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Options in Prophylactic Surgery to Prevent Ovarian Cancer in High-Risk Women: How New Hypotheses of Fallopian Tube Origin Influence Recommendations

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Opinion statement

In women at increased risk of developing ovarian cancer, risk-reducing salpingo-oophorectomy is the only intervention that has been shown to decrease mortality from ovarian cancer and is the standard of care for risk reduction. Prophylactic salpingectomy with delayed oophorectomy should be considered in high-risk premenopausal women in the setting of a clinical trial.

Introduction

The mortality rate from ovarian cancer has only marginally declined in the past 40 years, and according to the Surveillance Epidemiology and End Results (SEER) program, the 5-year overall survival among women with ovarian cancer was only 45.6 % in 2011 [1]. Like other malignancies, focusing on prevention and early detection via screening has been at the forefront of research with the goal of decreasing the mortality rate of ovarian cancer. While the majority of ovarian cancer is considered sporadic without a clear cause, nearly one in five cases are associated with an underlying genetic mutation. The *BRCA1* and *BRCA2* genes carry the most frequently identified germline mutations associated with increased risk of developing ovarian cancer. To date,

ovarian cancer screening strategies for women at high risk for developing ovarian cancer have failed to show a reduction in ovarian cancer mortality. Therefore, high-risk women who have completed child-bearing are recommended to have their ovaries and fallopian tubes removed to decrease their risk.

Pathology studies of the ovaries and fallopian tubes removed from high-risk women have identified preinvasive lesions and occult malignancies in the fallopian tubes that support the tube as a primary site of carcinogenesis. In fact, a large proportion of ovarian cancers in high-risk women appear to arise in the fallopian tube. This knowledge, along with epidemiologic data showing a decreased risk of ovarian cancer following tubal ligation or salpingectomy, has led to interest in the impact of risk-reducing salpingectomy in high-risk women with delayed oophorectomy nearer to the age of natural menopause. This article will review the recent updates to ovarian cancer screening strategies in high-risk women, provide supporting data for the fallopian tube as the origin of a proportion of ovarian cancer, and review recent studies and clinical trial opportunities pertaining to risk-reducing salpingectomy with delayed oophorectomy in high-risk women.

Ovarian cancer prevention and screening in high-risk women

Since the initial discovery of the tumor suppressor gene *BRCA1* in 1994, subsets of women have been known to be at an increased lifetime risk of developing epithelial ovarian cancer. In the past two decades, ten additional genes have been identified that are associated with an increased risk of ovarian cancer. In 2015, Norquist and colleagues published a study of 1915 women with ovarian cancer that underwent massive parallel sequencing using the targeted BROCA panel [2, 3]. Within that cohort, 18.1 % were found to have a germline genetic mutation. While the majority of mutations were in *BRCA1* (9.5 %) and *BRCA2* (5.1 %), other mutations identified in these women were in *BRIP1* (1.4 %), *RAD51C* (0.6 %), *RAD51D* (0.6 %), *PALB2* (0.6 %), *BARD1* (0.2 %), and the DNA mismatch repair genes (*MSH2*, *MLH1*, *PMS2*, and *MSH6*; 0.4 %) [3]. Given that approximately one in five women with a diagnosis of ovarian cancer have an identifiable genetic aberration and that nearly one third (31 %) with an inherited mutation do not have a family history of breast or ovarian cancer or a prior personal history of cancer, all women with a new diagnosis of epithelial ovarian cancer (EOC) should be referred for genetic counseling [4, 5].

Risk-reducing salpingo-oophorectomy (RRSO) is the only intervention that has been shown to reduce mortality from ovarian cancer. The National Comprehensive Cancer Network (NCCN), the American Congress of Obstetrics and Gynecology (ACOG), the US Preventative Services Task Force (USPSTF), and the Society of Gynecologic Oncology (SGO) recommend that women with a genetic mutation associated with hereditary breast and ovarian cancer syndrome (HBOC) undergo RRSO once childbearing has been completed and between the ages of 35 and 40 [5–8]. RRSO in women with *BRCA1* and *BRCA2* mutations reduces the risk of EOC by 80–88 % and reduces ovarian cancer-specific mortality by 79 % [9, 10, 11•]. Additionally, if RRSO is performed prior to menopause, a woman has a 49 % reduction in the risk of developing breast cancer [10]. There is also a 60–77 % reduction in all-cause mortality following RRSO in this high-risk population [10, 11•]. There remains a small residual lifetime risk of primary peritoneal cancer in BRCA carriers after RRSO (1.9–3.9 % lifetime risk) [11•]. Women with HBOC who are not ready to undergo

RRSO should be offered combined oral-contraceptive pills, an intervention that has been shown to decrease the risk of developing ovarian cancer by 50 % in BRCA carriers as well as average-risk women [8, 12, 13].

