

Salpingectomy as a Means to Reduce Ovarian Cancer Risk

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Abstract

Bilateral salpingo-oophorectomy (BSO) has become the standard-of-care for risk reduction in women at hereditary risk of ovarian cancer. Although this procedure significantly decreases both the incidence of and mortality from ovarian cancer, it affects quality of life, and the premature cessation of ovarian function may have long-term health hazards. Recent advances in our understanding of the molecular pathways of ovarian cancer point to the fallopian tube epithelium as the origin of most high-grade serous cancers (HGSC). This evolving appreciation of the role of

the fallopian tube in HGSC has led to the consideration of salpingectomy alone as an option for risk management, especially in premenopausal women. In addition, it is postulated that bilateral salpingectomy with ovarian retention (BSOR), may have a public health benefit for women undergoing benign gynecologic surgery. In this review, we provide the rationale for salpingectomy as an ovarian cancer risk reduction strategy. *Cancer Prev Res*; 8(5); 342–8. ©2015 AACR.

See related commentary by Mark H. Greene, p. 339

Introduction

Epithelial ovarian cancer is relatively uncommon, accounting for only 3% of cancers in women in the United States (1). Approximately 22,280 women are diagnosed each year. However, ovarian cancer is the leading cause of death from a gynecologic malignancy in the United States, and is the fifth leading cause of cancer-related deaths among women overall. Globally, there are approximately 192,000 new cases of ovarian cancer each year (2). Incidence rates are highest in European and North American countries and lowest in African and Asian countries. Although mortality rates have remained relatively stable in the United States, there has been a 41.2% increase in deaths from ovarian cancer from 1990 to 2010 worldwide (3). The differences in international rates may be partially explained by differences in reproductive patterns and contraceptive choices or by environmental factors.

Although early-stage ovarian cancer is highly curable, most women present with late-stage disease resulting in an overall 5-year survival of only 43.8% (4). Screening options for ovarian cancer are limited. Most studies involved some combination of transvaginal ultrasound and the serum-based marker CA-125,

neither of which has been shown to decrease ovarian cancer morbidity or mortality in either the general population or in *BRCA1/2* mutation carriers (5–7). Screening has also been associated with increased morbidity due to unnecessary surgery (8). Given the limitations of current screening modalities, the U.S. Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists discourage routine screening for ovarian cancer for the general population (9, 10).

Bilateral salpingo-oophorectomy (BSO) has become the standard-of-care for risk reduction in women at hereditary risk of ovarian cancer. Although this procedure significantly decreases both the incidence of and mortality from ovarian cancer, it affects quality of life and has other health hazards (11). Recent advances in our understanding point to the fallopian tube epithelium as the origin of most high-grade serous cancers (HGSC), the most common and lethal ovarian cancer subtype, and has led to the consideration of salpingectomy alone as an option for risk management, especially in premenopausal women. In this review, we provide the rationale for salpingectomy as an ovarian cancer risk reduction strategy in the context of our current understanding of the etiology of ovarian cancer.

Review of the Epidemiology of Ovarian Cancer

Reproductive history has been one of the key determinants of ovarian cancer risk. Multiple studies have demonstrated that increased parity has a protective effect against ovarian cancer, whereas nulliparity has been shown to increase risk of this malignancy (12, 13).

Women with infertility are at increased risk of serous ovarian cancer. This result has been attributed more to the cause of infertility itself rather than the treatments for this condition. Some studies implicate endometriosis as the cause of the increased ovarian cancer risk associated with infertility, with patients diagnosed with endometriosis having 1.75 to 2.75 times the odds of cancer as compared with those with other causes of

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infertility (14, 15). Specific subtypes of ovarian cancer associated with endometriosis include clear cell, endometrioid, and low-grade serous cancers. A systematic review of the literature indicates that the risk of ovarian cancer is increased in women with polycystic ovarian syndrome [OR, 2.52; 95% confidence interval (CI), 1.08–5.89; ref. 16].

