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Ovarian cancer prevention in high risk women

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Abstract

Ovarian carcinoma is the most lethal malignancy of the female genital tract. Population-based trials in the general population have not demonstrated that screening improves early detection or survival. Therefore, application of prevention strategies is vital to improving outcomes from this disease. Surgical prevention reduces risk and prophylactic risk reducing salpingo-oophorectomy (RRSO) is the most effective means to prevent ovarian carcinoma in the high risk patient although the risks do not outweigh the benefits in average risk patients. Other surgical and medical options have unknown or limited efficacy in the high risk patient. In this review, we define the patient at high risk for ovarian cancer, discuss how to identify these women and weigh their available ovarian cancer prevention strategies.

Introduction

In the United States, there were an estimated 22,280 new ovarian cancer cases and 14,240 deaths in 2016 (1). The vast majority of these malignancies are epithelial in origin (as opposed to germ cell or stromal tumors). Screening for epithelial ovarian, fallopian tube and primary peritoneal cancers (collectively termed ovarian cancer) poses several challenges: ovarian cancer is a rare disease affecting 1 in 70 women; until recently, a discernable premalignant lesion has been elusive; and the cost of a false positive screening test in women of reproductive age includes surgical castration and the morbidity associated with premature menopause. A survival benefit for screening women at average risk has not been demonstrated (2, 3). Thus, the U.S. Preventative Task Force recommends against screening for ovarian cancer in women in the general population. This recommendation against screening with CA-125 and transvaginal ultrasound does not apply to women with known

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genetic mutations that increase their risk for ovarian cancer, despite sparse evidence supporting a benefit to ovarian cancer screening in a high risk patient population(4). With a lack of data to support survival benefits from screening, preventative measures are encouraged for women at high risk for the developing ovarian cancer. Surgical removal of the fallopian tubes and ovaries is the recommended prevention strategy for women known to have an increased risk of developing this disease. The morbidity associated with surgical menopause makes identification of the high-risk individuals important for this prevention strategy.

Recent molecular and genetic advances have improved our understanding of ovarian cancer development and progression, allowing for improved identification of women at high risk for developing this malignancy. The histologic heterogeneity of ovarian cancer has long been recognized, but with the emergence of more robust clinico-pathologic, molecular, and genetic data over the past decade these distinctions have become more clearly defined. Type I tumors consist of low-grade serous (LGS), low-grade endometrioid, clear cell carcinomas (CCC), and mucinous carcinomas and are characterized by mutations in *KRAS*, *BRAF*, *PTEN*, *PIK3CA*, *CTNNB1*, *ARID1A*, *PPP2R1A*. Type II ovarian cancers are the most common of the ovarian cancer histotypes, consisting of high-grade serous (70%), high-grade endometrioid, carcinosarcoma, and undifferentiated carcinomas. Type II tumors are defined by *TP53* mutations, which are rare in Type I cancers (5-8). As shown in Table 1, each of these types have distinct risk factors and potential precursor lesions (8).

Defining the patient at high risk of ovarian cancer

As prevention of ovarian cancer often includes surgical intervention, clear definitions of which patients are truly at high risk must precede a prevention strategy. A genetic predisposition to breast or ovarian cancer is the most important known risk for the development of ovarian cancer and 18-24% of ovarian carcinomas may arise in conjunction with a hereditary predisposition (9-14). Germline genetic mutations are far more common amongst Type II ovarian cancers, while endometriosis and hormonal factors predispose to Type I ovarian malignancies, (8, 12, 15). Interactions between environmental, hormonal and genetic factors are likely to impact ovarian cancer risk in an individual patient, but an understanding of the interplay and hierarchy of risk factors is rudimentary at this time.

