Clinical Perspective

Optimization of Timing for Risk-Reducing Salpingectomy and Oophorectomy

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Most cases of ovarian cancer are diagnosed at an advanced stage, and long-term survival rates are low. Because no effective ovarian cancer screening has yet been developed, the primary focus to reduce ovarian cancer mortality is surgical prevention. For individuals with a significantly increased risk of ovarian cancer, risk-reducing bilateral salpingo-oophorectomy is highly effective, but uptake at the recommended age is suboptimal, likely because of concerns about premature menopause. Evidence suggests that many "ovarian" cancers originate in the distal fallopian tube, thus making bilateral salpingectomy after completion of childbearing with delayed oophorectomy an attractive but still unproven risk-reduction option for those who decline or are not yet ready for risk-reducing bilateral salpingo-oophorectomy. Two clinical trials (SOROCk [A Non-randomized Prospective Clinical Trial Comparing the Non-inferiority of Salpingectomy to Salpingo-oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers], NCT04251052; and TUBA-WISP2 [Tubectomy With Delayed Oophorectomy as an Alternative to Risk-Reducing Salpingo-oophorectomy in High-Risk Women to Assess the Safety of Prevention]; NCT04294927) are ongoing to determine whether bilateral salpingectomy with delayed oophorectomy is as effective as risk-reducing bilateral salpingo-oophorectomy to prevent ovarian cancer. The SOROCk trial is a national, prospective nonrandomized trial powered to test the hypothesis that bilateral salpingectomy with delayed oophorectomy is noninferior to risk-reducing bilateral salpingo-oophorectomy to reduce the incidence of ovarian cancer among people with deleterious germline *BRCA1* mutations. Gynecologists and gynecologic oncologists in both community-based and academic practices may perform risk-reducing surgeries and have their patients participate in the SOROCk trial. We review key aspects of the SOROCk clinical trial and discuss how surgeons can partner with SOROCk clinical trial sites and facilitate their patients' participation to help answer this important clinical question.

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Epithelial ovarian cancer is one of the most lethal gynecologic malignancies. High-grade serous carcinoma, the most common histologic subtype, is diagnosed at an advanced stage in more than 75% of cases,[1] and long-term survival rates are less than 30%.[2] Currently available ovarian cancer screening is not effective in reducing ovarian cancer mortality[3,4] and, in fact, causes harm in the general population (at average risk).[5] Even in the population at high risk, screening studies have failed to demonstrate a reduction in ovarian cancer mortality,[6] and the National Comprehensive Cancer Network no longer includes ovarian cancer screening in its guidelines for management of individuals at increased genetic risk of ovarian cancer.[7] Thus, the only current strategy available likely to significantly affect ovarian cancer mortality is surgical prevention.

The strongest risk factor for epithelial ovarian, fallopian tube, and peritoneal cancers (collectively referred to as ovarian cancer) is an inherited deleterious mutation in an ovarian cancer predisposition gene. Approximately 18% of ovarian cancers are associated with a deleterious germline mutation, most of which are attributable to *BRCA1* and *BRCA2* mutations (15%), but also include mutations in other ovarian cancer susceptibility genes, including *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, and *MSH6*.[8] Deleterious mutations in *BRCA1* and *BRCA2* are associated with a lifetime risk of ovarian cancer (cumulative risk to age 80 years) of 44–49% and

17–21%, respectively.[9,10] These risks are significantly higher than the approximately 1.3% risk in the general population,[1] and for *BRCA1* carriers, ovarian cancers occur at a much younger age, with the risk dramatically increasing after age 40 years.[9]

The most effective method for prevention of ovarian cancer in individuals at high risk is risk-reducing bilateral salpingo-oophorectomy. Guidelines recommend risk-reducing bilateral salpingo-oophorectomy between age 35 and 40 years for *BRCA1* mutation carriers and between age 40 and 45 years for *BRCA2* mutation carriers, according to the age at which the risk of ovarian cancer diagnosis becomes significant.[7,11,12] Prospective studies report that risk-reducing bilateral salpingo-oophorectomy provides an 80–96% reduction in ovarian cancer and reductions in cancer-related and overall mortality.[13–15] However, risk-reducing bilateral salpingo-oophorectomy causes premature surgical menopause and symptoms such as vasomotor symptoms, changes in sexual function, and mood disorders, in addition to long-term morbidities associated with early oophorectomy such as osteoporosis, increased risk of cardiovascular disease, and cognitive impairment.[16–18] Postsurgical hormone therapy mitigates many but not all of these risks and does not fully alleviate symptoms. In addition, hormone therapy is not an option for most individuals with a history of breast cancer, which patients with *BRCA1* and *BRCA2* mutations may have. In considering when to pursue risk-reducing surgery, individuals must weigh the benefits of ovarian function on their quality of life and