Additionally, women with HBOC may undergo ovarian cancer surveillance with semiannual transvaginal ultrasound and CA125 blood test starting at age 30–35 years [5]. However, there is little data to support these surveillance measures. While the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial of annual transvaginal ultrasound and CA125 blood test in average-risk postmenopausal women showed no difference in ovarian cancer mortality compared to no screening [14], the risk of ovarian cancer algorithm (ROCA), a calculated algorithm of the longitudinal change in each individual woman's CA125 levels, has recently shown promise as an ovarian cancer screening test in average-risk postmenopausal women [15, 16•]. In December 2015, the UK Collaboration Trial of Ovarian Cancer Screening (UKCTOCS) randomized trial in more than 200,000 average-risk postmenopausal women published that multimodal screening with ROCA reduced ovarian cancer mortality by 20 % ($p = 0.021$) compared to no screening. The ROCA® Test will be available for clinical use in average-risk postmenopausal women throughout the USA in 2016 [16•].

Among women at increased risk for ovarian cancer, ROCA is also being studied; however, survival data is not yet available. The Gynecologic Oncology Group protocol 199 prospective, nonrandomized trial in *BRCA1/2* carriers was designed to assess the impact of RRSO and ROCA on ovarian cancer incidence. Study accrual was completed in 2006, and the impact of ROCA in this study population is eagerly awaited [17]. Similarly, phase 2 of the UK Familial Ovarian Cancer Screening Study (UK FOCSS), a nonrandomized trial of ROCA every 4 months and annual transvaginal ultrasounds in high-risk women, has completed accrual. The primary objective of this study is to determine whether this strategy can detect ovarian cancer at an early stage in high-risk women [18]. As such, the UK FOCCS trial may provide evidence to support ovarian cancer screening efforts among women with HBOC who are not yet ready for RRSO.

While RRSO is considered the standard of care for ovarian cancer risk reduction, removing both ovaries in a premenopausal woman leads to immediate menopause. Aside from the increased risk of menopausal symptoms such as hot flashes and night sweats, women who undergo surgical menopause are at increased risk for osteoporosis, glaucoma, macular degeneration, cardiovascular disease, stroke, cognitive impairment, Parkinsonism, anxiety, depression, and decreases in sexual desire and function [19–21]. Additionally, surgical menopause before the age of 45 years in the general female population is associated with an increased risk of earlier death [19]. While RRSO carries an improvement in all-cause mortality among women with HBOC [10, 11•], the impact of surgical menopause in this population has not been well-studied. And, while estrogen therapy can mitigate some side effects of early estrogen deficiency, glaucoma, Parkinsonism, anxiety, depression, and sexual function disturbances do not appear to be ameliorated by estrogen therapy [19, 20]. Importantly, however, BRCA carriers that receive

hormone replacement therapy following RRSO appear to maintain the breast cancer risk reduction benefits of RRSO [22].

The role of the fallopian tube in ovarian cancer

The NCCN recommends that pathology processing of the fallopian tube and ovary after RRSO in women with HBOC be performed according to the sectioning and extensively examining the FIMbriated end of the fallopian tube (SEE-FIM) protocol [5]. This approach increases the available surface area for examination by 60 % and provides more comprehensive evaluation of the fimbria [23]. The SEE-FIM protocol was designed following a report in 2001 in which dysplastic changes were identified in the tubal fimbria in 50 % of high-risk women (women had at least three first degree family members with breast and/or ovarian cancer or a personal history of breast or ovarian cancer before the age of 50) who underwent RRSO [24]. The identification of the increased proportion of dysplastic changes in fimbria of high-risk women led to the discovery of serous tubal intraepithelial carcinoma (STIC) lesions, and STICs are located in the fimbria portion of the fallopian tube in more than 90 % of cases. Additionally, among high-grade serous ovarian cancer, up to 60 % have STIC lesions [25]. As such, the STIC is now considered the precursor lesion to these serous carcinomas.

Given the discovery that serous precursor lesions often arise in the fallopian tube, prophylactic salpingectomy with delayed oophorectomy (PSDO) has been suggested as an alternative to RRSO that could allow for longer benefit from endogenous ovarian hormones before menopause [26]. The ovarian cancer risk reduction associated with salpingectomy has been shown in several epidemiologic studies. While tubal ligation alone appears to reduce ovarian cancer risk by about 30 % [27–32], salpingectomy performed for sterilization or other benign indications among the general population conveys an even greater ovarian cancer risk reduction of 42–77 % [30, 32, 33, 34•]. Notably, the risk of serous ovarian and primary peritoneal cancer may be reduced by nearly 80 % among average-risk women undergoing salpingectomy for nonrisk reduction indications [30]. However, there is no data on the impact or safety of salpingectomy alone among women with HBOC and the risk of developing a malignancy within the ovary prior to completion oophorectomy has not been quantified. As such, completion oophorectomy appears to be vital to the concept of PSDO and, outside of a clinical trial, RRSO remains the standard recommendation for ovarian cancer risk reduction among high-risk women.