Germline Genetic Mutations Associated with the Development of Ovarian Cancer

When genetic testing for *BRCA1*, *BRCA2*, and Lynch syndrome first became available in the 1990s, testing was reserved for women affected with gynecologic cancers who had early-onset cancers or suspicious family histories. This recommendation was updated in 2005, when the United States Preventive Services Task force stated that benefits of *BRCA1* and *BRCA2* (*BRCA1/2*) testing outweighed potential harm and “strongly recommended” that genetics services should be offered to at risk individuals, while applying a wider net of eligibility criteria, which would include any woman with a diagnosis of ovarian cancer(16). In 2007, the National Comprehensive Cancer Network (NCCN) guidelines began recommending that all women diagnosed with ovarian cancer receive genetic counseling for *BRCA1/2* mutation testing (17). The rapid integration of Next-Generation Sequencing

(NGS) and multigene testing panels into clinical practice has posed fundamental challenges to the existing process of results disclosure and genetic counseling. For ovarian cancer risk assessment, the paradigm has shifted rapidly from a discussion of *BRCA1/2* mutations whose prevalence, penetrance, and management options have been extensively studied for 20 years, to panels of at least 15 genes whose prevalence, penetrance, and clinical implications are poorly understood (Table 2).

Although the most common genetic mutations predisposing women to ovarian cancer are deleterious germline mutations in the *BRCA1/2* genes, many additional genes that predispose women to ovarian cancer have been identified. Additional low- or moderate-risk associated genes presumably exist, but have yet to be identified. Even when no known genetic risk factors have been identified, patients with strong family histories of breast and ovarian cancer can be diagnosed with “hereditary breast and ovarian syndrome” (HBOS) if the family pattern of malignancy is suspicious enough. The majority of women with a suspected hereditary predisposition based upon personal or family history will not be found to have a known pathogenic mutation(18).

BRCA 1/2—Fifteen to twenty percent of ovarian cancer patients are *BRCA1/2* mutation carriers (13, 19-22). Both genes are tumor suppressors - autosomal dominant inherited genes that encode proteins involved in homologous recombination, a highly accurate double stranded DNA repair mechanism. *BRCA1/2*-induced carcinogenesis result from a “second hit” somatic mutations in the normal allele, leading to loss of BRCA function and subsequent interruption of DNA repair mechanisms via instability in homologous recombination repair (23, 24). A lifetime risk for the development of ovarian cancer for carriers of mutations in the *BRCA1* and *BRCA2* genes is estimated to be between 20–45% and 10–20%, respectively (9, 19, 25).

Although a family history of breast and ovarian cancer is strongly correlated to the detection of a *BRCA1/2* mutation, up to 50% of women with ovarian cancer who test positive for a *BRCA* mutation have no family history of either malignancy, supporting the importance of testing all women with a personal diagnosis of ovarian cancer, regardless of family history (9, 20, 26). Mutation carriers are more likely to be diagnosed with high-grade serous ovarian cancer than other histologic subtypes (11, 22, 26, 27).

Women with *BRCA1*, but not *BRCA2* mutations tend to be diagnosed with ovarian cancer approximately a decade younger than women with ovarian cancer without an identifiable genetic mutation (20, 22, 26). Additional sophistication in risk stratification by type and location of the BRCA mutation is anticipated as estimates of breast and ovarian cancer risks variation by type and location of *BRCA1/2* mutations have been reported(28). Epigenetic alterations in *BRCA* genes may also alter risk associated with the mutation(23). A suggestion that environmental and hormonal factors, such as age at first birth may modify risks associated with *BRCA1/2* mutations has been reported (29). Validation of these specific mutation based risks as well as nomograms that compile and interpret risks are anxiously awaited.