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health against the risk of developing cancer. This issue is particularly relevant for *BRCA1* carriers–the cumulative incidence of ovarian cancer in *BRCA1* mutation carriers is relatively low before age 40 years but reaches more than 10% by age 50 years; it is extremely low before age 50 years in *BRCA2* mutation carriers.[9,13]

Despite the proven benefit of risk-reducing bilateral salpingo-oophorectomy to prevent ovarian cancer, many individuals at high risk choose to delay or forego risk-reducing bilateral salpingo-oophorectomy, with estimated rates of uptake ranging widely from 17 to 80%.[19–23] In one analysis, more than 40% of *BRCA1* mutation carriers in the United States had not undergone risk-reducing bilateral salpingo-oophorectomy, and the mean age for those who did undergo risk-reducing bilateral salpingo-oophorectomy was 45 years,[21] well beyond the recommended age of 35–40 years. Reproductive concerns and apprehensions about premature menopause have been cited as reasons for delaying or declining risk-reducing bilateral salpingo-oophorectomy.[24–26] Rates of risk-reducing procedures would likely increase if alternative approaches that did not cause menopause were available and proven to be effective. Bilateral salpingectomy with delayed oophorectomy has been suggested as an alternative for individuals declining bilateral salpingo-oophorectomy. This approach would avoid or delay menopause and, although not yet proven, may be an effective alternative to risk-reducing bilateral salpingo-oophorectomy for preventing ovarian cancer.

THE FALLOPIAN TUBE EPITHELIUM AS CELL-OF-ORIGIN FOR "OVARIAN" CANCER

The assumption that high-grade serous carcinoma of the ovary originates from the ovarian surface epithelium was initially challenged with the identification of early precancerous lesions in the fallopian tubes of *BRCA1* carriers undergoing risk-reducing bilateral salpingo-oophorectomy.[27] These precursor lesions are called serous tubal intraepithelial carcinomas and are found only in the distal fallopian tube (predominantly the fimbria). When the fallopian tubes, including the fimbria, are sectioned every 2 mm in a standardized pathological evaluation called the sectioning and extensively examining the fimbriated end protocol,[28] serous tubal intraepithelial carcinoma lesions or invasive cancer is diagnosed in 5–9% of fallopian tubes of individuals with *BRCA1/2* mutations undergoing risk-reducing salpingo-oophorectomy, depending on age at the time of surgery. Subsequent genomic studies showed that the earliest alterations that precede serous tubal intraepithelial carcinoma formation include expansions of benign-appearing secretory cells that harbor *TP53* mutations. These expansions, called p53 signatures, are common to all individuals regardless of hereditary risk and are likely related to ovulation. *BRCA1/2* mutation carriers, however, are more likely to have progression from p53 signature to serous tubal intraepithelial carcinoma lesions, which exhibit morphologic features of malignancy, including increased proliferation, loss of cellular polarity, nuclear pleiomorphism, and mitoses. Genomic studies also showed that copy number alterations, the hallmarks of ovarian cancer, are manifested early in these preinvasive lesions.[29–34] The neoplastic cells from the distal fallopian tube subsequently implant on the ovary and other metastatic sites, including the omentum and peritoneum. Figure 1 demonstrates the histologic progression from normal fallopian tube epithelial to benign p53 signature, serous tubal intraepithelial carcinoma, and invasive high-grade serous carcinoma. Extensive clinical, pathologic, and molecular data now support that most high-grade serous carcinomas originate from fallopian tube epithelium rather than the ovarian surface epithelium.[35–40]

