when genomic data are becoming essential for clinical decision-making?

3. Surgical prevention strategies

A better understanding of the genetic predispositions, the likely sites of oncogenic origin, and the demographics of patients (such as age of cancer diagnoses) has led to surgical strategies to prevent ovarian cancers in certain women. However, understanding of the appropriate patients and timing and nature of the procedure (i.e., which organs are removed) continues to evolve. As described in this section, we are also learning more about the true relative and absolute impact of these interventions in their ability to prevent cancer, as well as their effects on the development of other cancers and the effects of early menopause on other medical comorbidities.

3.1. Endometriosis excision

3.1.1. Association with ovarian cancer risk/development and possible surgical implications

Although endometriosis is strongly associated with increased risk of developing type 1 ovarian cancer, translating knowledge of this relationship into surgically actionable methods to prevent these cancers is challenged by the low frequency of endometriosis, its early development in young populations, the multifocal nature of disease, the lack of clear genetic predisposition, and the potentially extensive types of surgeries involved.

Epidemiologic data on the association between surgical treatment for endometriosis and subsequent ovarian cancer risk is limited. However, one Swedish nested case-control study among women with a first-time hospital discharge diagnosis of endometriosis observed a strong reduction in risk of developing ovarian cancer after surgical removal of endometriosis (adjusted OR 0.30; 95% CI 0.12–0.74) and unilateral salpingo-oophorectomy (USO; adjusted OR 0.19; 95% CI 0.08–0.46) as treatments [52]. Bilateral oophorectomy was not assessed in this study, but is associated with lower risk in other populations (see below). Thus, the limited available data suggest that surgical treatment of endometriosis has an ancillary benefit of reducing risk of developing ovarian cancer.

3.1.2. Short- and long-term consequences

Many women undergo surgical procedures as part of pelvic pain work-up, confirmation of diagnosis, infertility and/or relief of pain. Since endometriosis is an estrogen-dependent disease, definitive treatment with removal of both ovaries leads to irreversible surgical menopause. The short and long-term consequences of surgical menopause will be discussed in Section 3.3.2 [39]. An alternate, more conservative approach is removal of endometriosis lesions; however, endometriosis often causes an inflammatory reaction that leads to fusion of several tissue planes and organs that may require extensive dissection and even removal of surrounding organs including of the intestinal, urinary or gynecologic tract. Furthermore, ectopic endometriosis tissue can, and often does, return for premenopausal women postoperatively. Pain relief can result from excision or fulguration of these lesions, but typically, is not long-lasting. Surgical intervention in the setting of endometriosis is further compounded by the fact that surgical procedures in themselves can incite inflammation and scarring, thus triggering new pain processes associated with postoperative healing and recovery [39].

For long-term health benefits, some have argued that ovarian cancer screening be offered to women with endometriosis [53]. However, given the rarity of ovarian cancer and inability to effectively screen for ovarian cancer in any group, even genetically high-risk predisposed patients, this suggestion is likely not realistic. Overall, the incidence of ovarian cancer is about 12.1 per 100,000 women per year and for clear cell or endometrioid tumors, which appear to be most strongly associated with endometriosis, the incidence is approximately 3 per 100,000 women per year. Even if women with endometriosis are at a 4-fold higher risk of these diseases, the number of cases would still be too small to support population-based screening. However, research to identify high-risk women among those with endometriosis should continue to identify those at risk.

3.2. Tubal procedures ± hysterectomy

3.2.1. Association with ovarian cancer risk/development and surgical techniques

"Tubal procedures" encompass a variety of surgical techniques from tubal sterilization to bilateral salpingectomy. Such procedures have the potential to prevent both type 1 tumors (through reducing peritoneal exposure to endometriosis and retrograde menstruation) and type 2 cancers, through altering or removing the putative cell of origin for this subtype. Thus, it would be reasonable to hypothesize that tubal surgeries would decrease ovarian cancer incidence and death rates of both tumor types.

