Current Science and Practice of Surgical and Nonsurgical Opportunities for Ovarian Cancer Prevention

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Abstract: Due to improved understanding of ovarian cancer pathogenesis, we have an unprecedented chance to decrease the burden of disease by maximizing opportunities for prevention. Innovations in surgical options for prevention stem from the discovery that many cases directly or indirectly arise from the fallopian tube. Surgical prevention with salpingectomy alone decreases risk by $\geq 50\%$. Effective hormonal and nonhormonal chemopreventive agents are also available. Risk stratification is key to ensuring that options for prevention are appropriately matched to individual risk profile. This evidence-based review provides a critical appraisal of the translational health research endeavors supporting ovarian cancer prevention in clinical practice.

Key Words: ovarian cancer, prevention, germline genetic mutation, salpingectomy, salpingooophorectomy, genetic testing

(*Clin Obstet Gynecol* 2024;67:676–686)

Ovarian cancer is a highly lethal malignancy with a 5-year overall survival rate of 50%.[1] While newly emerging therapies have improved outcomes over the past decade, prognosis remains overwhelmingly poor. This is in large part because screening to enable the early detection of precancerous lesions or cancer in its initial stages, when treatment is more likely to be curative, has been a relatively futile endeavor.[2,3] This is underscored by the most recent report of long-term outcomes following a diagnosis of serous tubal intraepithelial carcinoma (STIC), the putative precursor of the most prevalent histologic type of ovarian cancer—high-grade serous carcinoma (HGSC).[4] Even when microscopic STIC is discovered at the time of prophylactic bilateral salpingo-oophorectomy for BRCA1/2 pathogenic variant (PV) carriers, the 5-year and 10-year risks of developing subsequent peritoneal carcinomatosis may be as high as 10.5% and 27.5%[4]

The diverse origins and related biological heterogeneity of the diseases lumped together as "ovarian cancer" are major barriers to developing universally effective screening and prevention strategies. Classically, ovarian cancer has been subdivided into epithelial, sex cord stromal and germ cell tumors based on the presumed location of progenitor cells in the ovary.[5,6] While ovarian surface epithelium had long been considered the progenitor cell for epithelial ovarian cancer (EOC), more recent data indicate that most EOC does not originate from the ovary itself, but rather from the fallopian tube, endometrium, or other nonovarian sites.[2,7–9] This shift in understanding explains the lack of success seen with screening efforts to date and, importantly, provides viable, broad opportunities for prevention. Indeed, the utility of longitudinal screening with ultrasound and serum biomarkers may be largely limited for detecting the rare, slow growing ovarian cancers that do arise from ovarian tissue (germ cell tumors, sex cord stromal tumors, and low-grade epithelial carcinomas).[10]

As EOC encompasses the most common and lethal histologic subtypes, this review will focus on surgical and nonsurgical preventative measures for EOC. This includes prophylactic and opportunistic salpingectomy, prophylactic salpingo-oophorectomy, and tubal ligation as well nonsurgical interventions, most notably hormonal contraceptive measures, which mitigate DNA damage to the fallopian tube epithelium and decrease the chances of ectopic ovarian and peritoneal endometrium by dampening the frequency and/or amplitude of menses.[11,12] While newer screening bioassays are perhaps on horizon, there is much to be gained at this time by focusing on primary prevention strategies.

DEFINING EOC RISK

As primary prevention strategies for EOC now include options that take into account age and reproductive life plans for all people, it is important to define baseline risk. The general population can be trichotomized as average risk, intermediate risk, and high risk according to cumulative lifetime risk of EOC attributable to familial/genetic risk factors. These risk thresholds align with different strategies for primary prevention.[13] As germline genetic testing is fundamental to providing more personalized and proactive care to high-risk individuals, many advocate for universal germline testing around age 30.[14] This is supported by the fact that an estimated 3% to 4% of people in the general population carry germline mutations associated with increased cancer risk and yet a large proportion do not report a family history of the associated cancers.[15]

High-risk patients have high-penetrance germline mutations unequivocally known to confer a cumulative lifetime risk of ovarian cancer over 4%.[16–18] Approximately 20% of high-grade serous cancers (HGSCs) are attributable to high-penetrance germline mutations, most commonly BRCA1/2.[13] While germline genetic testing is recommended for all individuals diagnosed with ovarian, fallopian tube, or primary peritoneal cancers, 29% to 38% of affected individuals do not complete testing. This results in unfulfilled identification of at-risk relatives who could go on to choose targeted preventive measures.[19,20] Thus, prioritizing primary prevention, particularly in the form of a targeted prevention program based on risk factors, could have the most profound impact on ovarian cancer incidence and mortality.

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The authors declare that they have nothing to disclose.