SAFETY OF SALPINGECTOMY

According to the evidence that high-grade serous carcinoma originates in the fallopian tube, removal of the fallopian tubes alone may reduce the incidence of and death rates from "ovarian" cancer. Removing the tubes could theoretically affect the blood supply to the ovaries, but most studies have shown no detrimental effect of salpingectomy on ovarian function or hormonal levels.[41–47] The Society of Gynecologic Oncology has stated that salpingectomy should be considered in individuals undergoing hysterectomy, other pelvic surgery, or sterilization.[48] Regions in Canada and Germany have initiated programs to change surgical practice to include the practice of opportunistic salpingectomy.[49,50] In British Columbia, Canada, the gynecologic community received an educational initiative in 2010 to perform salpingectomy instead of alternative tubal sterilization procedures and to perform salpingectomy at the time of hysterectomy when ovaries were being preserved. Published surgical outcomes demonstrated no increase in surgical complications or hospital readmissions after opportunistic salpingectomy and only a minimal increase in operative time.[49,51] There were no indications of an earlier age at menopause.[52]

An initial report on outcomes from opportunistic salpingectomy in British Columbia supports that opportunistic salpingectomy may be an effective ovarian cancer prevention strategy at the population

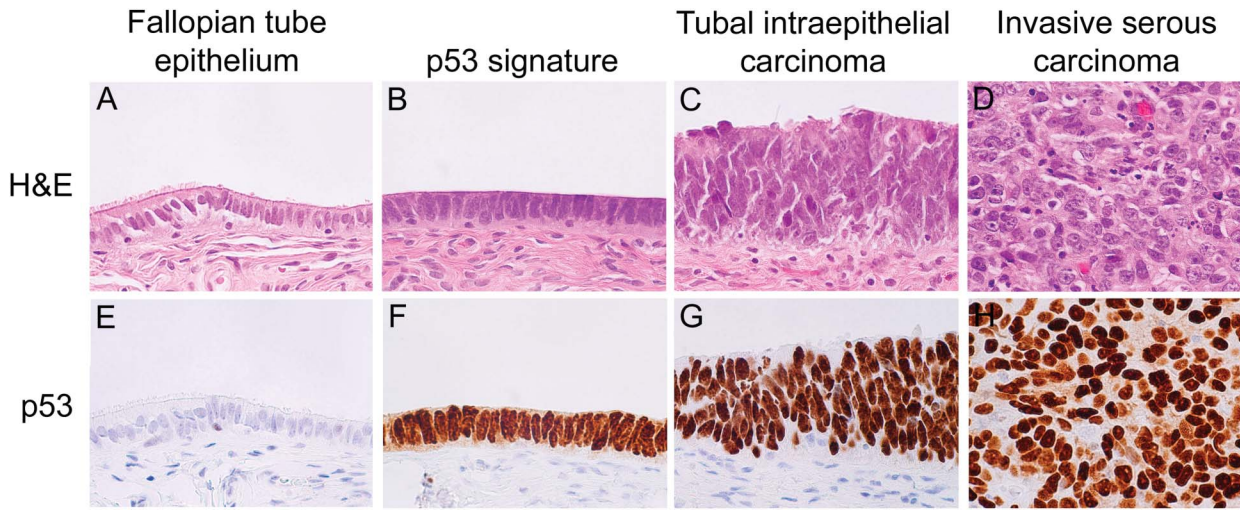

Fig. 1. Histological progression from normal fallopian tube epithelial to benign p53 signature, serous tubal intraepithelial carcinoma (STIC), and invasive high-grade serous carcinoma (HGSC). **A–D**. Histological transition from normal epithelium to benign p53 signature, STIC, and invasive HGSC. **E–H**. Intense nuclear p53 staining characterizes the benign p53 signature, STIC, and invasive carcinoma. Figure adapted from Gynecol Oncol 2011;123:5–12 with permission from Elsevier.
Pennington. Salpingectomy and Ovarian Cancer Prevention. Obstet Gynecol 2025.

level.[53] Of 25,889 individuals who underwent opportunistic salpingectomy between 2008 and 2017 (and 32,080 individuals in the control group), there was not a single case of serous cancer in the opportunistic salpingectomy group, significantly fewer than the age-adjusted expected number of 5.27 serous cancers (95% CI, 1.78–19.29). Fifteen serous cancers were observed in the control group. The same was true for all epithelial ovarian cancers, with an expected number of 8.68 (95% CI, 3.36–26.58), and the actual number was less than or equal to 5 (exact number not presented to protect patient privacy). The rates of common risk factors and protective factors for the opportunistic salpingectomy group placed them at slightly higher risk for ovarian cancer compared with the control group, suggesting that the results were unlikely because of confounding. In addition, the opportunistic salpingectomy group had the same risk of breast and colorectal cancers compared with the control group, suggesting that the lack of ovarian cancers in the opportunistic salpingectomy groups was unlikely to be attributable to selection bias.