In a 2012 meta-analysis, Rice et al. examined previous tubal ligation in average-risk women and found a 30% overall ovarian cancer risk reduction, with relative risks of 0.45 for endometrioid cancer and 0.75 for serous cancer [54]. Subsequent studies observed similarly stronger associations of tubal ligation with endometrioid and clear cell tumors versus serous [40,55,56]. Regarding tubal ligation technique, tubal excision (versus other sterilization methods) was related to a greater risk reduction for serous carcinoma and primary peritoneal carcinoma in a nested case-control study with 194 ovarian cancer cases [57]. But few other studies have examined this question. Further, data are limited on the tubal occlusion procedure with Essure® in regards to ovarian cancer risk.

Tubal procedures have predominantly been used in the setting of surgical sterilization and are quite common. There were >600,000 tubal ligation procedures in 2006 in both the inpatient and outpatient setting. The most typical timing was immediately postpartum including at the same time as cesarean delivery [58]. Some studies have suggested that tubal ligation at this juncture is the most protective for ovarian cancer risk [56]. Another relatively new approach to ovarian cancer prevention is "opportunistic salpingectomy" or the complete removal of the tubes as the sterilization method or in the setting of benign hysterectomy. Current data on ovarian cancer incidence and mortality for either average-risk or high-risk women following bilateral salpingectomy are limited as most studies examined women who underwent the procedure for specific medical conditions, which may be affected by confounding by indication for surgery. However, existing studies demonstrate a lower risk of ovarian cancer with salpingectomy that appears to be stronger than for tubal ligation alone, although the magnitude of risk reduction varies in current studies [59–61]. Lessard-Anderson et al. found a 64% lower risk of HGSC (odds ratio [OR], 0.36 [95% CI 0.13–1.02]) among women who underwent excisional tubal sterilization (i.e., complete salpingectomy, partial salpingectomy, or distal fimbriectomy) compared to those without sterilization or with nonexcisional tubal sterilization. Nonexcisional tubal sterilization versus no sterilization conferred a 41% risk reduction [57]. Madsen et al. conducted a Danish nationwide case-control study and found that bilateral salpingectomy was associated with a 42% reduction in epithelial ovarian cancer risk over a 29-year period (OR 0.58, 95% CI 0.36–0.95), while unilateral salpingectomy was not associated with risk (OR 0.90, 95% CI 0.72–1.12). Tubal ligation reduced overall risk (OR 0.87, 95% CI 0.78–0.98) and, among tumors with known histology, the strongest association was observed for endometrioid cancer (OR 0.66, 95% CI 0.47–0.93) [62]. It will take decades for demonstration of any survival or risk benefit from an opportunistic salpingectomy as they have only started being offered on a large scale in the mid-2010s [63].

3.2.2. Short- and long-term consequences

As we will discuss in Section 3.3.2, there are many health benefits associated with leaving the ovaries in situ. Because of the known health benefits related to hormone production, both tubes and ovaries are routinely left in situ by surgeons in the setting of benign indications for hysterectomy. However, there are no known health benefits of leaving the fallopian tubes in situ [63]. Short-term consequences of tubal procedures are related to contraceptive and surgical factors. Performing a bilateral salpingectomy instead of a tubal ligation makes future tubal reversal procedures impossible if a patient changes her mind about future fertility. Even though tubal re-anastamotic procedures are rare and seem to be declining in favor of other reproductive technologies, it is important that patients are counseled that bilateral salpingectomy procedures are a permanent process [64]. A more in-depth discussion related to surgical sterilization techniques, preoperative counseling, and factors associated with sterilization regret are outside of the scope of this article [65–68].