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DOI: 10.1097/GRF.0000000000000900

The familial and genetic factors that define average risk, intermediate risk, and high risk as well as the corresponding surgical interventions for reducing EOC risk are summarized in Tables 1 and 2. While BRCA1/2 pathogenic variants are the most widely recognized germline mutations associated with HGSC, many others significantly increase the cumulative lifetime risk of EOC, including MLH1, MSH2, MSH6, RAD51C, RAD51D, BRIP1, and PALB2.[32] Surgical prophylaxis earlier than recommended age should be considered for those with a significant family history of ovarian cancer, typically 5 to 10 years before the youngest affected family member.[33]

Identification and management of intermediate-risk individuals is less formulaic. Individuals may be considered intermediate risk based on a variety of well-established risk factors for EOC, with first-degree family history or moderate-penetrance gene mutations being the most relevant.[34] Having one affected first-degree relative confers a cumulative lifetime risk of 3% to 4%, and this increased risk persists in the absence of detectable genetic mutations.[21,34,35] Recent risk stratification found an OR of 2.15 (1.56 to 2.97) for ovarian cancer among patients with a first-degree family history of ovarian cancer.[36] At present, prophylactic salpingo-oophorectomy is controversial for individuals with pathogenic PALB2 variants; newer studies consistently show that the increased risk of EOC in these cases is dependent on family history.[21] Other factors associated with increased EOC risk include early menarche, late menopause, nulliparity/low parity, no history of lactation, endometriosis, and obesity.[37–42] How these all interact to predict risk remains unknown. In current practice, these factors are often considered along with patient age and personal preferences in a qualitative approach to risk assessment. This assessment is then used to guide shared decision-making about whether or not to proceed with risk reducing surgery along with its timing and extent.

Lastly, average-risk individuals are those who are not known to have genetic or familial risk factors for EOC ($<2\%$ lifetime risk).[1] Opportunistic salpingectomy (OS) as an alternative to tubal ligation, at the time of hysterectomy, and, ideally, other postreproductive elective intraperitoneal procedures is the recommended primary prevention strategy in this group.[3,43] Importantly, prophylactic salpingectomy for high-risk and intermediate-risk individuals differs from opportunistic salpingectomy for average-risk individuals. Prophylactic salpingectomy is offered as a standalone procedure, while opportunistic salpingectomy is offered as a secondary procedure at the time of another planned surgery. Unfortunately, deficiencies in medical coding and universal third-party payor coverage are current structural barriers to accessing opportunistic salpingectomy outside of gynecologic surgeries in the United States.[44] The option of an IUD or COC (for 5+ premenopausal years) to reduce EOC risk should be presented as the alternative to surgical prevention across all risk categories. A personal history of hormone-sensitive breast cancer is the main contraindication to these chemopreventive agents. Patients are often offered surveillance ultrasound and CA-125 as an alternative to prevention without adequate counseling about their limited sensitivity. This can lead to a detrimental false sense of security.

Surgical Prevention of EOC

Natural History and Carcinogenesis

Epidemiologic, clinical, pathologic, and molecular data gathered over the past 20 years indicate that the majority of HGSCs arise from precursor lesions in the Müllerian epithelium of the fimbriated ends of fallopian tubes, rather than from the ovary itself.[7,9,45] The precancerous landscape of the fallopian tube contains a spectrum of genetically heterogeneous, clonally independent "early serous proliferations" that precede the development of and coexist with HGSC.[8] The earliest discernable lesion is the p53 signature—a small stretch of 12 or more benign appearing, predominately secretory (nonciliated) p53 mutated cells.[46,47] These lesions have gamma-H2AX immunostaining indicative of DNA damage and are viewed as latent precursors, arising in 1% to 2% of the general population, that rarely eventuate in malignancy.[46–49] When discovered, they are most often found at the fimbriated end of the fallopian tube, making the fibria a highly p53 mutated anatomic structure in the human body.[48] It has been hypothesized that COCs are chemopreventive for HGSC by lowering the p53 mutational burden that forms in the fallopian tube epithelium over time due to DNA damaging ovulatory events.[50]

Precursor lesions with some proliferative capacity, termed tubal intraepithelial lesions in transition or serous tubal intraepithelial lesions (STILs) have also been described.[48] At the end of the spectrum is serous tubal intraepithelial carcinoma (STIC), thought to precede the diagnosis of HGSC by 7 or more years.[8,51] Importantly,

TABLE 1. Common Germline Mutations Associated With Increased EOC Risk[21–31]

Gene	Cumulative lifetime risk of ovarian cancer (%)	Recommended intervention	Recommended age of intervention
BRCA1	39-58	Risk reducing BSO	35-40
BRCA2	13-29	Risk reducing BSO	40-45
Lynch syndrome			
MLH1	4-20	Risk reducing THBSO	Completion childbearing
MSH2/EPCAM	8-38	Risk reducing THBSO	Completion childbearing
MSH6	< 1-13	Risk reducing THBSO	Completion childbearing
PMS2	1.3-3	Risk reducing THBSO	Completion childbearing
ATM	2-3	Insufficient evidence for BSO	NA
BRIP1	5-15	Risk reducing BSO	45-50
PALB2	3-5	Risk reducing BSO	45-50
RAD51C	10-15	Risk reducing BSO	45-50
RAD51D	10-20	Risk reducing BSO	45-50

BSO indicates bilateral salpingo-oophrectomy; THBSO, total hysterectomy bilateral salpingo-oophrectomy.