EVALUATING THE EFFICACY OF BILATERAL SALPINGECTOMY WITH DELAYED OOPHORECTOMY FOR OVARIAN CANCER PREVENTION IN INDIVIDUALS AT INCREASED RISK: TWO CLINICAL TRIALS

The number of individuals at high risk of ovarian cancer who undergo bilateral salpingectomy with delayed oophorectomy for risk-reduction outside of a clinical trial is unknown. Although this approach is not the gold standard and is yet unproven, there is concern that this approach is gaining acceptance without definitive data to demonstrate its efficacy. Prospective trials are needed to determine whether prophylactic salpingectomy prevents high-grade serous carcinoma and, if so, whether salpingectomy with delayed oophorectomy is as effective as risk-reducing bilateral salpingo-oophorectomy.

Two ongoing clinical trials have primary outcomes to determine whether bilateral salpingectomy with delayed oophorectomy is noninferior to risk-reducing bilateral salpingo-oophorectomy for the prevention of ovarian cancer in mutation carriers.

The TUBA-WISP2 study (Tubectomy With Delayed Oophorectomy as an Alternative to Risk-Reducing Salpingo-oophorectomy in High-Risk Women to Assess the Safety of Prevention; NCT04294927) is an international multicenter trial collaboration by the Radboud University Medical Center (Nijmegen, the Netherlands), M.D. Anderson Cancer Center (Texas), and the University of Washington. The SOROCk trial (A Non-randomized Prospective Clinical Trial Comparing the Non-inferiority of Salpingectomy to Salpingo-oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers; NCT04251052) is a multicenter clinical trial sponsored by the National Cancer Institute and the National Cancer Institute Community Oncology

Table 1. Differences in Clinical Trial Design for the SOROCk (A Non-randomized Prospective Clinical Trial Comparing the Non-inferiority of Salpingectomy to Salpingo-oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers) and TUBA-WISP2 (Tubectomy With Delayed Oophorectomy as an Alternative to Risk-Reducing Salpingo-oophorectomy in High-Risk Women to Assess the Safety of Prevention) Trials

	SOROCk Trial	TUBA-WISP2 Trial
Mutation carriers	*BRCA1* only	*BRCA1, BRCA2, BRIP1, RAD51C, RAD51D*
Age (y)	35–50	25–50, varies by gene
Menopausal status	Premenopausal and postmenopausal	Premenopausal only
Timing of delayed oophorectomy	Encouraged by age 40 or when comfortable	At least 2 y after BLS and up to 5 y past standard-of-care age
Primary end point	Time to development of incident HGSC	Cumulative tubo-ovarian cancer incidence at target age (46 y for *BRCA1* and 51 y for *BRCA2*)
Accrual goal (n)	2,262	1,500 *BRCA1* and 1,500 *BRCA2*
Results reporting	2036 (10-y accrual, 6 additional y of follow-up)	2036 (5-y accrual, 10 additional y of follow-up)

BLS, bilateral salpingectomy; HGSC, high-grade serous carcinoma.

Research Program (UG1CA189867). Each clinical trial has very different eligibility criteria, study designs, and statistical methods (Table 1). The two trials complement each other, and both have expected primary outcomes data estimated to be completed in 2036. The TUBA-WISP2 study protocol has been published previously.[54] Here, we discuss the SOROCk trial in detail because its protocol has not been previously published and because the study has a unique pathway that allows gynecologists and gynecologic oncologists to enroll their patients even if they do not have the study open at their institution.

THE SOROCK CLINICAL TRIAL

The SOROCk trial tests the hypothesis that risk-reducing bilateral salpingectomy with delayed oophorectomy is noninferior to risk-reducing bilateral salpingo-oophorectomy to reduce the incidence of high-grade serous carcinoma among people with deleterious germline *BRCA1* mutations. If found effective, risk-reducing salpingectomy with delayed oophorectomy would provide an alternative to risk-reducing bilateral salpingo-oophorectomy for *BRCA1* carriers who have completed childbearing and decline oophorectomy and would support generalizing this practice for prevention to people with other mutations.

The primary end point is time to development of incident high-grade serous carcinomas, specifically ovarian, fallopian tube, and peritoneal cancers. It is assumed that 99% of people with *BRCA1* mutation are cancer free at 4.5 years in the risk-reducing bilateral salpingo-oophorectomy group,[55] and an absolute difference of ≤1% is used to determine noninferiority (corresponding to 98% cancer free at 4.5 years in the bilateral salpingectomy group). Using a log-rank test with one-sided type I error of 0.0553 events from 2,262 patients will provide 80% statistical power. The study was activated on June 23, 2020. As of October 30, 2024, 637 participants have been enrolled.

