Commentary

Society of Gynecologic Oncology Recommendations for the Prevention of Ovarian Cancer

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Mortality from ovarian cancer may be dramatically reduced with the implementation of attainable prevention strategies. The new understanding of the cells of origin and the molecular etiology of ovarian cancer warrants a strong recommendation to the public and health care providers. This document discusses potential prevention strategies, which include 1) oral contraceptive use, 2) tubal sterilization, 3) risk-reducing salpingo-oophorectomy in women at high hereditary risk of breast and ovarian cancer, 4) genetic counseling and testing for women with ovarian cancer and other high-risk families, and 5) salpingectomy after childbearing is complete (at the time of elective pelvic surgeries, at the time of hysterectomy, and as an alternative to tubal ligation). The Society of Gynecologic Oncology has determined that recent scientific breakthroughs warrant a new summary of the progress toward the prevention of ovarian cancer. This review is intended to emphasize the importance of the fallopian tubes as a potential source of high-grade serous cancer in women with and without known genetic mutations in addition to the use of oral contraceptive pills to reduce the risk of ovarian cancer. ***Cancer*** **2015;121:2108-20.** *© 2015 American Cancer Society.*

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INTRODUCTION

Epithelial ovarian carcinoma is the most lethal of the gynecologic malignancies. The American Cancer Society estimates that 21,980 women will be diagnosed with ovarian cancer in the United States, and 14,270 will die of the disease in 2015.[1] Because early detection through screening and symptom detection has failed to reduce mortality,[2-9] the only currently available strategy likely to affect mortality is prevention.[10-15]

Over the last decade, there has been an important paradigm shift in our understanding of the pathogenesis of ovarian cancer and its etiology. First, ovarian cancer is now divided into 2 basic categories that have different etiologies, molecular pathogeneses, and clinical behaviors. Type 1 tumors are less common, tend to present at a lower stage, and usually arise from a precursor lesion.[16-20] Type 2 tumors are associated with an advanced stage and account for the majority of the deaths.[21-33] There is now evidence to support the idea of most type 2 ovarian cancers developing from neoplastic progression of epithelial cells of the fallopian tube; therefore, risk reduction might theoretically be achieved by salpingectomy.[34-39] As high-grade cancers of the fallopian tubes, ovaries, and peritoneum have similar molecular profiles, they are thought to represent the same disease. This article will continue to use *ovarian cancer* to describe the entire spectrum of these related high-grade carcinomas, including ovarian, fallopian tube, and peritoneal carcinomas.

The strategies with potential to contribute to ovarian cancer prevention, which will be discussed in greater detail in this article, include the following:

1. Oral contraceptives reduce the risk of both type 1 ovarian cancer and type 2 ovarian cancer and are considered safe for *BRCA1* and *BRCA2* mutation carriers.[13,40-43]
2. Tubal ligation/epidemiologic evidence indicates that tubal ligation is associated with a reduction in ovarian cancer in both the general population and high-risk women.[10,34-39,44,45]

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3. Risk-reducing salpingo-oophorectomy (RRSO) has been shown to reduce ovarian cancer by 80% in women with *BRCA1* and *BRCA2* mutations.

Two additional strategies will be considered:

4. Improved identification and genetic testing of women who are at inherited high risk (many women with ovarian cancer and triple-negative breast cancer are not referred for genetic counseling).
5. Salpingectomy as an alternative strategy to other sterilization techniques and opportunistically at the time of hysterectomy or other pelvic surgery to potentially reduce the incidence as well as death rates from ovarian cancer in the general population.[34,35,44]

Regions in Canada and Germany have initiated programs to change surgical practice to include opportunistic salpingectomy.[35,46] Currently, there are no recommendations for the prevention of ovarian cancer in the general population because it is a relatively rare cancer, but our new understanding of the role of the fallopian tube in the etiology of ovarian cancer has led us to propose the opportunistic removal of the fallopian tubes for the goal of preventing ovarian cancer.