TABLE 2. Ovarian Cancer Risk Stratification

Risk level	High risk	Intermediate risk	Average risk
Lifetime ovarian cancer risk	>4%	2%-4%	<2%
Population	Individuals with high-penetrance germline mutation(s)	Individuals with a family history of ovarian cancer* and negative genetic testing Individuals with moderate-penetrance germline mutations	All other individuals with fallopian tubes who have completed childbearing
Germline mutations	BRCA1, BRCA2, MLH1, MSH2, MSH6, BRIP1, PALB2, RAD51C &D	PMS2, ATM	NA
Recommended surgical intervention	Prophylactic bilateral salpingo-oophorectomy (BSO)†	Prophylactic bilateral salpingectomy (BS) or BSO based family history, age, patient preference	Opportunistic salpingectomy (OS)

*Estimated cumulative lifetime risk of 2% to 4% is based on a first-degree relative with ovarian cancer.
†In accordance with the 3.2024 NCCN guidelines, salpingectomy with delayed oophorectomy is an acceptable option for young high-risk patients. Consideration should be given to use of an IUD or COC to reduce EOC risk while ovaries remain in situ.

STIC lesions tend to arise in the vast surface area of fallopian tube fimbria, highlighting the significance of this anatomic portion of the tube.[52] Using current diagnostics, STIC is found in ~1 in 500 average-risk individuals (0.2%), in 1% to 10% of women with pathogenic BRCA1/2 variants undergoing prophylactic salpingo-oophorectomy (BSO), and in at least 50% of women with HGSC.[53–58] Unlike discrete precursor lesions or in situ carcinomas which can precede other types of epithelial cancer and can be cleared with surgical excision, STIC cells may disseminate from the fallopian tube well in advance of salpingectomy and render it an ineffective means of eliminating them.[4,59] It is hypothesized that disseminated STIC cells may implant and survive on peritoneal surfaces, particularly the immediately adjacent mesovarium, where they genetically evolve into HGSOC over several years.[60] This offers a possible explanation as to why some individuals with pathogenic BRCA1/2 variants may still develop peritoneal HGSOC years after RRSO.[4] Furthermore, this hypothesis suggests that finding STICs at the time of salpingectomy may indicate that surgery was performed too late to take full advantage of it as a preventative effects. Importantly, STICs associated with pathogenic BRCA1/2 variants may differ from sporadic STICs (STICs identified in fallopian tubes from average-risk individuals) in that the former are more genetically evolved and have higher malignant potential age for age.[61]

In addition to fallopian tube epithelium serving as the site of origin for most HGSC, the fallopian tube serves as a conduit between the endometrial cavity, the ovary, and the pelvis. It is well established that clear cell and endometrioid ovarian carcinomas likely arise from ectopic endometrial tissue implants in the ovaries and pelvic peritoneum. Thus, obstruction, interruption, or removal of the fallopian tube conduits between the endometrial cavity and pelvis decreases the risk of these histologic subtypes.[62–64] Altogether, these data are the basis for opportunistic salpingectomy and for the paradigm shift toward early salpingectomy followed by delayed oophorectomy for BRCA1/2 pathogenic variant carriers.

Opportunistic Salpingectomy

Procedural Standards. Opportunistic salpingectomy (OS) denotes removal of the bilateral fallopian tubes for the primary prevention of ovarian cancer during intraperitoneal surgery performed for other indications.[65] The performance of preventative salpingectomy differs from routine salpingectomy undertaken to treat conditions like hydrosalpinx or ectopic pregnancy in that it requires diligent excision of the fallopian tube fimbria. However, given that even unilateral salpingectomy alone has been proven to decrease the lifetime risk of EOC, salpingectomy should be executed with preventative intent whenever it is performed.[66] Proficiency in isolating and carefully transecting the tubo-ovarian ligament adjacent to the ovary without injuring the ovarian vessels is a key to performing preventative salpingectomy.[67] Even when salpingectomy is undertaken with preventative intent, residual fimbrial tissue has been found attached to the ovaries at the time of later oophorectomy in ~10% of cases.[68] This in part explains why salpingectomy is not 100% effective in preventing EOC and why completion oophorectomy is recommended for patients with BRCA1/2 pathogenic variants who undergo early salpingectomy (Fig. 1).