Eligibility includes individuals aged 35–50 years with a deleterious *BRCA1* mutation who are planning to undergo risk-reducing surgery. Individuals must have at least one ovary and fallopian tube in place at the time of enrollment and must have a normal CA 125 and pelvic ultrasonography results (benign-appearing cysts allowed). They may be premenopausal or postmenopausal. Individuals with a prior diagnosis of breast cancer (or other cancers) are eligible as long as they have not received cytotoxic chemotherapy within the past 30 days or radiotherapy to the abdomen or pelvis at any time. Individuals receiving endocrine therapy or maintenance *ERBB2/HER2*–targeted therapy are eligible. Box 1 provides a full list of eligibility criteria.

Participants choose whether they undergo risk-reducing bilateral salpingo-oophorectomy or bilateral salpingectomy with delayed oophorectomy. This study uses a nonrandomized trial design because randomization would limit feasibility due to physician and patient preferences. Individuals are counseled that risk-reducing bilateral salpingo-oophorectomy is the standard of care and is the recommended procedure. Participants who have declined or elected to defer risk-reducing bilateral salpingo-oophorectomy after proper counseling may choose bilateral salpingectomy. Concurrently planned hysterectomy is allowed with either arm. Hormone therapy is encouraged for those who do not have contraindications. Participants

Box 1. Eligibility Criteria for the SOROCk Trial (A Non-randomized Prospective Clinical Trial Comparing the Non-inferiority of Salpingectomy to Salpingo-oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers)

Eligibility criteria (all of the following conditions must be met):

1. Individuals aged 35–50 y, inclusive.
2. Patients who will undergo risk-reducing bilateral salpingo-oophorectomy (for the bilateral salpingo-oophorectomy arm) and patients who have declined or elected to defer bilateral salpingo-oophorectomy after proper counseling to clearly explain the standard of care for *BRCA1* mutation carriers and are undergoing salpingectomy (for the bilateral salpingectomy arm with delayed oophorectomy arm). Concurrently planned hysterectomy with either arm is permitted.
3. At least 1 intact ovary and fallopian tube are in situ at the time of counseling, consent, and registration. Prior hysterectomy is allowed provided that it did not include bilateral salpingectomy. Prior tubal ligation is allowed if one ovary and fallopian tube (with fimbria not removed) are present.
4. Positive Clinical Laboratory Improvement Amendments–approved test results for pathogenic or likely pathogenic germline *BRCA1* mutation in the patient. Documentation of the result is required.
5. Patients may be premenopausal or menopausal.
6. Pelvic ultrasonography (transvaginal imaging preferred, but transabdominal imaging is acceptable) and CA 125 level within 180 d of registration.
7. The patient or a legally authorized representative must provide study-specific informed consent before study entry.
8. Individuals who are currently pregnant or plan to become pregnant in the future through assisted reproductive technologies and who have received proper counseling are eligible. Individuals who are currently pregnant and plan bilateral salpingectomy at the time of a planned cesarean delivery are eligible. Patients must understand that they will not be able to become pregnant naturally in the future.

Ineligibility criteria (patients with any of the following are not eligible):

1. Individuals with a history of any cancer who have received cytotoxic chemotherapy within the past 30 d or radiotherapy to abdomen or pelvis at any prior time. Endocrine therapy or maintenance *ERBB2/HER2*–targeted therapy is allowed. Maintenance immune checkpoint inhibitor therapy is allowed. Maintenance therapy with poly (ADP-ribose) polymerase in inhibitor is allowed.
2. History of ovarian cancer, including low malignant potential neoplasms, primary peritoneal carcinoma, or fallopian tube carcinoma.
3. Patients medically unfit for the planned surgical procedure.
4. Patients with abnormal screening tests (pelvic ultrasonography, CA 125) suspicious for occult or gross pelvic malignancy within the past 180 d.
   a. An *abnormal pelvic ultrasonogram* is defined as morphologic or structural variations suspicious for ovarian malignancy. Complex cystic lesions felt to represent a benign lesion are not exclusionary. Simple cysts of any size are not exclusionary.
   b. An *abnormal CA 125 level* is defined as follows: greater than 50 units/mL in premenopausal individuals who are not current users of oral contraceptives, greater than 40 units/mL for premenopausal individuals who are current users of oral contraceptives, and greater than 35 units/mL in postmenopausal individuals.