While performing bilateral salpingectomy during hysterectomy or instead of tubal ligation might add some surgical complexity, studies do not show a clinically meaningful impact. For example, a retrospective study of 79 women who underwent hysterectomy alone and 79 women who underwent hysterectomy with bilateral salpingectomy found no differences in operative time, blood loss, length of hospital stay, surgical complications, or return to normal activity [69]. Similarly, a population-based intervention in British Columbia comparing salpingectomy at time of hysterectomy versus tubal ligation found no difference in adverse outcomes and only 13–16 additional minutes of intraoperative time [70]. Recently, a Nationwide Inpatient Sample (NIS) was used to examine 425,180 women undergoing hysterectomy from 2008 to 2013 and noted that there was a 45% decrease in the number of bilateral salpingectomies performed at time of hysterectomy during the study period. However, this decrease was mainly attributable to a steep decline in the number of hysterectomy with bilateral salpingo-oophorectomy (BSO) procedures performed. Bilateral salpingectomy with ovarian conservation was relatively uncommon, but increased over the study period from 1.1% in 2008 to 7.7% in 2013. Compared with women who underwent hysterectomy alone, women who underwent hysterectomy with bilateral salpingectomy (without oophorectomy) had similar risks of blood transfusion, postoperative complication, and postoperative infections, but a modest increased risk of postoperative fever (adjusted OR 1.33, 95% CI = 1.00–1.77) [71].

Long-term concerns about removal of the tubes involve the potential need for subsequent surgery as well as disruption to the ovarian blood supply, which may adversely affect ovarian reserve and lead to earlier age at menopause [69,72–75]. In the Rochester Epidemiology Project, 12% of women undergoing simple hysterectomy required a subsequent surgery in the following 1 to 15 years for hydrosalpinx formation, representing a 7.8% lifetime risk of surgery. Removing the tube in its entirety would essentially remove any risk of future hydrosalpinx development [63,76]. Regarding potential impacts on ovarian reserve, most studies have not found significant effects of tubal surgery with or without hysterectomy on ovarian function or hormone levels. However, some studies reported a reduction in follicles, increased follicle-stimulating hormone levels, or Doppler blood flow changes [77,78]. These studies have been limited by small sample sizes and there have been no prospective, randomized trials to inform patients and surgeons of long-term adverse risks of salpingectomy performed for benign indications. Nevertheless, unless the clinical operative situation dictates otherwise, many organizations recommend a salpingectomy at the time of hysterectomy given the possible risk reduction, lack of a clear benefit of keeping the tubes, and the number of benign lesions that may lead to evaluation and intervention.

3.3. BSO ± hysterectomy

3.3.1. Association with ovarian cancer risk/development and surgical trends

Hysterectomy is one of the most common procedures performed in the United States, though the overall incidence of ovarian removal at the time of benign hysterectomy decreased from 55% in 1999 to 35% in 2011 [79,80], likely secondary to increased awareness and research on the health benefits of ovarian preservation in average-risk women [81]. Approximately one out of eight women has their ovaries removed before natural menopause [81], with the majority of women having grossly

normal intraoperative ovarian appearance at time of ovarian removal [82,83].

A recent systematic review on behalf of the Gynecologic Surgeons Systematic Review Group identified studies that compared ovarian conservation to removal in women who underwent hysterectomy for benign indications. As expected, the prevalence of ovarian cancer was higher when ovaries were left in situ (ovarian cancer risk of 0.14–0.7% compared with 0.02–0.04% among those with BSO) [81]. A prospective cohort study of 25,448 postmenopausal women enrolled in the Women's Health Initiative (WHI) Observational Study examined hysterectomy with or without BSO on ovarian cancer risk in women with no family history of ovarian cancer. BSO decreased incident ovarian cancer cases (0.02% in BSO group; 0.33% in ovarian conservation group; number needed to treat, 323), although it is important to note that ovarian cancer was rare in this population [84]. A retrospective cohort study of 56,692 patients in Northern California found 54% underwent hysterectomy with BSO, 7% underwent hysterectomy with unilateral salpingo-oophorectomy (USO) and 39% underwent hysterectomy alone. Compared with hysterectomy alone, lower rates of ovarian cancer were observed in women who underwent BSO (hazard ratio [HR] 0.12, 95% CI = 0.05–0.28) or USO (HR 0.58, 95% CI = 0.18–1.9) [85]. This systematic review led to a grade 2C recommendation for BSO to be offered to women to reduce the risk of ovarian cancer [81].