Lynch Syndrome—Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the second most common inheritable cause of epithelial ovarian carcinoma (30-32). Lynch syndrome is an autosomal dominant cancer-susceptibility disease caused by germline mutations in mismatch repair (MMR) genes, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MLH3*, and *PMS2*, and is most commonly associated with colorectal and endometrial cancer. The MMR system works to remove single-strand breaks from DNA by recognizing and correcting short insertions and deletions and single base pair mismatches. When these MMR genes are mutated areas of sequence repeats, microsatellites, can change in size which causes frameshift mutations and DNA instability (31). The overall lifetime risk of ovarian cancer for women with Lynch syndrome is estimated at 8-12% (30-32). In a large study of over 10,000 individuals with Lynch Syndrome the estimated cumulative risk of ovarian cancer by the age of 70 was 24% for *MSH2*, 20% for *MLH1*, and 1% for *MSH6*, suggesting significantly different susceptibility based upon the specific gene mutation(33). In women with Lynch syndrome there is an overrepresentation of Type I non-serous histologies, specifically, endometrioid and clear cell types (34-36).

Rare genetic syndromes—The Li-Fraumeni syndrome is rare autosomal dominant cancer syndrome caused by heterozygous germline mutations in the tumor suppressor gene *TP53* (chromosome 17p13). Half of patients with this syndrome develop a first tumor by age 30, most commonly breast cancer, sarcoma, brain tumors and adrenocortical tumors. Although development of ovarian cancer is uncommon, the median age of women with Li-Fraumeni who develop ovarian cancer is 39.5 years old (37, 38).

Peutz-Jeghers syndrome is primarily attributed to mutations in *STK11/LKB1* and is clinically characterized by gastrointestinal hamartomatous polyposis, mucocutaneous pigmentation. In women with this disorder, there is an increased risk of stromal cell tumors arising from the female genital tract including from the ovary(39).

Other Mutations—Recent advances in Next Generation Sequencing (NGS) have enabled multi-gene panel testing to become increasingly available and inexpensive. Using this technology additional inherited genes implicated in ovarian cancer have been identified (11, 14, 24, 31, 40). Panel testing among a high risk population, will identify pathogenic mutations in moderate or high penetrance genes (other than *BRCA1/2*) in 3.8% of women (41).

The various genes that have been established to have emerging roles related to breast and ovarian cancer risk are detailed in Table 2. The proteins coded for by *RAD51*, *RAD50*, *ATM*, *MRE11* and *PALB2* all interact with *BRCA1/2* in homologous recombination repair. Inherited mutations in these genes are implicated in increased breast and ovarian cancer risk(24). Mutations in *RAD51C* and *RAD51D* are the most common of these genes and found in 1.5-4% and 0.9% of highly penetrant breast and ovarian cancer families conferring a moderate ovarian cancer risk susceptibility (11, 14, 24). In addition, *BRIP1* and *BARD1* have roles in repair of DNA damage checkpoint control and have been shown to correlate with moderate ovarian cancer susceptibility that may warrant their use in routine clinical genetic testing(24, 31). Genes with other biological roles including *SKI1*, *PTEN*, *CDH1* and *NFI* have also been implicated in increased ovarian cancer risk(24). Data on the gene-

specific penetrance and cancer spectrum for most of these variants and mutations is limited and the precise risk of ovarian cancer for an individual carrier of these mutations has not yet been established. Therefore, the clinical implications and risk of ovarian cancer from inherited mutations in these genes (or combinations of these genes) is not yet known, but presumed to be much lower than what is seen in *BRCA1/2* carriers (11, 14).

Non-genetic factors

Endometriosis—Endometriosis is a common estrogen dependent inflammatory disease found in approximately 5-10% of reproductive age women in the United States. Although the majority of women with endometriosis will not develop ovarian cancer, multiple studies have shown an increased risk of Type I ovarian cancer in those women with a history of endometriosis.^{2,19–21} A pooled analysis with over 23,000 women from 13 case-control studies demonstrated an increased risk of invasive epithelial ovarian carcinoma in women with a self-reported history of endometriosis specifically those with clear cell carcinoma (odds ratio 3.05, 95% CI 2.43-3.84), endometrioid (2.04, 95% CI 1.67-2.48), and low grade serous carcinoma (2.11, 95% CI 1.39-3.20). There was no increased risk associated with mucinous or high grade serous carcinoma of the ovary (42).