complete questionnaires (patient-reported outcomes) before surgery and at 6, 12, and 24 months from the initial surgery. Blood is drawn for research purposes before surgery, annually for 5 years, and at time of high-grade serous carcinoma diagnosis (if applicable); blood collection is optional, and participants may opt out. Any patients with a diagnosis of serous tubal intraepithelial carcinomas or precursor lesion or invasive cancer will undergo central pathologic review for confirmation. Participants receive follow-up annually for cancer incidence for 20 years or until funding is exhausted. Participants who choose bilateral salpingectomy may undergo completion oophorectomy at any time. They are counseled annually regarding the standard-of-care recommendations for completion oophorectomy by age 40 years and are encouraged, but not required, to undergo oophorectomy whenever they are ready to accept menopausal status.

BRCA2 mutation carriers are not included in this study because of the extremely low incidence of ovarian cancer in this population between age 35 and 50 years.[9,55] Individuals undergoing risk-reducing surgery between age 30 and 35 years are also excluded because it would take more than 10 years to develop incident cancer and delay the analysis of the primary end point (cancer incidence). The study was designed to answer this question as soon as possible. Knowledge gained from this trial will likely be relevant for people with mutations in *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, and others because the origin of high-grade serous carcinomas and the efficacy of surgical prevention are unlikely to be different.

Box 2. Steps for Participation of Your Patients in the SOROCk Trial (A Non-randomized Prospective Clinical Trial Comparing the Non-inferiority of Salpingectomy to Salpingo-oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers)

- Decision for risk-reducing surgery (risk-reducing bilateral salpingo-oophorectomy or bilateral salpingectomy, with or without concomitant hysterectomy).
- Confirmation of patient's mutation status (ensure copy of genetic testing report is in the medical record and ensure mutation is pathogenic).
- Obtain CA 125 level and pelvic ultrasonography.
- Refer patient to the closest participating SOROCk study team in your state.
  - All participating sites are listed on ClinicalTrials.gov, organized by state (https://clinicaltrials.gov/study/NCT04251052).
- The SOROCk study team will:
  - Consent patient for SOROCk study (clinic visit or telehealth or telephone).
  - Obtain records from you.
  - Administer study questionnaires, research blood (blood collection is optional).
  - Collaborate with you to ensure study requirements are met.
- Complete online education module (1 time, 5–15 min) and sign surgeon-credentialing form.
- Perform surgery.

Surgical considerations:

  - Ensure that the pathologist is aware of patient's genetic risk; request that specimens are entirely submitted and processed through the sectioning and extensively examining the fimbriated end protocol.
  - Perform intra-abdominal survey.
  - Collect peritoneal washings.
  - For oophorectomy: isolate the infundibulopelvic ligament and take the blood supply at the pelvic brim and high enough (at least 2-cm margin on the infundibulopelvic ligament) to ensure that the ovary is completely removed and no risk of ovarian remnant.
  - Postoperatively, consider hormone therapy to mitigate health risks of premature surgical menopause if no contraindications (estrogen-alone hormone therapy does not increase breast cancer risk in premenopausal *BRCA1* and *BRCA2* carriers).
- Postoperative follow-up:
  - 10-d to 60-d postoperative visit (clinic visit, telehealth, or telephone).
  - Annual follow-up (may be done by you or study team at clinic visit, by telehealth, or by telephone).
  - If patient had salpingectomy: annual counseling that completion oophorectomy is recommended by age 40 y (patient may decline or delay completion surgery) and signed risk-reducing bilateral salpingo-oophorectomy education acknowledgement form or documentation of counseling in note (may be done by you or study team at clinic visit, by telehealth, or by telephone).

A PATHWAY FOR GYNECOLOGISTS AND GYNECOLOGIC ONCOLOGISTS TO SUPPORT THE SOROCK TRIAL

The SOROCk study has a unique pathway that allows gynecologists and gynecologic oncologists in community-based and academic practices to partner with existing SOROCk clinical trial sites to answer this important clinical question. Any board-eligible or board-certified gynecologist or gynecologic oncologist may perform risk-reducing surgery for a patient and have their patient participate in the SOROCk trial; the surgeon does not need to formally belong to a National Clinical Trials Network/National Cancer Institute Community Oncology Research Program site.