3.3.2. Short- and long-term consequences

There are many consequences related to surgical menopause, with most of the effects being secondary to hormonal dysregulation with reduction of both serum estrogen and androgen levels [86]. In terms of short-term consequences related to the procedure itself, there are inherent risks to additional surgery. These surgical factors were examined using NIS data in women who underwent BSO compared to hysterectomy alone between 1979 and 2004. The addition of BSO increased risk of organ injury, circulatory/bleeding complications and postoperative gastrointestinal complications compared to hysterectomy alone, although the data are uncontrolled for the indication which may confound the observation [79]. In addition, hysterectomy with ovarian conservation versus BSO has been associated with less menopausal symptomatology such as hot flashes and vaginal dryness [87–89]. For example, among 1299 women who underwent a hysterectomy for a benign indication and were followed for 2 years post-surgery, having a concurrent bilateral oophorectomy was associated with a 2-fold (OR 2.01, 95% CI = 1.14–3.53) increase in odds of having the same or a higher number of problematic-severe symptoms (vaginal bleeding, pelvic pain, fatigue, back pain, abdominal bloating, sleep disturbance, urinary incontinence, or activity limitation) after hysterectomy as before surgery [89]. In addition to the menopausal symptomatology, a 2-year prospective study of 1277 women found that hysterectomy alone or with unilateral oophorectomy was related to better sexual function compared to hysterectomy with BSO [90]. Further, removal of ovaries led to a greater inability to achieve orgasm compared to women with ovarian conservation (OR 2.68, 95% CI 1.10–6.53) [90].

Long-term consequences of surgical menopause include a potential adverse impact on future bone health. A population-based study in women with BSO after the natural onset of menopause found a 32% increase in overall fracture risk when compared to postmenopausal women who retained their ovaries, possibly secondary to the small amounts of estrogen that are still secreted by the ovaries after menopause [91]. However, an analysis of 25,448 women in the WHI study did not find an increased risk of hip fracture in women who had underwent BSO [84]. Effects on neurologic health and cognition have been investigated. For women younger than age 50 years, two studies comprising 178,165 women found reduced risk of dementia comparing hysterectomy alone versus hysterectomy with BSO [92,93]. However, use of hormone therapy (HT) appeared to counteract this effect. Unilateral oophorectomy was also associated with reduced cognitive function [92–94]. There is also evidence that bilateral oophorectomy negatively impacts mood. A prospective 3-year study of women aged <46 years found a higher incidence of depression among women who underwent BSO (38%) versus women who underwent hysterectomy with ovarian conservation (17%) [95]. The risk of future pelvic organ prolapse after hysterectomy without BSO versus with BSO has also been examined. One study examining 549,223 records using the Scottish Morbidity Returns found women with hysterectomy with ovarian conservation versus bilateral oophorectomy were slightly more likely to require prolapse repair surgery in the future (HR 1.31, CI 1.11–1.55) over a 11.6-year follow-up. However, they did not observe any difference in future mid-urethral sling placement for treatment of stress urinary incontinence symptoms [96]. Urinary frequency symptoms improved with either method of hysterectomy (±BSO) and women with ovarian conservation had better relief of excessive nighttime voids than women who had underwent BSO in a 3-year prospective study among 314 women [95]. Overall, hysterectomy alone or with unilateral oophorectomy led to better composite pelvic function compared to hysterectomy with BSO [90].