PATHOGENESIS OF OVARIAN CANCER: TYPE 1

Traditionally, ovarian cancer was subdivided by histologic type, but as we learn more about the molecular genetics of ovarian cancer, we are re-evaluating these historical divisions. On the basis of recent morphologic, molecular, and immunohistochemical studies, there is a new understanding of ovarian carcinogenesis that divides ovarian cancer into 2 broad categories based on clinicopathologic, molecular genetic features and their putative precursor lesions. Type 1 ovarian cancers include low-grade serous, low-grade endometrioid, clear cell, and mucinous histology. The neoplastic processes of type 1 tumors are hypothesized to result from endometriosis, inflammation, incessant ovulation, and the microenvironment.[19,47,48] Typically, type 1 ovarian carcinomas are not as common or lethal as type 2 carcinomas. With the exception of clear cell carcinomas, they are usually indolent, are diagnosed at an earlier stage, and are associated with a benign precursor lesion.[16] The molecular abnormalities of type 1 carcinomas are distinct for each histology type and do not involve the TP53 mutations seen in type 2 carcinomas. These molecular findings can help the pathologist more accurately categorize the histologic cell types, but they have not contributed to improving the therapeutic efficacy of our treatments. Low-grade serous carcinomas have been found to have KRAS, BRAF, ERBB2, and PIK3CA mutations.[16] Low-grade endometrioid histology is associated with mismatch repair defects (MLH1 and MSH2) as well as PTEN and ARID1A mutations.[18,49-52] Clear cell carcinomas have been associated with ARID1A and PIK3CA mutations and alterations in PTEN.[20,53] Although clear cell carcinomas have aggressive behavior distinct from that of low-grade endometrioid carcinomas, they are included as type 1 ovarian carcinomas because of the shared association with endometriosis and the mutations seen in the PI3K/PTEN signaling pathway similar to those in endometrioid carcinoma. A clear progression has been shown in pathologic examinations and immunohistochemical studies from benign endometriosis to atypical endometriosis with a transformation zone to carcinoma.[54-57] Blood products and iron-induced oxidative stress, inflammation, and hyperestrogenism have been implicated as possible links between endometriosis and cancer.[48] On the basis of their morphologic appearance and similarities in molecular genetics, endometrioid and clear cell carcinomas appear to arise from endometriotic cysts, and this would explain a higher risk of these types of ovarian cancer in patients with endometriosis.[19,51,52,58,59] Endometriosis implants on the ovaries and peritoneal surfaces have been hypothesized to occur by retrograde menstrual flow into the peritoneal cavity. Thus, the role of tubal ligation in reducing type 1 cancers could be conjectured to be related to the obstruction of this pathway of endometriosis implantation. Pearce et al[52] reported a significantly increased risk of clear cell carcinoma (odds ratio [OR], 3.05; 95% confidence interval [CI], 2.43-3.84), low-grade serous cancers (OR, 2.11; 95% CI, 1.39-3.20), and endometrioid ovarian cancers (OR, 2.04; 95% CI, 1.67-2.48) in patients with self-reported endometriosis. Other investigators have hypothesized that some low-grade serous tumors originate from endosalpingiosis and that these cells may also be tubal in origin.[17,51,60]

There is difficulty in classifying mucinous tumors of the ovary and distinguishing them from metastatic tumors from the gastrointestinal tract.[61] Some investigators have proposed an origin from Walthard rests or paratubal cysts in cases of invasive mucinous cancers of gynecologic origin and Brenner tumors.[16,49] If this is true, removal of the fallopian tubes could potentially reduce the incidence of mucinous ovarian carcinomas as well.

PATHOGENESIS OF OVARIAN CANCER: TYPE 2

Type 2 ovarian carcinomas account for the majority of epithelial ovarian cancer deaths. These include the

TABLE 1. Evidence for a Tubal Origin for What Has Been Called Ovarian Cancer

1. No precursor lesion has been identified in the ovary for high-grade serous cancer. Reports of "dysplasia" in the ovary are rare.[76,77]
2. The molecular markers associated with high-grade serous ovarian cancer are consistent with a Müllerian embryonic origin (ie, tubal) and not with an urogenital origin (ie, ovarian). Gene expression studies show serous cancers resemble tubal epithelium rather than ovarian epithelium.[20,78]
3. Precursor STIC lesions or invasive cancer occur in 5% to 9% of tubes of women with *BRCA1/BRCA2* mutations undergoing RRSO. STIC lesions are associated with contiguous or multifocal molecular changes called p53 signatures, which are morphologically benign but have overexpression of p53 and a low proliferative index.[68-74,76,77,80]
4. There appears to be a progression from areas in the fallopian tube with a p53 signature with increasing genetic mutations of p53 as well as the expression of Ki67, a marker of proliferation, P16, and PAX8 to the pre-invasive STIC lesion. This progression correlates with histologic changes from the normal epithelium in the p53 signature to dysplasia to STIC visualized by hematoxylin-eosin staining of the tubal specimens.[16]
5. p53 signatures are found in approximately one-third of normal tubal specimens as well as those from *BRCA* mutation carriers. However, the association of the p53 signature with STIC is more frequent in tubes of women with *BRCA* mutations.[29]
6. When the fallopian tube is examined in cases of serous cancer of the ovary, the tube is involved in 71% of cases, and STIC lesions are found in 47%. The p53 mutations of the ovarian cancer and the STIC-associated lesions are identical. Similarly, peritoneal cancers have tubal involvement in 79% and STIC in 47% when the tubes are microsectioned.[22,25]
7. Gene profiling of the tubal lesion and the invasive cancer match, and this suggests a common clonal origin. Telomere length studies also suggest a tubal origin.[28,79,81]
8. Recently, human tubal epithelium has been transformed in the mouse into serous carcinoma.[28,75]

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; STIC, serous tubal intraepithelial carcinoma.