Risk Reduction Relative to Tubal Ligation. Considering the major role that the fallopian tube plays in the pathogenesis of HGSC and endometriosis-associated EOC, the EOC risk reduction afforded by salpingectomy is compelling. The achievable risk reduction has been demonstrated across multiple large international studies, with the net decrease in HGSC risk following bilateral salpingectomy ranging from 42% to possibly as high as 80%.[13,65,69–73] Early readout from the prospective effectiveness study of opportunistic salpingectomy in British Columbia, Canada projects that salpingectomy will substantially decrease the incidence of high-grade serous, endometrioid and clear cell ovarian cancer (NCT05300711). Because salpingectomy puts the endometrial cavity and the pelvis in discontinuity, it serves to decrease the risk of endometriosis-associated EOC by as much as 40%.[2,13] This same effect occurs with tubal ligation, which has led to several investigations comparing its' efficacy to that of salpingectomy for prevention of these histologic subtypes. One pooled analysis showed that tubal ligation alone may be as effective as salpingectomy in decreasing endometriosis-associated EOC.[64] A more recent meta-analysis found a significant, albeit weaker association between tubal ligation and an overall decreased EOC risk (OR: 0.70, 95% CI = 0.6-0.781).[74] Some have suggested that the strength of these associations be

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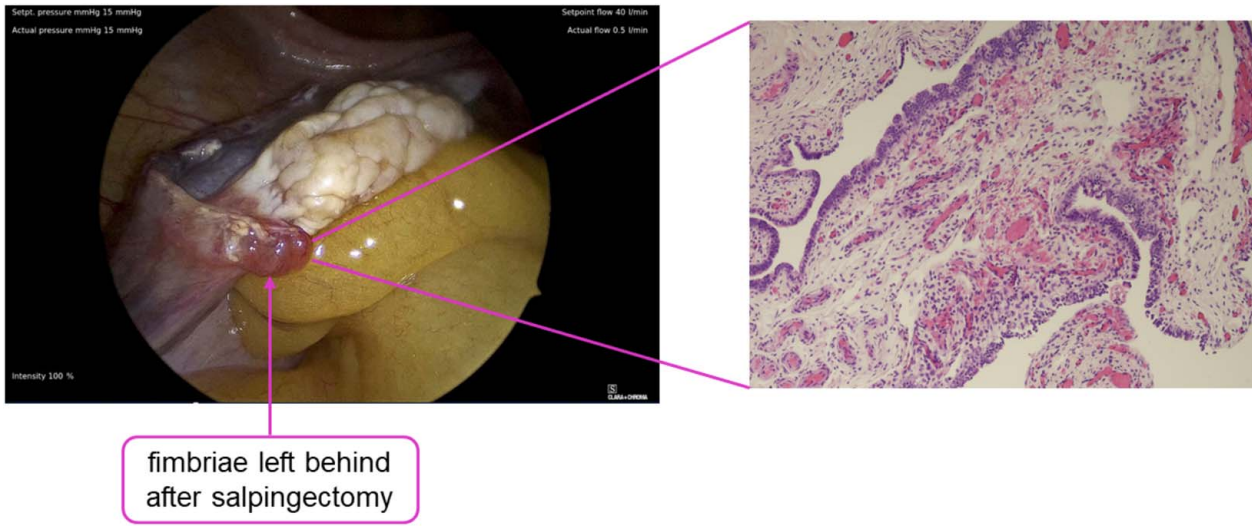

FIGURE 1. This image and photomicrograph show fimbria adjacent to the left ovary in a 41-year-old patient with a history of bilateral salpingectomy for permanent contraception. The image was captured upon her return to the operating room for bilateral oophorectomy following a diagnosis of breast cancer and subsequent germline genetic testing revealing a BRCA1 pathogenic variant. full color online

interpreted with caution as the effect size may in part be attributable to the inclusion of some individuals who inadvertently underwent salpingectomy.[70] A recent report out of Denmark comparing the ovarian cancer risk reduction afforded by tubal ligation versus salpingectomy indicates that tubal ligation may lower the risk by < 10% (OR: 0.91, 95% CI: 0.83-0.99)—again, with the greatest risk reduction observed for endometrioid EOC (OR: 0.64 95% CI: 0.47-0.88).[69] A 2023 study comparing OS to standard bilateral tubal ligation following vaginal delivery showed that for every 10,000 patients, "salpingectomy would result in 25 fewer ovarian cancer cases, 19 fewer ovarian cancer deaths, and 116 fewer unintended pregnancies than tubal ligation."[75] Tubal ligation and partial salpingectomy are likely inferior to complete salpingectomy because the fimbria, where STIC formation most commonly occurs, are retained.[76] Given that salpingectomy is more effective than tubal ligation for the prevention of pregnancy and of HGSC, multiple national and international level organizations have advocated for salpingectomy as the preferred form of permanent contraception, and for OS at the time of other elective pelvic surgery for postreproductive individuals with an estimated lifetime risk of EOC under 2% (average risk).[67,77–79]

Importantly, while OS significantly decreases the lifetime risk of ovarian cancer, it is an imperfect EOC prevention strategy. This is an important qualifier. The risk reduction has anatomic and surgeon skill constraints. It is also likely age dependent. Recent data suggest that the impact of salpingectomy on lowering the overall risk of EOC is probably greatest when it is performed upon completion of childbearing and that the effect size significantly wanes when salpingectomy is performed at or after age 50.[69]