Data on the impact of postmenopausal hormone replacement therapy on ovarian cancer risk have been contradictory. Meta-analyses of observational studies indicate that ever use of hormone replacement therapy is associated with a statistically significant 15% to 20% increase in the odds of ovarian cancer (17, 18). However, data from the Women's Health Initiative (WHI) showed no significant increase in risk in those randomized to combined estrogen–progesterone replacement therapy as compared with those taking placebo (HR, 1.57; 95% CI, 0.77–3.24; ref. 19).

Oral contraceptive use has been consistently associated with reduced risk of ovarian cancer in multiple studies. In a meta-analysis of 45 studies, ever use of oral contraceptives resulted in a statistically significant 27% reduction in risk (20). A dose–response effect has been reported: increasing duration of use resulted in larger reductions in ovarian cancer incidence, with an approximately 20% reduction in risk for every 5 years of use. The protective effect of oral contraceptive use persists up to 30 years after discontinuation of this medication. For women with *BRCA1* and *BRCA2* mutations, use of oral contraceptives reduced ovarian cancer risk by 50% (95% CI, 0.33–0.75; ref. 21). Conversely, no significant association was found between increased breast cancer risk and oral contraceptive use in this high-risk population.

Tubal ligation (TL) has been shown to be protective against ovarian cancer both in the general population and in individuals at increased risk. A meta-analysis of 13 observational studies showed that the risk of epithelial ovarian cancer was decreased 33% in those who underwent tubal ligation (22). The benefits of tubal ligation lasted up to 14 years after the procedure and applied to serous, endometrioid, clear cell, and mucinous subtypes. Similar risk reductions have been reported among *BRCA1* carriers (23, 24).

Biology of Ovarian Cancer

The recent discovery of germline mutations that confer an increased risk of ovarian cancer has identified a small group of women at significantly increased risk of the disease. Women with deleterious germline mutations in the *BRCA1/2* genes have a lifetime risk of ovarian cancer, which ranges from 36% to 46% for *BRCA1* mutation carriers and from 10% to 27% for *BRCA2* mutation carriers (25). Inherited germline mutations of *BRCA1* and *BRCA2* account for 9% and 8% of ovarian cancers, respectively. Somatic *BRCA1/2* mutations have been reported in 5% to 10% of sporadic ovarian cancer cases. Several studies report *BRCA1* silencing through promoter hypermethylation in 5% to 40% of cases (26). Alterations in the *BRCA1/2* genes result in dysfunctional DNA repair through the homologous recombination pathway (27).

There has been a remarkable paradigm shift in the understanding of the origin of HGSC. Historically, it was assumed that ovarian tumorigenesis initiated in the ovarian surface epithelium (OSE) or from cortical inclusion cysts that contain OSE. This view has recently been challenged by the identification of serous tubal intraepithelial carcinomas (STIC) and occult invasive serous

carcinomas in 10% to 15% of the fallopian tubes examined from women with *BRCA1/2* mutations who undergo BSO for prophylaxis (28, 29). These STIC precursor lesions closely resemble traditional HGSCs, and are not found in the corresponding ovaries of the prophylactic specimens. Lending support to the proposal that STICs are the precursor lesion to HGSC is the finding of identical TP53 mutations in STICs and both concomitant ovarian and/or peritoneal cancers (30, 31). In addition to these findings in women with a genetic predisposition to ovarian cancer, subsequent studies found similar STICs and early invasive tubal carcinomas in 50% to 60% of women with sporadic ovarian cancer (28, 30, 32, 33). STICs are characterized by increased nuclear size, hyperchromasia, nucleolar prominence, mitotic activity, and loss of cell polarity (28, 34).

Even earlier fallopian tube lesions have been suggested to precede STICs and further support the fallopian tube as a primary site of tumor origin. The best characterized of these precursors is the "p53 signature," defined as a focus of 12 or more cells with normal morphology, but with strong p53 immunostaining (35). The p53 signature localizes mainly at the fimbriated end of the fallopian tube (36). p53 signatures are found in over 90% of STICs, have been reported in direct association or even contiguous with STICs, and share identical TP53 mutations with both STICs and invasive cancers, all features that provide strong evidence of a clonal relationship among these tissues (30).