most common high-grade serous carcinomas but also high-grade endometrioid adenocarcinomas, undifferentiated carcinomas, and carcinosarcomas.[16,18,20,22,23,26-28,49,62,63] These aggressive cancers present in late stages and harbor p53 mutations in 95% of cases. *BRCA* genetic mutations and other germline mutations in homologous recombination genes are associated with type 2 cancers.[64-66] Historically, fallopian tube cancers were considered rare, partly because the criteria for fallopian tube carcinoma required that the ovaries not be involved or contain less tumor than the tubes.[67] Because in most of these carcinomas ovarian involvement and an ovarian mass were seen, they were traditionally characterized as ovarian primaries without close inspection of the fallopian tubes. A preponderance of evidence from 2 areas of study, histopathology of RRSO specimens and molecular genetic studies of serous cancers, now suggests that these carcinomas frequently originate from precursor lesions in the fallopian tubes. In the last 2 decades, investigators performed detailed analyses and microsectioning of the ovaries and fallopian tubes at the time of RRSO in women with *BRCA1* and *BRCA2* mutations; unsuspected small cancers and pre-invasive lesions were found in 5% to 9% of cases.[68-74] In more than 70% of these cases, the fallopian tubes were involved. Cases of unsuspected cancers at RRSO involving only the ovaries were rare, and no precursor lesions were seen in the ovaries. The precursor tubal lesions are called serous tubal intraepithelial carcinomas, and staining has shown p53 mutations in these lesions.[16,21,29] Serous tubal intraepithelial carcinoma lesions in the fallopian tubes have also been found in 50% to 60% of sporadic serous ovarian cancers.[23,25] Further study of cases of ovarian cancer in both *BRCA1* and *BRCA2* mutation carriers as well as sporadic cases have confirmed that p53 mutations occur in more than 90% of serous cancers and that the p53 mutations seen in the ovaries match the specific mutations seen in the precursor lesions found in the fallopian tubes; this suggests a clonal origin.[22,23] Similar findings have been shown for peritoneal serous cancers.[25] Gene profiling studies have found serous cancers to express Müllerian biomarkers such as PAX8, to more closely resemble the fallopian tubes, and to lack mesenchymal markers such as calretinin of the ovaries.[66] Serous tubal intraepithelial carcinoma lesions have short telomeres, a feature associated with precancerous lesions. Lastly, models of serous cancer in the mouse have shown the transformation of tubal epithelium into serous carcinoma.[28,75] Thus, most high-grade serous cancers are likely metastatic from the tube at the time of presentation in a woman with ovarian cancer.[20,22,23,47,76] This evidence is summarized in Table 1 and Figure 1.[82]

On the basis of a pathologic evaluation showing that 71% of high-grade serous cancers demonstrate evidence of a precursor lesion in the fallopian tube, it is theorized that removal of the fallopian tubes would reduce the incidence and death rates from ovarian cancer.[22] The recent identification of serous precursor lesions in the fallopian tubes of women with high-grade serous carcinomas without a genetic predisposition makes opportunistic salpingectomy in certain surgical situations worthy of consideration in the general population and not just in those women who are genetically at high risk.[34,37,83] The majority of women with a genetic predisposition for ovarian carcinoma are yet to be identified, and this allows opportunities for improvement in ovarian cancer prevention.