Procedural Risks. Investigations examining the safety of OS have largely shown it to be a low-risk option for primary prevention for those who have completed childbearing.[80,81] A noninferiority study showed that OS did not increase intraoperative/postoperative blood loss or increase operative time (10.0 vs. 9.9 min) compared with tubal ligation at cesarean section or postpartum following vaginal delivery.[82] A large meta-analysis of 320,443 women undergoing various approaches to surgical sterilization at cesarean delivery similarly found that salpingectomy did not increase the risk of infection, blood loss, transfusion, readmission, or length of stay compared with other sterilization techniques.[83] Similarly, complication rates are not increased by the addition of OS to hysterectomy.[80]

It has been hypothesized that salpingectomy may compromise ovarian blood supply and that this may, in turn, have deleterious effects on ovarian function—perhaps decreasing oocyte quantity or quality, and/or ultimately contributing to earlier onset of menopause.[84] Several studies have evaluated the validity of this hypothesis. One meta-analysis of 12 studies examining the effect of OS on ovarian reserve did not find any statistically significant differences in anti-Müllerian hormone levels between cohorts of patients who did and did not undergo OS.[85] A 2024 systematic review of 102 studies concluded that while short-term ovarian function is not adversely impacted by salpingectomy, assessment of long-term adverse effects is needed.[86]

The relationship between OS and age of onset of menopause is debatable. One Swedish study reported higher rates of menopausal symptoms 1-year postoperatively among patients having had salpingectomy at the time of hysterectomy compared with those who underwent hysterectomy alone.[87] Conversely, a retrospective cohort study performed in Canada found that those who had hysterectomy with OS were actually less likely to have a physician visit for menopause during follow up compared with those who underwent hysterectomy alone.[88] Currently, there is insufficient evidence to support withholding OS. The authors typically counsel patients that OS, when performed correctly, is not known to substantively affect ovarian hormone production or age of onset of menopause, but that research is ongoing. There are 2 active ongoing trials exploring the association between salpingectomy and onset of menopause, the Hysterectomy and OPPortunistic SAlpingectomy (HOPPSA) trial and the Stop Ovarian Cancer Young (STOPOVCAyoung) trial.[89,90]

Expanding Access to OS. The possibility of expanding access to OS beyond the scope of gynecologic surgery is an

area of active investigation. Consideration of OS at the time of other common elective intraperitoneal surgeries, such as hernia repair, appendectomy, cholecystectomy, urologic procedures, and gastric bypass has been proposed as a viable risk reduction strategy for average-risk patients who have completed childbearing.[44] The feasibility of OS at the time of nongynecologic surgery was first tested in a prospective study based in Austria. Patients over the age of 45 undergoing elective cholecystectomy were counseled about OS at the time of their surgery. Notably, 62% of patients accepted the intervention and OS was completed in 93% of cases, largely by a general surgeon without additional port placement. STIC was recovered in 1 of the 98 patients, highlighting the value of this opportunistic surgery.[91] OS is currently being prospectively studied at the time of elective colorectal surgery in British Columbia Canada (NCT05300711). Preliminary results were presented by Gillian Hanley at the 2023 AACR Special Conference on Ovarian Cancer, showing similar acceptability and feasibility. OS at the time of urologic procedures, specifically radical cystectomy, is also under investigation at Johns Hopkins Hospital (NCT06312124). To date, 2 of 30 patients have potentially been saved from an impending HGSC by excision of fallopian tubes harboring intraepithelial precursors (unpublished data). These endeavors to integrate OS more broadly into surgical practice are supported by data demonstrating that OS is a cost-effective intervention when added to laparoscopic cholecystectomy, as well as to other abdominopelvic procedures.[92,93]

Prophylactic Bilateral Salpingo-Oophorectomy

Procedural Standards. Prophylactic bilateral salpingo-oophorectomy (BSO) is the gold standard for ovarian cancer prevention for high-risk patients. Fortunately, prophylactic BSO can typically be performed as an outpatient minimally invasive endoscopic procedure. Pelvic washings for cytology should be obtained immediately upon entry to the abdomen. The visceral and parietal peritoneum should be thoroughly surveyed throughout the abdominal cavity and abnormal findings biopsied. Excision of the ovaries should include transection of the infundibulopelvic ligament ~2 cm proximal to the ovary. Excision of the fallopian tubes should extend to the cornua and include all visible fimbria.[94]

Risk Reduction. The advantage of prophylactic BSO for high-risk patients is well established. Cochrane reviews have reported that the procedure confers a 68% reduction in overall and a 94% reduction in ovarian cancer-associated mortality for individuals with germline BRCA1/2 pathogenic variants.[21,95] Oophorectomy likely also reduces breast cancer risk in premenopausal patients; however, the magnitude is uncertain and may be gene specific.[96]