Molecular evidence that endometriosis is likely a precursor lesion to clear cell carcinoma and endometrioid carcinomas has been described. Mutations in both *PIK3CA* and *ARID1A* have been found in high frequency in clear cell carcinoma and endometrioid carcinomas as well as benign endometriotic lesions in close proximity, suggesting that loss of expression of these genes likely occurs early in the development of endometrioid carcinomas (43, 44).

Hormonal Factors—Multiple hormonal and reproductive factors influence the subsequent risk of epithelial ovarian carcinoma. Supporting a link between hormonal milieu and ovarian cancer, a large meta-analysis of estrogen replacement therapy following hysterectomy in women demonstrated an increased ovarian cancer risk of 22% (95% CI, 18%-27%) per 5 years of use. This risk was not seen when estrogen and progesterone were taken together (45). A protective effect of progesterone in ovarian cancer prevention has been suggested both by animal models as well as the observation of a protective effect from progesterone only oral contraceptive pills (46). Parity, use of oral contraceptives (OCP), and lactation have all been described as protective factors while infertility may increase the risk of developing ovarian carcinoma (15, 47, 48).

Nulliparity is the strongest of the hormonal risk factors for ovarian cancer(47). Pregnancy is characterized by a state of suppressed ovulation, low levels of gonadotropins, and increased levels of circulating estrogens and progesterones, all of which may impact ovarian cancer risk. A 40% risk reduction has been demonstrated after a woman's first birth and an 80% reduction was seen in those women with greater than 5 pregnancies(49). Parity is most protective against the development of endometrioid ovarian cancer (15, 50).

Despite the interaction between nulliparity and ovarian cancer, defining infertility as an independent risk factor for ovarian carcinoma is challenging. An early retrospective cohort study published in the 1980's women found no increased risk of epithelial ovarian carcinoma among 2,335 infertile women(51). Subsequent studies, however, showed a modest increased

risk of ovarian cancer amongst women treated for infertility (41, 47, 52). The association of endometriosis with infertility further complicates estimates of the true risk of ovarian cancer with infertility. An increased risk of ovarian cancer among women with endometriosis as the cause of infertility was first described in 2002 and the published odds ratio was 1.73, (95 % CI: 1.10, 2.71) (53). A Dutch cohort study, the OMEGA study, is unique in its detailed available data on reproductive and hormone-related variables. In this study, the risk of ovarian cancer between women for whom endometriosis was a cause of subfertility (n = 2288) was compared with women who had other causes of subfertility (n = 6616) with a hazard ratio of 4.1 (95% CI 1.6–10.7) (54).

Identifying women at high risk

Improved identification of women with genetic mutations that put them at increased risk for ovarian cancer is crucial to population level prevention. Widely implemented genetic counseling and testing informs individuals of their risk thereby allowing the application of appropriate risk-reduction strategies to reduce ovarian cancer incidence and mortality over time.

Despite recommendations for genetic testing by multiple professional societies, testing rates for women with ovarian cancer remain consistently at 20-30% (55, 56). Cascade testing has been the traditional care delivery model for genetic counselling and identification of additional at-risk patients. When deleterious mutations are identified, blood-relatives of the affected patient are referred for genetic testing limited to the identified mutation. A negative result effectively classifies those at general population risk. Family members with positive results are triaged to risk-reducing strategies. Identified mutation carriers can then enter the “high-risk” pipeline, gaining access to targeted screening, risk-reducing medications and surgeries, and/or clinical trials (17, 57).

There are no specific recommendations for when (at what age) to perform cascade testing. In general testing is not recommended for minors, but it should occur no later than age 35, the earliest age at which risk-reducing surgery for ovarian cancer is recommended. Individuals with a family history of affected individuals under the age of 35 may benefit from earlier testing.