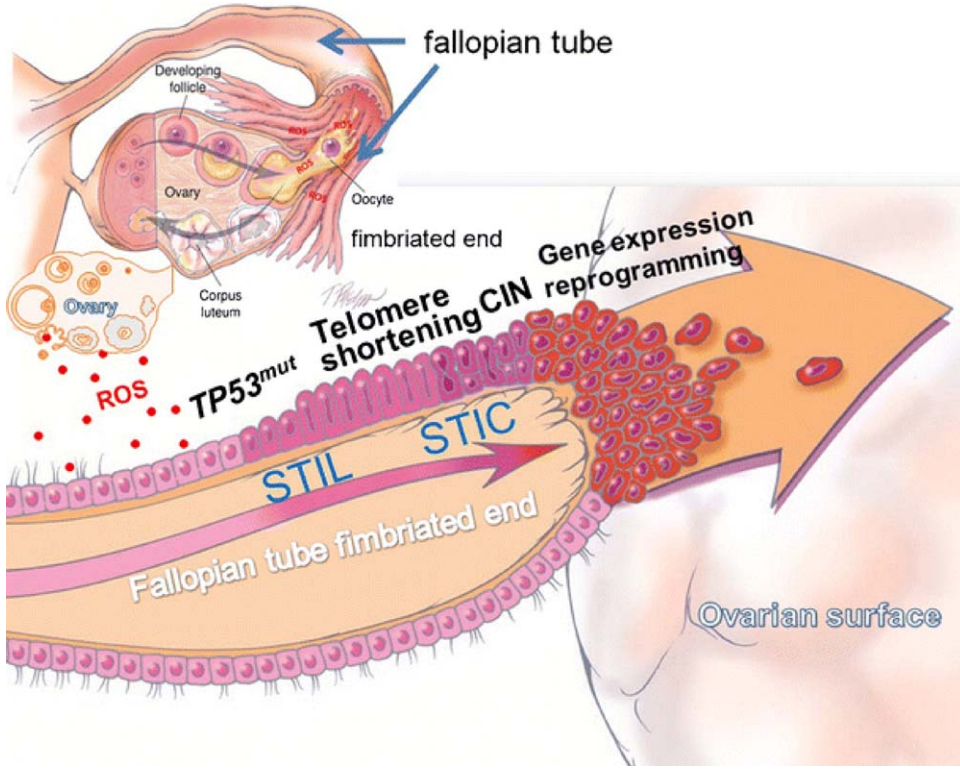

Figure 1. Hypothesis for the tubal origin of ovarian HGSC. We hypothesize that normal FTE is the cell of origin of many "ovarian" HGSCs. Rupture of the dominant follicle at ovulation exposes the underlying ovarian stroma to fimbrial epithelium, which can implant on the ruptured ovarian surface. Inflammation and repair occur in the presence of follicular fluid, which contains a high concentration of ROS (red dots). The increased genotoxic effects may facilitate the selection of TP53 mutations in epithelial cells, which clonally expand. As a result, telomere shortening occurs and enhances underlying CIN, and this creates a repertoire of tumor subclones in STILs, some of which may acquire malignant phenotypes (STIC) and exfoliate onto the ovarian and peritoneal surfaces. In summary, FTE may lead to ovarian HGSC by 2 different mechanisms: 1) normal FTE implants on the ruptured ovarian surface at ovulation and invaginates to form an inclusion cyst that subsequently undergoes malignant transformation (possibly after a TP53 mutation), or 2) STIC cells implant on the ovary and then form a tumor mass. In both instances, the ovarian HGSC is of tubal origin. CIN indicates chromosomal instability; FTE, fallopian tube epithelium; HGSC, high-grade serous carcinoma; ROS, reactive oxygen species; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion. Reprinted with permission from Kuhn E, Kurman RJ, Shih L. Ovarian cancer is an imported disease: fact or fiction? *Curr Obstet Gynecol Rep*. 2012;1:1-9.[82]

REDUCING RISK AND PREVENTION OF OVARIAN CANCER

Low parity, infertility, and early menarche or late menopause have all been associated with an increased risk of ovarian cancer.[84] Lifestyle factors such as exercise and fat intake have not clearly been associated with ovarian cancer, although obesity has also been associated with an increased risk of ovarian cancer in some series. The Collaborative Group on Epidemiological Studies of Ovarian Cancer reported a meta-analysis of 47 studies revealing that for women who do not use postmenopausal hormones, for each 5 kg/m^2 increase in the body mass index, there is a 1.10-fold increase (95% CI, 1.07-1.13) in the risk of ovarian cancer.[42] The Ovarian Cancer Association Consortium reported that a high body mass index is associated with an increased risk of type 1 ovarian cancers (borderline serous, invasive endometrioid, and invasive mucinous carcinomas) but not high-grade serous cancers.[85] Obesity is also associated with polycystic ovary syndrome and hyperandrogenism, which may also play a role in increasing ovarian cancer risk.[86] More research is needed to clarify the impact of lifestyle on ovarian cancer risk.

USE OF ORAL CONTRACEPTIVES

For women with an average risk of ovarian cancer, use of oral contraceptives is associated with a 40% to 50% lifetime risk reduction.[13] A greater benefit is achieved with longer oral contraceptive use, and the benefit can last for 15 years after discontinuation of use.[87]

Furthermore, the risk reduction does not differ between the use of the current low-dose pills and the high-dose formulations used in the past (OR, 0.5; 95% CI, 0.3-0.7)[88,157] or between histologic cell types (except mucinous types).[41,42,58,89] The effects of oral contraceptives on serous tubal intraepithelial carcinoma lesions or whether any precursor lesions can be reversed by these hormonal effects are less clear.[90-92]

Gierisch et al[93] recently completed a systematic review of data on the cancer risk of oral contraceptive pill use in the general population and concluded that there is a small increased risk of breast cancer (OR, 1.08; 95% CI, 1.00-1.17). There is also a known increase in the thrombosis risk, and women at higher risk for these events should avoid these agents (ie, women with a family history of thromboembolic disease and smokers).[94] The Agency for Healthcare Research and Quality guidelines on oral contraceptives summarize the risks, and the reader is referred to this resource for details.[58]

Women with *BRCA1* or *BRCA2* mutations should consider taking oral contraceptive pills to reduce their ovarian cancer risk.[95,96,158] There is increasing protection with duration of use, and this is similar to the case for the general population.[41,43] A meta-analysis of 18 case-control and retrospective cohort studies comprising a total of 2855 breast cancer cases and 1503 ovarian cancer cases in *BRCA1* and *BRCA2* mutation carriers identified a significant reduction in the risk of ovarian cancer for *BRCA1* and *BRCA2* mutation carriers who used oral contraceptives (summary relative risk [SRR], 0.50; 95% CI, 0.33-0.75).[43] The duration of oral contraceptive pill use was important; a 36% risk reduction in ovarian cancer incidence occurred with each additional 10 years of use (SRR, 0.64; 95% CI, 0.53-0.78). Most importantly, there was no significant association between modern oral contraceptive use and breast cancer risk in these women (SRR, 1.13; 95% CI, 0.88-1.45). An increased risk of breast cancer occurred with oral contraceptive formulations that were used before 1975, but this risk was not found for the more recent formulations.[43] It is unclear whether oral contraceptives would be helpful in optimizing the risk reduction of ovarian cancer after a bilateral salpingectomy in which ovaries are retained in *BRCA1*/*BRCA2* mutation carriers. In a case-control study by the Hereditary Ovarian Cancer Clinical Study Group, a history of both oral contraceptive use and tubal ligation was more protective against ovarian cancer than either alone (72% risk reduction) for *BRCA1* and *BRCA2* mutation carriers.[97]