Procedural Risks. Decision-making related to prophylactic surgery occurs at a very young age for many women. The risks of bilateral oophrectomy before menopause are increasingly evident.[97] Beyond immediate onset of menopausal symptoms, which can be very detrimental to quality of life as well as to psychosocial and sexual health, premenopausal oophorectomy predisposes people to higher rates of osteoporosis, metabolic syndrome, cardiovascular disease, and cognitive impairment.[98–100] Nonetheless, patients with germline BRCA1/2 pathogenic variants consistently report that the peace-of-mind they experience following prophylactic BSO balances many of the negative aspects of surgical menopause.[101,102] This is understandable, given that their age-adjusted hazard ratio for all-cause mortality with oophorectomy is 0.32 (95% CI: 0.24-0.42).[103] The net health impact of prophylactic BSO for intermediate-risk premenopausal patients may be more net neutral or even net negative, particularly when hormone replacement therapy is withheld. The clinical guide published by Liu et al[21] for moderate-penetrance genes is a helpful reference when it comes to this patient population. The authors propose that prophylactic BSO be restricted to patients with germline mutations known to increase ovarian cancer risk to or beyond the 3% to 4% risk associated with having an affected first-degree relative.[21] Prophylactic salpingectomy is also an acceptable an option, particularly for those with a negative family history.

Fortunately, hormone replacement therapy following bilateral oophorectomy is generally not contraindicated and should be offered to premenopausal patients who do not have a personal history of breast cancer.[104–106] Published data from the Dutch TUBA study and unpublished data from the United States. WISP trial indicate that even with hormone replacement, early menopause due to bilateral oophorectomy negatively impacts menopause-specific quality of life and sexual function.[107] Given this and what we now know about the fallopian tube origin of HGSC, there is growing interest in the feasibility and safety of a staged prophylactic BSO—with early bilateral salpingectomy as soon as reproductive goals are met while delaying oophorectomy until closer to the natural age of menopause to sustain ovarian endocrine function.[108] The cancer prevention efficacy afforded by this strategy for high-risk women is under intense investigation and is recommended in the 3.2024 edition of NCCN for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy.[108] The prospective TUBA-WISP II study, the PROTECTOR study, and the SOROCk studies are currently underway to further explore the safety and efficacy of delayed oophorectomy in high-risk patients.[107]

Impact of Surgical Management of Endometriosis on EOC Risk

Risk-prediction modeling has showed an increased OR for ovarian cancer [OR: 1.6 (1.32-1.95)] among those with endometriosis.[36,74,109–111] While it appears reasonable to think that treatment of endometriosis might mitigate this, supporting data are scant. Melin and colleagues showed a significant decrease in ovarian cancer risk among patients with endometriosis following unilateral oophorectomy as well as excision of endometriosis. This association held up in both univariate and multivariate analyses.[112] However, given the small and highly specific patients included in these studies, further, more generalizable data is needed to better understand this association.

The Role of Hysterectomy in EOC Prevention

Given that many clear cell and endometrioid ovarian cancers arise from ectopic endometrial implants on the ovary and/or peritoneum, it stands to reason that hysterectomy, which is known to decrease endometriosis recurrence, might also decrease the risk of these histologic subtypes of EOC. This idea is supported by data analysis from the prospective cohort Nurses' health studies which found hysterectomy to be associated with decreased ovarian cancer risk (HR: 0.80, 95% CI: 0.66-0.97).[113] The strength of this association was more robust for nonserous tumors.[113] Unfortunately, attempts to validate this finding have been

unsuccessful. A large prospective cohort study in the United Kingdom compared the outcomes of 41,912 patients who underwent hysterectomy with conservation of at least one adnexa to those with intact uteri and found no association between hysterectomy and ovarian cancer incidence (HR: 0.98, CI: 0.85-1.13, $P = 0.765$).[114] Authors of a pooled analysis of 11 case-control studies and a separate large meta-analysis concluded that hysterectomy is not risk reducing for ovarian cancer.[74,115] Interestingly, among women with a known history of endometriosis, hysterectomy was associated with a slight decrease in ovarian cancer risk (OR: 0.93, 95% CI: 0.69-1.26) and the strength of this association increased after adjusting for duration of hormone therapy use (OR: 0.69, 95% CI: 0.48-0.99).[115] Thus, routine hysterectomy for the sole purpose of ovarian cancer prevention is not advised. Hysterectomy is performed when there is concomitant endometrial cancer risk, benign uterine indications or intent to use estrogen monotherapy for postoperative hormone replacement.

NONSURGICAL OPTIONS FOR OVARIAN CANCER PREVENTION

Oral Contraceptives

Oral contraceptives (COC) have long been considered the most effective agents for the chemoprevention of ovarian cancer. Ovulation suppression is the proposed mechanism of action. Interventions that decrease the number of ovulatory cycles and the number and intensity of menstrual cycles a women experiences in her lifetime lower the risk of HGS, endometrioid, and clear cell ovarian cancers. This may be because ovulation causes monthly oxidative base and DNA damage in the fallopian tube epithelial, particularly the fimbriated end due to its close proximity to the ovary.