Another important consideration in regards to long-term consequences is the impact of BSO on overall life expectancy. A cohort study of women in Olmsted County, MN comprised of women undergoing unilateral or bilateral oophorectomy from 1950 to 1987 was matched to a referent population who did not have their ovaries removed. Women who underwent BSO ($n = 1097$) before age 45 years had increased mortality from cardiovascular heart disease compared with referent women ($n = 2390$), and this was more pronounced in women who did not receive estrogen hormone therapy (HT) to at least age 45 years. No mortality differences were observed in the 1293 women who underwent unilateral oophorectomy [97,98]. Long-term health outcomes were also assessed in the prospective, observational Nurses' Health Study comprising 29,380 participants who underwent a hysterectomy with or without oophorectomy for benign disease over a follow-up period of 24 years. Bilateral oophorectomy was associated with an increased risk of all-cause mortality regardless of age or menopausal status at surgery [99]. Interestingly, although the risks of breast and ovarian cancer were reduced with BSO, lung cancer incidence and total cancer mortality increased [99]. Further, the WHI analysis in women who underwent BSO compared to hysterectomy + USO found significantly higher cardiovascular mortality (OR 1.41, 95% CI 1.09–1.83) in the women who had underwent BSO [100]. In young women, the increase in mortality may be modified by use of estrogen as further stratification within the WHI data found the risk of cardiovascular death was only significant in women younger than 45 years with BSO who did not use estrogen HT (HR 1.84, 95% CI 1.27–2.68) [97].

Given these known short and long-term consequences, Parker et al. applied a Markov decision analytic computer model to calculate risk estimates for average-risk women undergoing oophorectomy and determined in a hypothetical cohort of 10,000 women aged 50–54 years of age that by the time the cohort reached 80 years old, only 47 fewer women would have died from ovarian cancer, but 838 more women would have died from cardiovascular heart disease and 158 more due to hip fracture leading the authors to conclude a BSO should be used with great caution in average-risk women [101]. These conclusions were based on the fact that cardiovascular disease remains the most common cause of death in women in these age groups. For example, BSO before age 55 increased risk of dying by age 80 from coronary artery disease to 15.95% from a baseline risk of 7.57%, and increased risk of dying by the age of 80 from osteoporotic hip fracture to 4.96% from a baseline risk of 3.38% [81,102].

However, in high-risk populations of women undergoing risk-reducing bilateral salpingo-oophorectomy (RRSO), there is thought to be a net benefit of ovarian removal [103]. Despite this, there has been controversy surrounding the role of postoperative HT given the early age of menopause and adverse menopausal effects at young ages as mentioned above. While HT can alleviate some of these issues, it is also related to increased risk of breast cancer. A recent prospective,

longitudinal cohort study of *BRCA1* mutation carriers was conducted between 1995 and 2017 with a mean follow-up of 7.6 years comprising 80 centers in 17 different countries. Overall, HT use after RRSO was not associated with an increased risk of breast cancer in *BRCA1* mutation carriers. Estrogen-alone HT had a lower cumulative incidence of breast cancer compared to estrogen plus progesterone HT with a 12% incidence compared to 22% incidence (absolute difference 10%, log rank $P = 0.04$). For women who never used HT, the breast cancer incidence was 10.7% compared to 10.3% for women who had ever used HT (absolute difference, 0.4%; $P = 0.86$) [104]. Ultimately this study will likely lead to practice-changing implications with shifts towards hysterectomy at time of RRSO along with use of estrogen-alone HT in the postoperative period. HT can also improve quality of life. However, HT use in regards to cardiovascular disease and mortality in high-risk women is not fully understood at this time. Postoperative counseling regarding use of HT must weigh in a patient's personal comorbidities, family history and interpretation of the current known risks and benefits on an individualized basis. More research is needed to study the effects of HT use after RRSO on other health conditions, such as cardiovascular disease.