USE OF BILATERAL TUBAL LIGATION

Tubal ligation has been associated with a decreased risk of ovarian cancer.[98-102] In a 2011 meta-analysis, Cibula et al[10] concluded that previous tubal ligation in women at average risk for ovarian cancer was associated with a 34% overall risk reduction (specifically, the relative risks were 0.40 for endometrioid cancer and 0.73 for serous cancer); however, no significant risk reduction was found for women with mucinous or borderline tumors who had undergone previous tubal ligation.[10]

There are a few small studies of ovarian cancer risk reduction with tubal ligation in *BRCA1* and *BRCA2* mutation carriers. The largest study by Antoniou et al[103] 2009 reported a 57% risk reduction in *BRCA1* (relative risk, 0.43). Narod et al[104] in 2001 reported on *BRCA1* carriers benefiting from bilateral tubal ligation with an OR of 0.39 ($P = .002$), and with bilateral tubal ligation in addition to oral contraceptives, the OR for ovarian cancer was 0.28 (95% CI, 0.15-0.52). The reduction in risk was not confirmed for the *BRCA2* subgroup. The risk reduction of tubal ligation was comparable to that with oral contraceptive pill use.[102-107]

RRSO IN WOMEN AT HEREDITARY INCREASED RISK

The most proven method for the prevention of ovarian cancer in women who carry a deleterious *BRCA1* or *BRCA2* mutation is RRSO.[108,156] Prospective studies have reported a 70% to 85% reduction in ovarian cancer and a 37% to 54% reduction in breast cancer as well as a reduction in cancer-related mortality and overall mortality.[109,110] All guidelines have now been updated to recommend that this procedure be performed between 35 and 40 years of age in women with *BRCA1* and *BRCA2* mutations.[14,143,144] Guidance for women who are at high risk according to strong family histories or who have been identified with a genetic mutation other than *BRCA1* or *BRCA2* generally follows the guidelines for *BRCA1* and *BRCA2* mutation carriers, but there are fewer data for these groups to support the value of salpingo-oophorectomy. Some syndromes such as Peutz-Jeghers syndrome are associated with cancer at a younger age, so the timing of RRSO should be individualized according to the age of incident cancers in the family or the specific mutation. Flexibility in the timing of RRSO may also be appropriate for *BRCA2* carriers who present with ovarian cancer at a later age than *BRCA1* carriers. The cumulative incidence of ovarian cancer in *BRCA1* mutation carriers is low under the age of 40 years but reaches more than 10% by the age of 50 years, whereas it remains low until the age

of 50 years for *BRCA2* mutation carriers.[111] Women who have chosen mastectomy for breast cancer risk reduction can concentrate their decision making on the age of onset of ovarian cancer because bilateral mastectomy provides 90% to 95% risk reduction for breast cancer.[109,110,112,113]

For those not choosing mastectomy, the risk reduction of breast cancer with salpingo-oophorectomy must be considered. If RRSO is performed before the age of 40 years, the risk reduction for breast cancer is 56% in *BRCA1* mutation carriers (OR, 0.44; 95% CI, 0.29-0.66) and 46% in *BRCA2* carriers (OR, 0.57; 95% CI, 0.28-1.15), with the effect persisting at least 15 years after the procedure.[112] Finally, all high-risk women should consider whether to use tamoxifen or undergo mastectomy to reduce their breast cancer risk.[113,114] These decisions about ovarian cancer and breast cancer risk reduction are linked because the ovarian status has an effect on the breast cancer risk, and it is best to consider the overall health benefits and tailor decision making to each woman. Sigal et al[115] modeled immediate prophylactic RRSO and prophylactic mastectomy after the detection of *BRCA1* or *BRCA2* carrier status, and they found that the *BRCA1* carrier gained 6.8 to 10.3 years and the *BRCA2* carrier gained 3.4 to 4.4 years in life expectancy, and the benefit increased as the age at which the prophylactic surgery occurred decreased from 50 to 30 years.[115]

RRSO is associated with minimal surgical complications. Kenkhuis et al[116] examined the results of 159 women who underwent RRSO and found that 154 had laparoscopic surgery with an intraoperative complication rate of 1.3%. Conversion to laparotomy occurred at a rate of 0.6%, and the postoperative complication rate was 3.1%.[116] After RRSO, women were noted to experience increased vasomotor symptoms, decreased sexual function, dyspareunia, and vaginal dryness.[117] Sexual function has been shown to be a predictor of satisfaction with risk-reducing surgery.[118] Women who underwent RRSO had more menopausal symptoms and worse sexual function than those receiving surveillance, with some studies demonstrating the use of hormonal replacement therapy (HRT) having a mixed and mild impact on the level of endocrine and sexual symptoms.[117,119-122] RRSO has also been viewed as worth the perceived costs of menopausal symptoms, sexual satisfaction, and body image concerns after risk-reducing surgery for many women[119,120,123-125] as a tradeoff for peace of mind or lower distress due to proven cancer risk reduction.