In 2015, the Society of Gynecologic Oncology recommended oral contraceptives for reducing the risk of EOC and as a safe option for patients with high-penetrance genetic mutations.[116] This recommendation was based on several epidemiological studies, most notably on a pooled analysis of 23,257 women with ovarian cancer and 87,303 women without ovarian cancer showing a dose response for oral contraceptives and ovarian cancer risk—longer duration of oral contraception use results in greater ovarian cancer risk reduction.[117] Interestingly, while some amount of risk reduction persists for 30 years after cessation of oral contraceptives, the risk reducing effect begins to attenuate in the first 5 to 10 years after cessation.[117] The magnitude of this risk reduction has been found to be high as 50% when oral contraceptives are used for at least 10 years.[118]

For those with BRCA1/2 pathogenic variants, the safety of oral contraceptives for ovarian cancer prevention has been questioned. The concern stems from a large Lancet study that revealed a moderate rise in breast cancer risk immediately after taking oral contraceptives at the general population level. Notably, for these average-risk patients, this increase returned to baseline within 10 years of stopping oral contraceptives.[119] This has been attributed to the young age of most COC users, such that the likelihood of a breast cancer diagnosis in the decade around which they are most likely to use COCs is low. This furthermore highlights why this return to baseline is not applicable to the high-risk BRCA mutation carrier group, for whom the likelihood of a breast cancer diagnosis at a young age is high.[103] A large meta-analysis of individuals at high risk for developing breast cancer due to high-penetrance germline mutations, such as BRCA1/2 pathogenic variants, found no significant association between oral contraceptives and breast cancer risk when modern, lower-dose oral contraceptive formulations are prescribed.[120]

Still, subsequent studies have continued to provide conflicting results. Some suggest that risk is modestly increased despite modern formulations, while others find no association.[121–125] The most compelling data stem from Schrijver and colleagues, who looked at hypothetical cohorts of patients using previously established incidence rates and found similar results to those previously described for the general population. In this model, breast cancer incidence briefly increases after initiation of oral contraceptives for BRCA1/2 pathogenic variant carriers. However, after age 40 the net benefit of oral contraceptives (particularly for ovarian cancer risk reduction) appears to exceed the net risk of breast cancer after this age for this population.[121] Validation using real-world patient data is needed.[103] Certainly, prophylactic bilateral mastectomy simplifies the risk-benefit discussion when it comes to oral contraceptive use for the chemoprevention of ovarian cancer.[103] For high-risk patients undergoing a staged BSO, the latest NCCN guidelines suggest that oral contraceptive use be considered in in the interim between early salpingectomy and delayed oophorectomy to decrease ovarian cancer risk.[20]

Intrauterine Device

The rise in IUD use as a preferred method of contraception in parallel with a relative decline in oral contraceptive use over the past 20 years has raised questions about whether IUDs may play a role in preventing ovarian cancer.[126] Suppression of menstruation is the proposed mechanism of ovarian cancer prevention, as well as the sterile inflammatory environment they produce.[127–129] The majority of menstruating individuals experience some retrograde menstruation which exposes the fimbria to catalytic iron and the genotoxic effect of reactive oxygen species. Transferrin-containing fluid in retrograde menstrual blood induces DNA double-strand breaks that can potentially lead to DNA damage and genomic instability in the tubal epithelium. The related decrease in bioburden of retrograde menstruation with IUD use may also contribute to a decrease in endometriosis-associated EOC. For metal IUDs, which neither contain hormones nor diminish menstruation, alterations in the pH of the reproductive tract due to the sterile inflammation they create may have a protective effect.[128,130]

A recent systematic review and meta-analysis compared the impact of ever-use to never-use of an IUD on ovarian cancer risk. Across 269,045 patients, ever-use of the IUD reduced ovarian cancer compared with never-use; this association was strengthened when only studies pertaining to the levornogestrel IUD (LNG-IUD) system were included in the analysis. An overall risk reduction of ~33% was observed among ever users of any form of IUD, while a 42% risk reduction was seen in those using the LNG-IUD.[131] These data are consistent with an earlier review by Wheeler and colleagues and with the more recent prospective NOWAC study, which found the age-adjusted relative risk of EOC to be 0.49 (95% CI: 0.30-0.82) in LNG-IUD users.[132,133] Conversely, a 2021 prospective cohort study using data from the New England Case-Control study (NEC) and for the Nurses' Health studies found no

association between IUD use and ovarian cancer risk.[134] However, this finding is potentially attributable to a much higher rate of tubal ligation among never-users (14% vs. 0.3%). Other criticisms of this study include limited power and recall bias due to the fact that history of IUD use was collected after ovarian cancer diagnosis.[134]

NSAIDs/Aspirin

Increased understanding of prostaglandin involvement in tumor growth pathways has prompted inquiries about the anticancer effects of COX2 inhibition, which in turn has led to consideration of aspirin as a chemopreventive agent.[135,136] Furthermore, while full-dose aspirin has anti-inflammatory effects mediated through COX2 inhibition, low-dose aspirin predominately exerts antiplatelet effects by irreversibly blocking COX1. The antiplatelet effect of low-dose aspirin may inhibit the requisite angiogenesis needed for tumor growth beyond 1 cm^3.[137] Notably, exploration into nonaspirin NSAIDs has not found them to be protective (HR: 1.19, 95% CI: 1.00-1.41).[138]