4. Recommendations

4.1. Women with high-risk genetic mutations

BRCA1 and *BRCA2* mutations contribute to HBOC. An estimated 9–24% of epithelial ovarian cancer cases are due to germline mutations in these tumor suppressor genes. For example, the risk of ovarian cancer by age 70 is 39–46% for *BRCA1* mutation carriers and 10–27% for *BRCA2* mutation carriers [105–108]. Additional high-risk mutations for ovarian cancer include *BRIP1*, Lynch syndrome genes (*MSH2*, *MLH1*, *MSH6*, *PMS2* and *EPCAM*), *RAD51C* and *RAD51D*. For women in these mutation populations, there is strong evidence that RRSO significantly decreases ovarian cancer risk. For example, in one study, RRSO was associated with decreased overall mortality as well as a 79% (HR 0.21, 95% CI 0.12–0.39) reduction in the risk of ovarian, fallopian tube or peritoneal cancers among women with *BRCA* mutations [109–112].

Less is known regarding the effectiveness of bilateral salpingectomy followed by a delayed oophorectomy (BS/DO) in preventing ovarian cancer among women with high-risk genetic mutations. However, a recent, non-randomized, prospective pilot study allowed 43 *BRCA1* carriers and *BRCA2* carriers, aged 30–47 years, to decide between screening, RRSO, and BS/DO. In the BS/DO group, *BRCA1* carriers were instructed to undergo delayed oophorectomy by age 40 years and *BRCA2* carriers by age 45 years. Among all women, 19/43 (44%) chose BS/DO, 12/43 (28%) chose RRSO and 12/43 (28%) chose screening. No intraoperative complications occurred and no occult cancer was found in the BS/DO group. Only one serous tubal intraepithelial carcinoma (STIC) was found in the RRSO group. Patients were overall satisfied with their procedure choice and had a reduction in cancer worry and anxiety even in the BS/DO group [113].

Notably, clinical trials are currently underway to assess the effectiveness of BS/DO versus RRSO on ovarian cancer risk reduction in a high-risk patient cohort [103]. For example, the TUBA study is a prospective, non-randomized multicenter study that aims to determine if salpingectomy after completion of childbearing followed by delayed oophorectomy will improve menopause-related quality of life without increasing ovarian or breast cancer risk compared to standard treatment with BSO at the recommended age in *BRCA* carriers [114]. Two other clinical trials are underway that seek to answer similar questions. One U.S. research group is comparing three arms of non-randomized patients with screening, BSO, and salpingectomy with delayed oophorectomy among *BRCA* mutation carriers (NCT01907789). A French study is offering a radical fimbriectomy as an alternative to BSO for *BRCA* mutation carriers who want to avoid surgical menopause. Radical fimbriectomy is only offered to women who refuse BSO (NCT01608074). Although current clinical recommendations do not include bilateral salpingectomy alone as an option, clinicians should consider offering BS/DO for high-risk women who strongly wish to delay surgical menopause, particularly for child-bearing or medical reasons, and who are informed of the limitations of our understanding of risk reduction.

In general, risk reducing recommendations in high-risk women are that RRSO should be performed at age 35–40 years for *BRCA1* carriers, 40–45 years for *BRCA2* carriers and 45–50 years for *BRIP1*, *RAD51C*, *RAD51D* and Lynch syndrome carriers. It is important to note that a hysterectomy is recommended in addition to BSO in Lynch syndrome given the increased risk of endometrial cancer, and optional for women with *BRCA1* given a possible association with pap serous uterine cancer. Other uterine and cervical factors should also be considered. Surgical technique for RRSO requires removal of all tissue from the ovaries and fallopian tubes. The ovarian vessels should be isolated and ligated 2 cm proximal to the end of the identifiable ovarian tissue for a complete dissection. The fallopian tube should be divided at its insertion into the uterine cornu and the ovary removed at the utero-ovarian ligament as close to the uterus as possible. If a bilateral salpingectomy is performed, it involves removal of the fimbriated end to the uterotubal junction but without the intramural (uterine) portion. Inspection of the diaphragm, liver, omentum, bowel, paracolic gutters, appendix, ovaries, fallopian tubes, uterus, bladder serosa and cul-de-sac should always take place in any RRSO performed in this subset of patients. It is imperative to inform pathology of known high-risk mutations as a complete, serial fine sectioning of the ovaries and fallopian tubes is necessary along with microscopic examination for occult cancer [103].