It is important to emphasize that RRSO is indicated only for women at high risk for breast and ovarian cancer and has been shown to reduce ovarian cancer only in women with *BRCA1* and *BRCA2* mutations. Preservation of ovaries is advisable for average-risk women. A recent analysis including 28 years of follow-up of participants in the Nurses' Health Study found the hazard ratio for deaths from all causes in women who had undergone hysterectomy that included bilateral oophorectomy was 1.12 (95% CI, 1.02-1.21) in comparison with women who had undergone hysterectomy with ovarian conservation. In a subgroup analysis, bilateral oophorectomy was associated with significantly greater mortality only in women under the age of 50 years who had never used estrogen replacement therapy,[126,127] and there was no age at which bilateral oophorectomy improved survival. Cardiovascular mortality was higher in women who had undergone oophorectomy without estrogen replacement before the age of 45 years. A study using decision analysis calculated that the optimum age at which ovarian conservation benefited long-term survival in woman at average risk of ovarian cancer was through 65 years. These health considerations outweigh the risk reduction of breast (hazard ratio, 0.75; 95% CI, 0.68-0.84) and ovarian cancer (hazard ratio, 0.004; 95% CI, 0.01-0.09)[126,127] for women at average risk of breast and ovarian cancer.

Similar deleterious health effects of RRSO have been observed in studies of *BRCA1* and *BRCA2* mutation carriers, although the benefit due to the reduction of cancer mortality is more important in these women. In *BRCA1* and *BRCA2* mutation carriers, RRSO was associated with cardiovascular disease, osteopenia and osteoporosis, and noncancer mortality[120,128-131] when it was performed before the age of 45 years and without HRT.[126,127,132] Elevated lipids and hypertension have been associated with RRSO.[133] The risk for fracture is greatest if the ovaries are removed before the age of 45 years.[134] Women who have not had breast cancer can receive estrogen replacement therapy after RRSO both to alleviate menopausal symptoms and possibly to mitigate the other effects of early menopause. However, the magnitude of this benefit has not been well studied, and the optimal duration for estrogen replacement therapy after RRSO is not known. Those who choose to retain their uterus must be treated with a combination of estrogen and progesterone HRT to mitigate the increased risk of unopposed estrogen on endometrial cancer. There are 2 observation studies that showed no increased risk of breast cancer with HRT use after RRSO, but these studies were nonrandomized with small cohorts, and the number of women with *BRCA2* was insufficient to make any conclusion. Women who have chosen prophylactic mastectomy

are typically more comfortable with estrogen replacement.[135] Women with a personal history of breast cancer are less likely be offered and to choose estrogen replacement.[135] In the general population, there is concern that the progesterone component of HRT (not the estrogen component) may increase breast cancer. Women choosing to keep their uterus may want to use a levonorgestrel-containing intrauterine device so that they can take estrogen replacement without the need for systemic progestin after RRSO.[136,137]

IDENTIFICATION OF WOMEN AT HEREDITARY INCREASED RISK OF OVARIAN CANCER

Risk-reducing strategies for women with an inherited risk for ovarian cancer can reduce the incidence of ovarian cancer and breast cancer, cancer mortality, and overall mortality.[109] It is imperative that women at inherited increased risk be identified and offered genetic counseling to assess their risk.[14,138,139] Only 20% of women with ovarian cancer in the community setting and up to 48% in an academic center are referred for genetic counseling.[140,141] It was estimated in 2012 that approximately 24% of women with ovarian cancer had undergone genetic testing.[142] Risk assessment guidelines, including the National Comprehensive Cancer Network guidelines,[143,144] have been published elsewhere. Other than a personal history of ovarian cancer, the main features are a strong family history of breast/ovarian cancer or ovarian/endometrial/colon cancer, a young age at onset and multiple cancers in the same person, male breast cancer, and ethnicity. The most common germline mutations associated with ovarian cancer occur in *BRCA1* and *BRCA2* and are associated with lifetime risks of ovarian cancer of 18% to 54% and 2.4% to 19% respectively.[111] *BRCA1*- and *BRCA2*-related hereditary ovarian cancers are typically type 2, with a majority having high-grade serous histology. In a recent study at the University of Washington, 360 ovarian cancer patients were studied with massively parallel sequencing for 21 tumor suppressor genes, and 24% were found to have germline genetic mutations associated with ovarian cancer.[64] *BRCA1* mutations were found in 11%, *BRCA2* mutations were found in 6.4%, 0.5% of mutations were found in Lynch genes, and the remainder were found in other homologous recombination genes. Histologic cell types found in patients with germline mutations included serous, endometrioid, clear cell, and carcinosarcoma types, but most were high-grade serous types. Notably, 31% of women with an inherited mutation had no prior personal history of cancer or family history of breast or ovarian cancer. The age at the diagnosis of cancer associated with a germline mutation was surprising in that 10% were less than 40 years old, 65% were between the ages of 40 and 59 years, 20% were between the ages of 60 and 69 years, and 5% were older than 69 years. The median age was not dissimilar to that of women testing negative for germline mutations. Conclusions from these data support National Comprehensive Cancer Network and Society of Gynecologic Oncology guidelines for universal genetic counseling and testing for all women with ovarian cancer (including fallopian tube and peritoneal cancer).[143,144] Other mutations for which the risk of ovarian cancer has been quantified include Lynch syndrome, which is associated with a 12% lifetime risk of ovarian cancer (most commonly endometrioid and clear cell cancer), and Peutz-Jeghers syndrome (STK11), which is associated with sex cord stromal tumors.[14] New genes associated with a hereditary risk of ovarian cancer are being rapidly identified with new technologies and panel testing.