Preclinical ovarian cancer studies have historically relied on cultured ovarian surface epithelium, transgenic mouse models targeting the ovarian surface epithelium, or xenograft mouse models, all of which generally did not reflect the behavior of ovarian cancer in humans. New models have now been developed to focus on fallopian tube epithelium and better reflect the human disease, again adding credence to the fallopian tube site of origin. Levanon and colleagues (37) reported a mouse model using human fallopian tube secretory epithelial cells (FTSEC) transformed using multiple oncogenes and transplanted by intraperitoneal injection into mice. The transformed human FTSEC generated tumors in mice that resembled HGSC, an important proof-of-concept study confirming the potential for transformed fallopian tube cells to initiate tumorigenesis. Another new mouse model was recently reported that shows *de novo* HGSC arising from the fallopian tube. In this model, fallopian tube secretory cells were targeted for mutation of *TP53*, *PTEN*, and *BRCA1* or *BRCA2* using cell type–specific *PAX8*-driven Cre expression. The mutations resulted in HGSC and STIC arising from the fallopian tube as observed in the human disease. In these mice, HGSC metastasizes to the ovary and peritoneum much like the pattern seen in humans (38).

Evidence for Prophylactic Salpingo-Oophorectomy

BSO, surgical removal of the fallopian tubes and ovaries, is a proven ovarian cancer prevention strategy. The procedure has been shown to dramatically reduce the risk of ovarian cancer among women at average and high genetic risk of the disease. Analysis of long-term follow-up data from participants in the Nurses' Health Study (NHS) observational cohort demonstrates that when performed at the time of hysterectomy for benign disease in average risk women, incidental BSO is associated with an ovarian cancer HR of 0.06 compared with women who underwent hysterectomy without BSO (39).

The benefits of prophylactic BSO for women at increased genetic risk are clear. A meta-analysis that included 10 studies demonstrates that prophylactic removal of the fallopian tube and ovaries reduces future risk of ovarian cancer in high-risk women by >80% (25). A recent report from an observational cohort of roughly 5,800 mutation carriers confirms a similar reduction in ovarian cancer risk and importantly a 77% reduction in all-cause mortality to age 70 years (11). The residual risk of ovarian cancer is attributed to the failure to identify occult cancers at the time of the surgery, or the subsequent development of primary peritoneal cancer. BSO has also been associated with a reduction in breast cancer risk, especially when performed in premenopausal women with *BRCA2* mutations (40, 41). Prophylactic BSO is recommended at ages 35 to 40 years and once child bearing is complete for all women with hereditary breast and/or ovarian cancer syndrome. Although effective, the overall public health impact of prophylactic BSO in high-risk women is relatively minor as only 7% to 10% of ovarian cancer occurs in mutation carriers.

Oophorectomy has significant side effects that limit its utility as an ovarian cancer prevention strategy. Oophorectomy in premenopausal women increases the risk for cardiovascular morbidity, osteoporosis and endocrine-associated symptoms, including hot flashes and difficulties with sexual function (42–45). At least some of these side effects may be reduced by the use of hormone replacement therapy (HRT), but results from the WHI have significantly influenced women and physicians who now often avoid use of HRT (46). Although long-term HRT is frequently contraindicated in women with a prior history of or at risk for breast cancer, short-term hormone replacement therapy does not appear detrimental (47).

The noncancer implications of BSO in postmenopausal women are less clear. Postmenopausal ovaries produce low levels of estradiol and testosterone (48, 49), and it is hypothesized that these hormones play a role in postmenopausal cardiovascular and skeletal health (50, 51) and regulation of vasomotor symptoms (52). Some reports have identified an increased risk of coronary heart disease (CHD), stroke, hip fracture, lung cancer, and all-cause mortality (42, 53, 54) in postmenopausal women undergoing oophorectomy, whereas other studies have demonstrated no effect on these same endpoints (43, 55). The effectiveness of estrogen replacement therapy (ERT) alone in reducing side effects attributable to oophorectomy in postmenopausal women is controversial. Data from the WHI demonstrate that ERT following hysterectomy increases the risk of thromboembolic events and stroke, reduces hip fractures, and does not affect coronary heart disease (19). These effects may differ when therapy is started early around the time of menopause (56).