Alternate models of genetic testing

The availability of prophylaxis for individuals at high genetic risk of cancer has prompted exploration of improved methods to identify women at high risk (57). Similar to other medical services, genetic counseling is typically provided using an in-person, labor intensive, service delivery model consisting of new patient consultations and follow-up visits. Both the enhanced integration of genetic counseling into cancer care delivery and workforce shortages of genetic counselors have prompted exploration of alternate delivery models. Two randomized trials have shown that telephone genetic counseling is non-inferior to in-person genetic counseling for hereditary breast and ovarian cancer in areas of knowledge, satisfaction, delivering patient-centered communication, minimizing adverse reactions/distress, and promoting informed decision making (58, 59). An added benefit to telephone counseling is a cost savings due to shorter counseling sessions, less patient travel,

and lower overhead costs (59). Telemedicine (such as videoconferencing) models, referred to as telegenetics has also demonstrated high patient satisfaction, reduced cost and improved access to genetic counselling services (60-62). A demonstration project of online genetic counseling showed this to be effective, feasible and cost-efficient (63).

Referrals for genetic counseling and testing are hindered by various patient-, provider-, and system-level barriers, such as a patient's lack of awareness of her family history, the limited time that providers generally have to collect a family history, and complex and inconsistent referral criteria. Engagement of advocacy groups in the education and support of individuals identified as having an inherited cancer predisposition might complement physician or counselor-led education. Provider education and training on topics related to genetic cancer risk could also be improved. Implementation research to determine improved methods of reaching and testing at-risk individuals for genetic testing as increased access to genetic counseling is a priority.

By focusing on family history and personal cancer diagnosis to select patients for genetic testing, up to 50% of families found to harbor *BRCA1/2* mutations with no known family history of breast or ovarian cancer would have evaded clinical attention prior to a cancer diagnosis (64, 65). A histology-based referral strategy has been suggested in order to gain the maximum yield of high-risk individuals from genetic testing (27). The highest rates of *BRCA1/2* mutations are found amongst women with high grade serous histology (up to 25%) and focused efforts to prioritize this group for referral to testing should be made (22, 26, 27). Genetic testing by the oncology team for women diagnosed with high grade serous ovarian cancer followed by reflex referral to genetic counseling if results are positive has been piloted with high acceptability of patients and providers (66). Increasingly, reflex immunohistochemistry on tumor specimens can streamline histology-based triage to genetic testing. For example, using microsatellite instability (MSI) screening on clear cell and endometrioid ovarian cancers can help to identify those women for whom germline testing for Lynch syndrome mutations is indicated (67).

A universal testing strategy - that *all* women undergo *BRCA* genetic testing after age 30 - has also recently been suggested (68). Decreases in the cost associated with genetic testing have made this approach feasible. Cost-effective universal genetic screening has been modeled successfully among Ashkenazi Jewish women if carriers undergo prophylactic surgery (69, 70). Two reasons make universal genetic testing amongst Ashkenazi Jewish women feasible: the high prevalence of *BRCA1/2* mutations amongst Ashkenazi Jewish women (2.5% compared to the general population prevalence of 0.002-0.006%); and the specificity of testing because the founder mutations in the population are very well-characterized (70). Universal genetic testing in an unselected population remains controversial for several reasons, including the resulting need for more comprehensive testing technologies for screening, which would be expensive, and the identification of variants of unknown significance (71-73).

Surgical prevention for women at high risk of ovarian cancer

For women at high risk of developing epithelial ovarian carcinoma, specifically those with *BRCA1/2* mutations, prophylactic bilateral salpingo-oophorectomy reduces the risk of ovarian cancer. These “previvors” - individuals who are carriers of a predisposition to cancer who haven't yet developed the disease – must be extensively counseled on the risks and benefits of prophylactic surgery. This includes the risk of developing cancer given the mutation present, the degree of cancer prevention, fertility desires, and the effects of surgical menopause (Figure 1).