Offering all affected women genetic counseling and testing will inform their families of appropriate risk-reduction strategies and, over time, will likely have some impact on the reduction of ovarian cancer incidence and mortality in the US population. The taking of a family history in the primary care physician office, the identification of high-risk families, and referral for genetic counseling and risk-reducing surgery will save lives.

NOVEL STRATEGIES: USE OF SALPINGECTOMY

Because the majority of high-grade serous cancers have precursor lesions in the fallopian tube, salpingectomy could presumably reduce the incidence of type 2 ovarian cancer. Salpingectomy should have at least the same benefit as bilateral tubal ligation, and on the basis of the proposed etiology of type 1 cancers, there may also be a benefit from salpingectomy for the prevention of some type 1 ovarian cancers.[36] Currently, there are no data showing a reduction in ovarian cancer risk in either the average-risk population or those at inherited high risk; it will take decades to demonstrate a change in mortality from opportunistic salpingectomy, and the proper mechanism for the conduct of such a clinical trial is undergoing international discussion.

Because leaving ovaries in situ has known health benefits related to hormone production, many surgeons routinely leave the ovaries and tubes in situ at the time of hysterectomy. However, there is no known benefit of retaining the fallopian tubes at the time of

hysterectomy.[34,38] Furthermore, women who retain their adnexa after hysterectomy have a risk of future surgery to remove the adnexa; this risk was estimated to be 12% by Morse et al[145] in a Rochester epidemiologic project. Twenty-eight percent of these surgeries were caused by a diagnosis of hydrosalpinx, so salpingectomy at the time of hysterectomy could have prevented those subsequent surgical procedures. Most studies have shown no detrimental effect of salpingectomy on ovarian function or hormonal levels,[38-40,146,147] whereas others have reported a reduction in follicles and increases in follicle-stimulating hormone levels or changes in Doppler blood flow as a result of removing the tubes.[148,149] A recent study by Findley et al[150] found no difference between intraoperative complications and anti-Müllerian hormone levels postoperatively in patients undergoing hysterectomy who were randomized to salpingectomy or hysterectomy alone. Morelli et al[38] performed a retrospective review of 79 patients undergoing total laparoscopic hysterectomy with prophylactic bilateral salpingectomy and a matched-control group of 79 women undergoing total laparoscopic hysterectomy without salpingectomy. They evaluated anti-Müllerian hormone, follicle-stimulating hormone, estradiol, ovarian follicle formation, and ovarian volume as well as Doppler blood flow. No differences between the 2 groups were detected in any of these parameters. In addition, no differences were found in the operative time, change from preoperative to postoperative hemoglobin levels, length of hospital stay, return to normal activity, or surgical complications. In a population-based intervention in British Columbia, McAlpine et al[46] recently showed that there was no increase in adverse outcome with salpingectomy at the time of hysterectomy or instead of tubal ligation. Salpingectomy added only 13 to 16 minutes to the surgical time. Thus, the perioperative risk for women undergoing salpingectomy who are already undergoing hysterectomy or planning permanent tubal sterilization is quite low. In Germany, Dietl et al[34,35] are advocating the removal of fallopian tubes when one is operating on the patient for other conditions.

INTERVAL RISK-REDUCING BILATERAL SALPINGECTOMY UNTIL BILATERAL OOPHORECTOMY IN WOMEN AT HEREDITARY INCREASED RISK

There is proven benefit to RRSO in women with *BRCA1* and *BRCA2* mutations. However, it is important to acknowledge that approximately 30% of women who are known carriers of *BRCA1* and *BRCA2* mutations choose not remove their ovaries, and the mean age at RRSO for those who do is in the late 40s. Some women are unwilling to remove their ovaries in hope of future fertility or to avoid the consequences of premature menopause. In addition, the majority of women who have inherited genetic risk are not identified as high-risk and are, therefore, incorrectly in the average-risk pool.