Data on the impact of elective BSO on disease endpoints have been derived largely from observational cohort studies comparing women with and without ovarian conservation at the time of hysterectomy for benign disease. Parker (39) reported outcomes for 29,380 NHS participants who underwent hysterectomy, approximately half of whom also underwent BSO. Disease endpoints were confirmed by one or more of the following: self-report, medical record review, and death certificate. After adjustment for relevant risk factors, including use of ERT, BSO was associated with increased risk for overall mortality (RR, 1.12), fatal and nonfatal CHD (RR, 1.17) and stroke (RR, 1.14), and reduced risk for breast (RR, 0.75), ovarian (RR, 0.04), and all cancer (RR, 0.9). Lung cancer incidence (RR, 1.26) and total cancer mortality (RR, 1.17) were increased. Risk for hip fracture was not

affected. The effect of BSO on CHD and stroke was most pronounced in women who underwent hysterectomy before the age of 50 years and who never used ERT. A separate population-based cohort study demonstrated increased mortality (HR, 1.67) for women undergoing bilateral oophorectomy before the age of 45 years (43). A more recent report from WHI investigators focused on 25,448 women ages 50 to 79 years at enrollment who were in the observational arm of the study who reported a prior history of hysterectomy. With a median follow-up of roughly 7.6 years, BSO had no effect on the risk of fatal or nonfatal CHD, coronary artery bypass grafts, angioplasty, stroke, total cardiovascular disease, hip fracture, or death. BSO decreased ovarian cancer risk and had no effect on the incidence of breast, colorectal, or lung cancer. The findings were not influenced by the age at the time of hysterectomy or use of ERT (55). Potential explanations for these conflicting results include details related to study design, methods for risk factor adjustments, and duration and method of follow-up. Because of these contradictory data, it remains a significant challenge for clinicians to reliably inform a woman contemplating oophorectomy about the implications of the procedure for her.

The finding that at least some HGSC arises in the fallopian tube raises the intriguing hypothesis that it may be possible to reduce ovarian cancer mortality among women with a genetic susceptibility to HGSC through bilateral salpingectomy with ovarian retention (BSOR), a surgical procedure that removes the fallopian tubes but leaves the ovaries *in situ*. In support of this hypothesis are the following: (i) HGSC is the most common and lethal epithelial ovarian cancer subtype associated with *BRCA1/2*, and consequently a strategy that prevents primarily HGSC is likely to have a major impact on ovarian cancer mortality, and (ii) tubal ligation, a surgical procedure that involves disruption and/or interruption of the fallopian tube has been consistently found to provide a 50% reduction in epithelial ovarian cancer risk (20, 22). BSOR avoids the long-term complications of oophorectomy-associated changes in sex hormone levels. The effectiveness of BSOR in preventing EOC will depend, to a large extent, on the proportion of cancers that arise in the fallopian tubes, which remains unknown. BSOR is an appealing prevention strategy for premenopausal high-risk women for whom BSO is recommended but who are reluctant to have their ovaries removed due to hormonal implications. For these women, BSOR might serve as a temporary measure until definitive risk-reducing surgery is desired. Retention of ovarian function until the age of natural menopause may abrogate the negative sequelae of bone and cardiovascular health associated with early surgical menopause. In addition to removing the fallopian tube, BSOR prevents any menstrual spillage that is thought to be the origin of endometriosis and possible endometrioid and clear cell ovarian cancer (57).