Thresholds for surgical intervention

Thresholds for surgical intervention for women with non-genetic and low-penetrance risk factors for ovarian cancer need to be weighed and may vary by patient and surgeon. The benefits of ovarian preservation for women at average risk have been described up to age 55 and may extend to women of even older age (74, 75). Careful individualization of counselling and treatment must take into account the patient's personal history of cancer, age, wishes regarding fertility and concomitant medical comorbidities, particularly if considering prophylactic surgery. Often prophylactic surgery might be planned in conjunction with another surgical procedure in order to minimize surgical and anesthetic risk as well as postoperative morbidity. Expert opinion on management recommendations for women with genetic risk of breast and ovarian cancer are summarized in Table 2 (76).

Management of women with variants of unknown significance and pathogenic variants in genes with unknown penetrance is at this time undefined. Without accurate and pertinent data regarding the true risk associated with low penetrance gene mutations, there is potential for misunderstanding and the overuse of prophylactic surgery based upon the knowledge gained from genetic testing. The public awareness and appetite of individuals for access to their own genetic data, in order to inform their own health-related decision-making, is growing and direct-to-consumer genetic testing is increasingly available (73, 77). Patients' perceptions of their cancer risk may be quite different than their actual risk, prompting health decisions and interventions where risks and benefits may be differentially weighed (78, 79).

The presence of variants of uncertain significance should not at this time trigger intervention other than follow-up until the variant is further characterized. A low or moderate risk genetic mutations may justify cancer screening, chemoprevention, and/or even prophylactic surgeries that would not be considered based upon by family history alone. But, screening or prevention strategies could potentially be executed that are out of proportion to the risk, when that risk is of a small magnitude. A small study of 24 patients with variants of unknown significance after *BRCA1* and *BRCA2* testing suggests the potential for inadequate understanding of the results as 10 of the 19 participants who interpreted the unknown variant as pathogenic underwent preventive surgery (79). Additional education for patients and providers as well as guidelines for intervention are needed to provide direction through this deluge of new information.

Risk-reducing salpingo-oophorectomy

For women with known increased genetic risk of ovarian cancer, risk reducing salpingo-oophorectomy (RRSO) is a proven ovarian cancer prevention strategy (80-84). A 2009 meta-analysis including 10 studies demonstrated a greater than 80% reduction in future ovarian cancer following RRSO in high risk women (80). This outpatient procedure can be performed safely laparoscopically with low reported intraoperative and postoperative complications (85). Multiple professional societies endorse prophylactic risk-reducing surgery for these women between the ages of 35-40 or when childbearing is complete (69, 86-88). For *BRCA1* carriers this rationale results from the young median age at diagnosis - *BRCA1* associated ovarian cancer rises in the late 30s to early 40s, and reaches more than 10% by the age of 50 years. Flexibility in the timing of RRSO can be considered for women with *BRCA2* germline mutations for whom the risk of ovarian cancer is 2-3% by the age of 50 (19).

Occult ovarian cancers have been detected in 2-10% of specimens from *BRCA1/2* patients who have undergone RRSO (89-91). When detected at the time of RRSO, women with occult ovarian cancers have 5-year survival rates that are higher than those of women with clinically detected ovarian cancer (83). Given this occult cancer risk and the importance of surgery in ovarian cancer treatment, surgeons who perform these procedures should be comfortable operating in the retroperitoneal space to allow isolation of the ovarian blood supply sufficiently proximal to its insertion into the ovarian hilum. Patients should be counseled during the informed consent process about the potential to identify frank cancer during prophylactic surgery.