When a surgeon is planning to perform risk-reducing surgery on a patient who may be eligible, they may refer the patient to any SOROCk clinical trial site in their state. All participating sites are listed under "Contact and Locations" on ClinicalTrials.gov, organized by state (https://clinicaltrials.gov/study/NCT04251052). The SOROCk site investigator will consent the patient for the study; counseling and consenting may be done remotely or through telehealth to reduce patient burden. The SOROCk study team is responsible for ensuring that all study requirements are met, including confirmation of mutation status, ultrasonography, and CA 125 level (which may be ordered by the referring surgeon). The study team will reach out to the referring surgeon and serve as a resource to them if they have any questions. The referring surgeon must view an online education module about considerations for risk-reducing surgery (5–15 minutes) and sign a credentialing form. This one-time requirement does not need to be repeated for subsequent patients. The referring surgeon performs the patient's surgery and routine clinical follow-up. The clinical trial study team obtains the

appropriate documentation from the surgeon (eg, operative note, pathology report, follow-up notes) and works directly with the participant for other study requirements such as patient-reported outcome questionnaires. Box 2 shows the steps to have a patient participate in the SOROCk trial.

WHAT CAN WE DO PERSONALLY TO HELP PREVENT OVARIAN CANCER RIGHT NOW: A CALL TO ACTION

Because risk-reducing surgery can effectively prevent ovarian cancer in individuals with inherited risk for ovarian cancer, individuals at risk must be identified and offered genetic counseling and genetic testing to assess their risk. Risk assessment guidelines, including the National Comprehensive Cancer Network guidelines, are published elsewhere.[7,56] Genetic testing should include all known ovarian cancer susceptibility genes, not just *BRCA1* and *BRCA2*. After someone with a deleterious mutation is identified, cascading that testing to all living family members (including cousins) should be pursued. The majority of such relatives currently do not undergo cascade genetic counseling and testing.[57] We urge clinicians to personally discuss the importance of cascade testing with their patients. Many more individuals at risk may be identified if the patient will contact relatives needing testing, and this action can save lives.

Helping patients enroll in the SOROCk trial and TUBA-WISP2 trial will provide important data for future patients at risk of ovarian cancer. If bilateral salpingectomy with delayed oophorectomy is proven to be effective, many more individuals with genetic risk may choose to undergo a risk-reducing procedure at an appropriate age, and we can prevent cancers we would have missed in patients who would have otherwise declined risk-reducing bilateral salpingo-oophorectomy. In addition, proving that salpingectomy prevents ovarian cancer would likely also increase uptake of opportunistic salpingectomy in the general population, with additional opportunities to prevent ovarian cancer on a larger scale. In contrast, if bilateral salpingectomy were found to be inferior to risk-reducing bilateral salpingo-oophorectomy, this information would also be critical; many individuals are already adopting bilateral salpingectomy as a risk-reducing procedure in the absence of prospective clinical trial data. Surgeons can support the SOROCk and TUBA-WISP2 trials by identifying individuals with ovarian cancer susceptibility mutations (through increased genetic testing and cascade testing), by referring eligible mutation carriers to the sites participating in the SOROCk trial (https://www.nrgoncology.org/SOROCk and https://clinicaltrials.gov/study/NCT04251052) and the TUBA-WISP2 trial (https://clinicaltrials.gov/study/NCT04294927), by partnering with existing SOROCk clinical trial sites if they perform these risk-reducing surgeries, and by encouraging colleagues at other institutions to do the same. The success of these trials rests on a critical partnership between the community and academic centers.

In conclusion, compelling evidence suggests that most cases of ovarian cancer originate in the fallopian tube, making bilateral salpingectomy with delayed oophorectomy an attractive but as-yet unproven option for risk-reduction in individuals with a high risk of ovarian cancer. Although risk-reducing bilateral salpingo-oophorectomy is the standard of care for ovarian cancer risk reduction, many individuals decline risk-reducing bilateral salpingo-oophorectomy by the recommended age because of concerns about menopause and sexual health. The SOROCk and TUBA-WISP2 trials will determine whether salpingectomy with delayed oophorectomy is as effective as risk-reducing bilateral salpingo-oophorectomy for ovarian cancer prevention. Salpingectomy with delayed oophorectomy is a patient-centered approach to cancer prevention, and these trials are our chance to answer this important question for our patients.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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