There have been several recent editorials and opinion articles discussing the potential role of interval salpingectomy after the completion of childbearing followed by later oophorectomy in women with *BRCA1* and *BRCA2* mutations who decline the standard recommendation for RRSO.[36] It is emphasized to the reader that although salpingectomy followed by oophorectomy is intriguing, there are no actual data on risk reduction for ovarian cancer by salpingectomy, and there are clear data that RRSO reduces the risk of both breast and ovarian cancer and improves survival in women with *BRCA1* and *BRCA2* mutations. Salpingectomy followed by oophorectomy should be offered only to those who are unwilling to undergo salpingo-oophorectomy at the recommended age. Walsh et al[64] documented the age distribution of women with ovarian cancer and genetic carrier status, and they found that 10% were under 40 years of age and that 30% were between 40 and 50 years of age; therefore, the appeal of salpingectomy is to allow potential disruption of the pathogenesis of cancer at a younger age. LeBlanc et al[37] has initiated a prospective trial of this approach that they call radical fimbriectomy, with the resection of the tube and the adjacent ovarian capsule where the fimbriae are attached to the ovarian serosa as an extra precaution due to the uncertainty of the location of the precursor cells at the time of the procedure. Kwon et al[44] recently published a Markov model of cost for RRSO versus salpingectomy at the age of 40 years followed by oophorectomy at the age of 50 years. This study showed that both strategies met standard cost-effective criteria, but RRSO was less costly. When quality of life was included, they estimated that salpingectomy followed by oophorectomy was the most cost-effective for quality-adjusted life years. MD Anderson, in collaboration with FORCE (Facing Our Risk of Cancer Empowered), performed a survey of high-risk genetic carriers of *BRCA1* and *BRCA2* genes and found that a third of the 204 participants would be willing to participate in an intervention trial of interval salpingectomy before delayed oophorectomy. The average age of the group was 35 years.[151] To date, no studies have compared the actual impact of bilateral salpingectomy and RRSO on the reduction of ovarian cancer, quality of life, or menopausal symptoms.

It is also important to recognize that women who refuse premenopausal oophorectomy will not get the associated reduction in breast cancer risk. Proponents of salpingectomy for ovarian cancer risk reduction argue that health choices are not one size fits all, and women who prefer to keep their ovaries for quality-of-life reasons can manage breast cancer risk by screening, chemoprevention (tamoxifen), or mastectomy.[113,152-154] Another concern is that women will undergo interval salpingectomy and may never decide to undergo oophorectomy. Although there is conclusive evidence that RRSO reduces ovarian and breast cancer and reduces cancer death and all-cause mortality,[110,112,155] there are no data at this point that quantify these outcomes for a 2-stage procedure of salpingectomy followed by oophorectomy. Therefore, 1-stage RRSO between the ages of 35 and 40 years should remain the standard of care for high-risk women. Prospective trials are needed to determine whether prophylactic salpingectomy is protective and, if so, the magnitude of risk reduction from salpingectomy and delayed oophorectomy versus RRSO.

The technique for salpingectomy is relatively straight forward. In risk-reducing surgery for high-risk patients, peritoneal washings should be taken, and the entire fallopian tube should be removed up to the cornua when the uterus is being preserved. The fimbriae may be adherent to the adjacent ovarian capsule, and this may require excision of the adjacent capsule of the ovary in high-risk patients. The utero-ovarian ligament, the infundibulo-pelvic ligament, and all vascular supply to the ovary should be preserved.[37] For pathology processing, the entire fimbriae should be embedded for microscopic examination in low-risk women, whereas in high-risk women, additional serial sectioning of the entire fallopian tube is required.[21,22] p53 and Ki67 immunohistochemical stains may be used to characterize any subtle changes in high-risk (*BRCA1* and *BRCA2* mutation carrier) patients.

In conclusion, all women deserve to receive the information needed to allow them to make decisions that they believe are in their best interest. This is especially challenging for women at increased risk for breast and ovarian cancer. This document is intended to help facilitate an open dialogue between health care providers and their patients. The following recommendations are based on the previous analysis of the current literature:

1. Women with epithelial ovarian cancer should have individualized genetic counseling followed by elective genetic testing, which should include *BRCA1* and *BRCA2*. Patients' family members can then proceed with testing if indicated and counseling about risk-reducing strategies.
2. Oral contraceptives reduce the risk of ovarian cancer for average-risk women and *BRCA1* and *BRCA2* mutation carriers. Appropriate counseling about side effects and contraindications will allow each patient to weigh the risks and the benefits.
3. RRSO between the ages of 35 and 40 years is recommended for risk reduction in women at increased genetic risk of ovarian cancer. The age of RRSO may also be individualized according to the earliest age of onset in the family and personal choices.
4. Salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years. Women delaying or refusing risk-reducing oophorectomy will not receive the breast cancer risk reduction provided by oophorectomy.
5. Salpingectomy can be considered in average-risk women undergoing hysterectomy, other pelvic surgery, and sterilization at the completion of childbearing.
6. The entire ovary and fallopian tube should be microsectioned, completely embedded, and microscopically examined in women with deleterious mutations in *BRCA1* and *BRCA2* to improve the detection of early tubal and ovarian cancers.[21,22]
7. The fimbria of the fallopian tube in non–high-risk women undergoing routine salpingectomy should be embedded and microscopically examined.
8. Decisions about ovarian cancer risk reduction, including RRSO, need to be made in concert with decisions about mastectomy and breast cancer risk reduction. Referral for consultation for breast cancer prevention such as mastectomy and tamoxifen use is in the best interest of high-risk women. Uterine cancer risk and estrogen replacement plans must be considered by women who wish to retain their uterus.

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