Over the past decade, several meta-analyses have explored a possible connection between aspirin use and ovarian cancer risk. In reviewing thousands of patients from 15 case-control and 8 cohort studies, Zheng et al[139] detected an 11% lower rate of ovarian cancer among aspirin users. Similarly, an analysis of the prospective nurses' health studies showed that aspirin use reduces the risk of ovarian cancer. In fact, low-dose aspirin was associated with a 23% risk reduction in ovarian cancer (HR: 0.77, 95% CI: 0.61-0.96).[138] Likewise, low-dose aspirin was found to be associated with a 44% reduction in ovarian cancer risk in a Danish Cancer Registry.[140] Hurwitz and colleagues examined the frequency of aspirin use and found that the benefit appears to be limited to the subgroup of patients taking it 6 times a week. Interestingly, this benefit was still present after accounting for multiple other ovarian cancer risk factors.[141] Taken together, these data support a modest reduction in ovarian cancer risk associated with near daily aspirin use.

Weight Management

The well-established correlation between obesity and multiple other solid malignancies, most notably endometrial cancer, has prompted interest in targeting this modifiable risk factor for ovarian cancer prevention.[42] While the data in aggregate are inconclusive, there is some indication that obesity may be relevant. The collaborative group on epidemiological studies of ovarian cancer evaluated 25,157 women with and 81,311 women without ovarian cancer across 47 studies and found that obese women incur a 13% increased risk of ovarian cancer.[142] However, most of the 43 studies included in a 2017 systematic review exploring the relationship between obesity and ovarian cancer failed to show that BMI significantly influences ovarian cancer risk. Interestingly, the studies in this review that looked at high waist-hip ratio (WHR) and/or waist circumference found these measures, which some posit are better measures of obesity, to be positive predictors. However, WHR and waist circumference were not found to be predictive in the few studies that detected a positive association between BMI and ovarian cancer risk. Thus, the validity of associations between ovarian cancer and these 3 measures of obesity (BMI, WHR, and waist circumference) is questionable.[142–145] A large meta-analysis by Liu et al[146] found that being overweight or obese categorically increases the risk of ovarian cancer, except in postmenopausal women. This may explain the inconsistencies seen in the aforementioned 2017 systematic review because its analysis was not age stratified. In their meta-analysis, Liu et al[146] observed an increased relative risk of 1.31 (95% CI: 1.04-1.65) for premenopausal overweight patients and 1.50 (95% CI: 1.12-2.0) for obese patients. In line with this, several studies have consistently found that higher BMI at younger age (childhood, adolescence, and early adulthood) increases the risk of ovarian cancer.[147,148]

Another possible confounding factor in the relationship between ovarian cancer and obesity is PCOS. PCOS, which has a strong correlation with elevated BMI, is associated with an increased risk of borderline ovarian tumors.[149] Furthermore, BMI has been associated with an increased risk of serous ovarian tumors.[150] Despite this, modern data has failed to show a definitive connection between obesity and borderline tumors in the absence of PCOS as a confounding factor, highlighting the need for more research on this topic.[151,152]

Curiosity about the extent to which interventions like bariatric surgery, GLP-1 agonists and other medical weight loss interventions contribute to decreasing ovarian cancer risk naturally arises. A recent meta-analysis out of Australia looking at cancer risk after bariatric surgery found that there was a significant inverse association between bariatric surgery and the development of ovarian cancer (RR: 0.45, 95% CI: (0.44-0.71, $P < 0.00001$).[153] While some research has suggested that there is improved survival among diabetic ovarian cancer patients who utilize medications like metformin compared with those who do not, there are no existing data on overall ovarian cancer risk reduction with GLP-1 agonists or metformin, although future investigation may be of interest.[154,155]

CONCLUSION

For all of the unfulfilled promise of ovarian cancer screening and treatment, viable options for ovarian cancer prevention now exist. Implementation of a primary prevention strategy for this highly lethal disease is entirely feasible and could save thousands of lives and millions of health care dollars in the United States annually. The recent discovery of the fallopian tube origin of ovarian cancer makes surgical prevention through bilateral salpingectomy with ovarian conservation possible. Germline mutation status, family history, polygenic and modifiable risk factors, age and individual preferences should be used to inform risk assessment, with careful consideration given to timing of surgery and the inclusion of oophorectomy. Efficacious nonsurgical options for ovarian cancer prevention include oral contraceptives, IUDs, aspirin, and interventions to sustain healthy range body mass metrics.

For science to reduce the burden of cancer for all people and, in this case, for ovarian cancer prevention to be accessible to all people, people must know about it and be able to choose it. Achieving this means overcoming some major obstacles from knowledge mobilization to health policy change and insurance reform to solving long-standing diagnostic challenges and identifying a STIC interception strategy. As it currently stands, an ounce of prevention is worth a pound of screening and a ton of treatment. The unprecedented chance to decrease the incidence and mortality from ovarian cancer through prevention starts in the hands of OB-GYN.

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