For women at average risk of ovarian cancer, performing BSOR at the time of hysterectomy for benign disease is another compelling prevention opportunity. Until very recently, salpingectomy was typically not performed as part of a standard hysterectomy procedure unless the ovaries were also being removed. Approximately 600,000 hysterectomies are performed in the United States each year, 50% of which are performed in women less than 50 years of age, in whom the ovaries are frequently retained. Performing salpingectomy at the time of hysterectomy in these women could reduce overall ovarian cancer incidence by up to 15% if the procedure were 100% effective in preventing ovarian cancer as roughly 15% of women diagnosed with ovarian

cancer have had a prior hysterectomy (58, 59). Likewise, premenopausal women seeking permanent contraception could opt for BSOR rather than tubal ligation, which leaves the fimbria intact. However, because tubal ligation is associated with a significant reduction in ovarian cancer risk it will be important to evaluate the marginal benefit of performing BSOR in terms of additional cases prevented. Most important will be prevention of HGSC due to the aggressive nature of this subtype and evidence that tubal ligation may have greater protection toward the endometrioid and clear cell subtypes (60). Tubal ligation is frequently performed in the postpartum period, which may increase the complexity of the BSOR procedure due to increased blood flow or anatomic issues related to an enlarged uterus.

Salpingectomy involves the resection of the complete terminal part of the tube from the uterine level to the ovary and can be performed laparoscopically, transvaginally, or during open abdominal surgery. When performed for prevention, it has been recommended that the procedure be accompanied by inspection of the abdomino-pelvic cavity and the collection of pelvic washings (61). Data are accumulating to suggest that the salpingectomy procedure at the time of hysterectomy is feasible and safe and does not affect short-term ovarian function. In 2010, investigators in British Columbia initiated a province-wide ovarian cancer prevention initiative by educating obstetricians and gynecologists about the potential benefits of salpingectomy. They encouraged physicians to consider removal of the fallopian tubes at the time of hysterectomy even when the ovaries were retained and in lieu of tubal ligation for women electing permanent sterilization. Compared with before the intervention, there was a significant uptake in salpingectomy procedures, especially among women less than 50 years of age. Bilateral salpingectomy required minimal additional operative time (16 and 10 minutes on average for hysterectomy and sterilization, respectively) and was not associated with increased hospital stays, readmissions, or surgical complications (62). In two recent studies, the addition of salpingectomy to a laparoscopic hysterectomy procedure with careful preservation of the blood vessels adjacent to the ovarian hilum did not impact antimüllerian and follicle stimulating hormone levels, ovarian volume, or antral follicle count and blood flow up to 3 months following the procedure (63, 64). Combined, these data support the concept that bilateral salpingectomy at the time of hysterectomy is feasible and does not increase surgical morbidity or impact short-term ovarian function. However, additional data in more patients and longer follow-up are required before the safety and efficacy of the procedure can be established. Especially important will be additional information on ovarian function beyond 12 months following the procedure. Although current rates of BSOR in the United States are unknown, the approach appears acceptable to women. One-third of 205 *BRCA* mutation carriers with a median age of 35 indicated a definite interest in the procedure (41). Recent survey studies confirm that roughly 60% of physicians counsel women about the potential benefits of BSOR at the time of hysterectomy (65) and roughly 54% of physicians perform the procedure (66). However, only 7.2% of physicians prefer BSOR as a primary sterilization procedure.

Next Steps

Although our view of epithelial ovarian cancer initiation has improved drastically with the understanding that carcinogenesis can begin in the fallopian tube epithelium, many knowledge gaps

must be acknowledged when we consider moving forward for this new prevention strategy. For example, STIC are identified in only 50% to 60% of sporadic HGSC; does this mean that the other 40% to 50% arise through a different mechanism? STIC observations are a single snapshot in time, making it difficult to make definitive conclusions based on these descriptive studies alone. In cases without an identified STIC, the initial STIC may no longer be visible if invasive carcinoma has overgrown the site of initiation. Another question that remains to be addressed is the mechanism underlying the apparent preference for tumor growth or metastasis and dominant mass development at the site of the ovary, despite cancer initiation in the fallopian tube (32, 67). Furthermore, we do not know how early these transformed cells may be able to "seed" onto the ovary or peritoneum. In addition, a small study of women with unexpected cancers diagnosed at RRSO reported an intriguing observation that *BRCA1/2* mutation carriers with invasive carcinomas were younger than women with noninvasive carcinoma (STIC; ref. 68). This would suggest that the natural history is different for these two groups of women, yet larger studies are required to more carefully evaluate this issue.