This risk reduction provided by RRSO is not complete and annual (0.2% versus 0.1%) and 20-year cumulative (3.9% versus 1.9%) risks of *BRCA1/2*-associated primary peritoneal cancer still exists following the surgery (83). Despite this persistent small risk of malignancy, a reduction in all-cause mortality associated with RRSO among *BRCA* mutation carriers has also been confirmed (82). A decrease in breast cancer risk and breast cancer specific mortality as high as 50% likely contributes to the all-cause mortality reduction from this procedure in *BRCA1/2* mutation carriers (80, 83, 84, 92). In 2015 a prospective study from the Netherlands, which included 822 *BRCA1/2* mutation carriers with a median follow-up of three years, contradicted multiple previous reports by showing no protective effect of oophorectomy on breast cancer risk (hazard ratio = 1.0, 95% CI 0.67 to 1.77). Evolving evidence suggests that the breast cancer risk reduction may be quite different for *BRCA1* compared to *BRCA2* mutation carriers which may partially explain these reported differences. The types of breast cancers that occur in *BRCA1* versus *BRCA2* mutation carriers differ considerably. The majority (75%) of breast cancers associated with *BRCA1* are ER negative, PR negative and HER2 negative; whereas breast cancers among *BRCA2* mutation carriers tend to mirror those of the general population (ER and PR positive, HER2 negative). A recent prospective observational study demonstrated age-adjusted hazard ratio associated with oophorectomy was 0.96 (95% CI = 0.73-1.26) for *BRCA1* and 0.65 (95% CI = 0.37 to 1.16) for *BRCA2* mutation carriers (93). This difference in risk is consistent with the molecular phenotypes of the breast cancers associated with these two genetic abnormalities.

The significant side effects associated with RRSO and subsequent surgical menopause on the previvor must be considered. In pre-menopausal women, oophorectomy increases the risk for cardiovascular morbidity, osteoporosis and endocrine associated symptoms including hot flashes and difficulties with sexual function (94). The long-term effects on overall health and quality of life remain critical questions related to RRSO among *BRCA1/2* mutation carriers. Although many deleterious health effects of menopause do occur amongst *BRCA1/2* mutation carriers following RRSO, they must be balanced against the known cancer prevention afforded by the procedure (95). Symptoms of estrogen withdrawal including vaginal dryness, changes in sexual function and dyspareunia have been demonstrated as prevalent negative side effects for women after RRSO (96-98). Fear of these symptoms can also influence previvors satisfaction with their decision to undergo this risk-reducing procedure (96). For the majority of *BRCA1/2* mutation carriers, the impact on health related quality of life of surgical menopause appears to be outweighed by the cancer risk reduction (97-101).

Hormone replacement therapy can mitigate many of these side effects of menopause. Women undergoing RRSO without hysterectomy may consider using a levonorgestrel-containing intrauterine device so that they can take estrogen replacement without the need for systemic progestin after RRSO (12). Despite the safety of short-term use of estrogen replacement therapy, both previvors and physicians are often wary of its use due to perceived risks of cancer promotion (98, 102, 103). The choice to undergo prophylactic mastectomy may alter this perceived risk. Results of a randomized, prospective trial of hormone replacement in ovarian cancer survivors demonstrating an improved survival with use of hormonal treatment lends additional support to the safety and possibly even of benefit for replacing hormones following oophorectomy (104).

A modern understanding of the fallopian tube – applying opportunistic salpingectomy to the high risk patient?

In 2001, Piek *et al.* first described “dysplastic changes” in the fallopian tubes removed from women with increased risk of developing ovarian carcinoma (105).

Subsequent careful microscopic examination using a newly developed “sectioning and extensively examining of the fimbriated end” protocol (SEE-FIM) of the grossly normal fallopian tubes and ovaries from women with *BRCA1/2* mutations revealed occult tubal cancer and pre-cancers designated as serous tubal intraepithelial carcinoma (STIC). The relationship between STICs and high-grade serous and endometrioid cancers is supported by the ubiquitous presence of *TP53* mutations and their typical location within the fimbriated end of the fallopian tube (5, 8, 106).