However, PSDO is an attractive concept and two recent studies have investigated both BRCA carriers' and HBOC providers' attitudes toward a clinical trial of PSDO [26, 35]. BRCA carriers identify the seriousness of ovarian cancer and the uncertainty of the impact of salpingectomy on ovarian cancer risk as the main barriers to considering PSDO. HBOC providers appear primarily concerned about the loss of breast cancer risk reduction with delayed oophorectomy, the risks of undergoing two operations, and the uncertainty of the effect of salpingectomy on ovarian cancer risk [35]. Holman and colleagues performed an online survey of

BRCA carriers to determine the interest in participating in a study of PSDO. Of the 204 women surveyed, 34.3 % indicated interest in a study of this nature, 35.3 % were unsure if they would participate, and 30.4 % reported that they would not be interested [26].

Another study analyzed the views of genetic professionals and gynecologic oncologists in the UK on PSDO in high-risk women. They reported that the potential barriers to offering an interval salpingectomy were the lack of data on the precise level of benefit (83 %), increased surgical morbidity (79 %), loss of breast cancer risk reduction associated with premenopausal oophorectomy (68 %), need for long-term follow-up (61 %), and a proportion not undergoing delayed oophorectomy (66 %). However, 77 % of the respondents supported PSDO in the setting of a clinical trial [36].

From a cost standpoint, up-front RRSO carries the lowest cost and highest life expectancy; however, the value of quality of life is challenging to measure. Kwon and colleagues performed a Markov Monte Carlo simulation modeling cost/benefit estimates for BRCA carriers without a personal history of breast or ovarian cancer undergoing (a) RRSO at age 40, (b) bilateral salpingectomy at age 40, or (c) bilateral salpingectomy at age 40, followed by bilateral oophorectomy at age 50. In addition to cost and survival benefit, up-front RRSO also resulted in the lowest number of subsequent breast (40 % relative risk reduction) and ovarian cancers (20 % relative risk reduction). However, when quality of life measures were included, they estimated that PSDO yielded the highest quality-adjusted life expectancy. In this analysis, it was assumed that women who underwent up-front RRSO did not use hormone therapy. As such, the quality-adjusted life expectancy for these women may have been underestimated [37].

At present, several trials are attempting to answer important questions associated with salpingectomy and/or PSDO in high-risk women. In France, a prospective observational trial in *BRCA 1/2* carriers is quantifying the morbidity of radical fimbriectomy and completion oophorectomy, the rate of occult lesions in fimbriectomy specimens, the incidence of breast cancers, and compliance with subsequent oophorectomy (NCT01608074) [38]. Additionally, a nonrandomized prospective observational trial of PSDO in *BRCA 1/2* carriers is open in the Netherlands with a primary objective of assessing menopause-related quality of life associated with PSDO versus RRSO (NCT02321228) [39]. Similarly, a nonrandomized proof-of-concept trial in *BRCA 1/2* carriers in the USA of patient-selected interventions: (a) screening every 6 months with symptom assessment, physical exam, pelvic ultrasound, CA125, and HE4 levels; (b) salpingectomy with delayed oophorectomy 3 years after salpingectomy; or (c) up-front RRSO is enrolling (NCT01907789). The primary aim of the study is to determine compliance with delayed oophorectomy following salpingectomy with secondary objectives of assessing quality of life and whether salpingectomy decreases the risk of ovarian cancer [40]. A larger clinical trial called Women choosing Interval Salpingectomy with Delayed oophorectomy to postpone Menopause (WISDOM) is under development. The primary aim of this nonrandomized, two-arm trial is to examine changes in sexual function among women who opt for PSDO versus RRSO. Secondary aims include the impact of these surgical interventions on depression, anxiety, and sleep quality, as well as the impact on ovarian cancer risk and compliance with completion oophorectomy.

In summary, RRSO remains the standard of care to reduce ovarian cancer mortality among women at increased risk. Current NCCN and SGO guidelines support salpingectomy in women with HBOC in the context of a clinical trial [5, 8] and, as the rate of RRSO in *BRCA 1/2* carriers is currently estimated at only 70 %, PSDO and salpingectomy alone as options warrant further investigation [8]. Ongoing and future studies of these alternative interventions in high-risk women will help provide guidance to patients and providers on the impact of these procedures on ovarian and breast cancer risks, quality of life, and compliance with delayed oophorectomy.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Financial Disclosure
The authors have no financial disclosures.

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