4.2. Average-risk women

The risk of ovarian cancer after hysterectomy without removal of the ovaries is 0.1–0.75% [115]. Death from ovarian cancer after conservation of both fallopian tubes and ovaries was 0.03% in the Nurses' Health Study [99]. However, given hysterectomy is one of the most commonly performed surgeries in the United States and the tubal origin of many high-grade serous tumors, many physicians and patients are now considering prophylactic removal of fallopian tubes under certain circumstances. The intricacies of contraceptive counseling in this setting are outside the scope of this article [65,116]. The current knowledge base regarding surgical prophylaxis for ovarian cancer risk reduction has led the American College of Obstetricians and Gynecologists (ACOG) to recommend the following in relation to average-risk women: (1) the surgeon and patient should have a conversation regarding removal of the fallopian tubes when undergoing hysterectomy, (2) when a surgeon is discussing laparoscopic sterilization methods, bilateral salpingectomy should be presented as an option, (3) prophylactic salpingectomy should be considered to be an option for surgeons to prevent ovarian cancer in their patients, and (4) randomized controlled trials are needed to support surgical prophylaxis as a method for ovarian cancer risk reduction in average-risk women [64]. However, BSO is not recommended for average-risk populations. Notably, a 2016 report on ovarian cancer by the National Academy of Medicine recommended "[development] and [validation of] a dynamic risk assessment tool accounting for the various ovarian cancer subtypes" and "[quantifying] the risk–benefit balance of nonsurgical and surgical prevention strategies for specific subtypes and at-risk populations," emphasizing the need to identify women at high-risk among those without high-penetrance germline mutations to target prevention strategies [117].

Surgical technique for bilateral salpingectomy involves removal of the fimbriated end to the uterotubal junction without need for removal of the interstitial portion in this group of average-risk women as opposed to known high-risk mutation carriers. In all women, fimbrial attachments to the ovary should be removed in their entirety. Surgeons must use care to not disrupt the blood supply to the ovary and should make efforts to preserve the utero-ovarian ligament. Pathologists

examining the tubes from average-risk women should process the surgical specimen using representative sections of the fallopian tube, but in the presence of any suspicious lesions should perform an entire section of the fimbriae [64]. It is important to note that plans to perform an opportunistic salpingectomy should not change the route of hysterectomy selected by the provider and patient [118].

5. Future directions

While there have been significant advancements in understanding of the biology of ovarian cancer, an understanding of the role of the fallopian tube in ovarian carcinogenesis is evolving. Although BSO is an effective risk-reduction strategy, there are many quality-of-life issues that greatly impact a woman's well-being in addition to long-term negative health consequences, including early mortality. The quick uptake of BSO in average-risk women undergoing hysterectomy provides a cautionary tale to widespread use of bilateral salpingectomy among average risk women, although initial studies suggest few short-term side effects of this approach. Among high risk women, the recent report demonstrating no intraoperative complications and overall satisfaction with the delayed oophorectomy is encouraging; however, longer-term data on ovarian cancer risk reduction compared with RRSO is needed to inform clinical recommendations [113]. As we await the results on prospective studies of bilateral salpingectomy with delayed oophorectomy as well as improved risk prediction models for normal risk women, we must continue to critically appraise all the known data while weighing all the clinical benefits or risks that a patient must endure to maintain a risk-reduction balance that makes sense to her and her family.

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Author contributions

Drs. Crum and Tworoger developed the concept for the review and supervised the drafting of the manuscript. Drs. Mallen and Soong reviewed the literature and drafted the manuscript. All authors participated in critical revision of the manuscript for important intellectual content and have approved the final article.

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