With this new understanding that HGSC most commonly originates in the fallopian tube, we must reevaluate our approach to ovarian cancer prevention. Fundamental changes are required from basic science to clinical practice. Laboratory researchers must now define the fallopian tube epithelium as the baseline for identifying molecular changes that can be targeted for prevention, in contrast to previous studies using ovarian surface epithelium. Longstanding questions regarding the impact of ovulation and ovarian hormones must also be reconsidered from this new perspective in which the fallopian tube epithelium is the predominant at-risk cell type.

Clinically, new approaches to prophylactic surgery must be evaluated to determine the value of salpingectomy as an alternative primary prevention procedure in women at high-risk, or opportunistic salpingectomy, performed at the time of benign gynecologic surgery or tubal sterilization for women at general population risk. Although a two-step surgical strategy that includes BSOR before menopause followed by postmenopausal oophorectomy offers an attractive alternative to the current standard of BSO after age 35 in high-risk women, there are currently no data demonstrating long-term benefits, including reduction in incidence of ovarian cancer, improved overall survival, or preservation of ovarian function with the two-stepped surgical approach. Several studies have found that the reduction in the risk of breast cancer associated with oophorectomy before menopause may be abridged by delaying removal of the ovaries until closer to the time of natural menopause (69–71). Ovarian preservation could lead to a reduction in cardiovascular disease and bone loss and improved quality of life. Because the timing of the progression from p53 overexpression to STIC to invasive disease within the fallopian tube or metastasis is not well characterized, there are no data to guide the optimal timing of the two surgeries, or whether the timing should differ by the type of mutation (e.g., *BRCA1*, *BRCA2*, or a mismatch repair mutation). The impact of a two-staged surgical approach on quality of life is not known. It is also not known what percentage of women would ultimately decline the second surgery, or delay it beyond the age of natural menopause, and how that would impact their risk of ovarian cancer. The interaction of prophylactic salpingectomy with other risk reducing measures, such as oral contraceptive use, multiparity, or prior TL is unknown. Finally, there are little data on the

overall cost benefit ratio of the two-staged surgical approach in terms of competing risks and benefits. Many of these uncertainties regarding the long-term consequences of BSOR also apply to average risk women who undergo hysterectomy or TL. Uncertainty regarding the effectiveness of BSOR is particularly important in this group, as average risk women are unlikely to undergo later oophorectomy.

Before this new, theoretically attractive approach replaces the current standard of BSO in premenopausal high-risk women, there is a window of time within which many of these questions can be addressed to develop a base of evidence. The ideal study design would be a prospective randomized trial that would compare the benefits and risks of BSOR alone followed by delayed oophorectomy, with the benefits and risks of BSO as a single surgery. Such a trial would, however, be costly and raises some questions about the potential ethical concerns associated with a randomized assignment of type of surgery among high-risk women. An alternative approach would be to create a consortium of clinicians who are managing the gynecologic health of women and who would agree to follow a common protocol with the collection of common data elements and biospecimens. Both high-risk and average-risk women undergoing hysterectomy for benign conditions could be eligible to participate. The protocol would emphasize a shared decision-making process with clinician and patient reviewing the current level of evidence for the two-staged versus a single-step approach in high-risk premenopausal

women and incorporation of salpingectomy as part of the standard hysterectomy in average-risk women as part of their choice of surgical approach. A cohort study could identify variables that are associated with the choice and timing of surgery, including demographic, training and health care setting of the clinicians, and demographic, health status, and mutation status of the patients. The cohort would create a valuable resource for scientists to explore molecular, clinical, and behavioral ancillary studies. The Ovarian SPORE community in collaboration with the cooperative group consortia are ideally suited to take a lead in developing this consortium, which would be of great value for women and their clinicians as they face the decision of oophorectomy in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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