Evidence to support the origination of “ovarian” cancer from the fallopian tube include the following; STICs have been seen in approximately 5-15% of women with germline mutations, such as *BRCA 1/2*, that place them at increased risk of developing ovarian carcinomas (89, 107-109); when the fallopian tubes of women with advanced ovarian cancers are closely examined by SEE-FIM, STIC are detected in 50–60% of cases (110); identical *TP53* mutations have been seen in STICs and adjacent high grade serous ovarian carcinomas, which suggests a clonal relationship (111, 112); and the molecular expression

of high grade serous carcinomas more closely resembles that of the fallopian tube than the ovarian surface epithelium (8, 106).

A modern understanding of the fallopian tube as the site of origin for many ovarian cancers, has led to the suggestion that opportunistic salpingectomy could be implemented as a potential cancer prevention strategy in the general population. Scandinavian population based cohort studies have demonstrated a significant decrease in epithelial ovarian cancer following salpingectomy (113, 114). The implementation of opportunistic salpingectomy is feasible amongst women undergoing tubal ligation, hysterectomy or other pelvic surgery (115).

Approximately 30% of women who carry a deleterious mutation in *BRCA1/2* choose not to undergo RRSO or to delay this procedure due to quality of life and health associated risks of premature menopause. Salpingectomy with delayed oophorectomy has been proposed as an alternative to RRSO in order to postpone the onset of premature menopause and its effect on non-cancer menopause-related morbidity and quality of life(116). Modeling of the cost-effectiveness of this approach demonstrated acceptability and a survey of previvors and key stakeholders demonstrated interest and acceptability of this approach (117, 118). Several prospective studies are in various phases of development and patient accrual (119, 120).

Despite the theoretical benefits of salpingectomy with delayed oophorectomy, at this time the safety of this approach has not been adequately studied and this “staged procedure” is not recommended. Concerns about delayed removal of the ovaries are two-fold and include the continued risk of developing ovarian carcinoma from non-tubal tissues as well as lack of breast cancer risk reduction that afforded to *BRCA1/2* mutation carriers by premenopausal oophorectomy (119, 121, 122). These risks may be modified by a patient's specific risks and fears as well as her choice to undergo prophylactic breast surgery. As our understanding of the specific risks of breast versus ovarian cancer associated with specific mutations, methylation patterns and other epigenetic changes evolves, salpingectomy with delayed oophorectomy may become a justifiable choice for select patients (23, 28, 93).

Tubal ligation

Tubal ligation is associated with a decreased risk of ovarian cancer in the general population as well as amongst *BRCA1/2* mutation carriers (113, 123, 124). In the general population opportunistic salpingectomy has gained in popularity as the surgical sterilization method of choice (compared to tubal ligation)(115). As such, tubal ligation no longer has a role in surgical prevention of ovarian cancer in women known to be at high risk for the development of this malignancy.

The role of hysterectomy

Like tubal ligation, the risk of ovarian cancer is decreased following hysterectomy in the general population (113, 123). In women known to be at high risk of ovarian cancer, prophylactic oophorectomy should be encouraged at the time of hysterectomy. Whether hysterectomy should accompany RRSO is a common clinical question. STIC lesions have not been identified in the interstitial portions of the fallopian tubes (the portion left behind within the uterus when RRSO is performed without concomitant hysterectomy), the ovarian

cancer protection afforded with RRSO alone is not thought to be improved upon by removing the uterus. Hysterectomy can, however simplify hormonal therapy in women who will receive tamoxifen for reduction of breast cancer risk or estrogen for menopausal symptoms, since both of these agents are associated with an increased risk of endometrial cancer (12, 18).

Women with Lynch syndrome have an increased risk of endometrial cancer and a hysterectomy should be part of cancer prevention surgery when bilateral salpingo-oophorectomy is performed. In contrast, the role of hysterectomy in uterine cancer prevention in women with *BRCA1/2* mutations is debatable as an increased risk of endometrial cancer has not been consistently demonstrated. Endometrial cancers tend to present with symptoms, leading to an early stage at diagnosis. Hysterectomy increases morbidity associated with the RRSO procedure – many *BRCA1/2* mutation carriers are wary of additional time in the hospital or recovery time after surgery due to multiple competing health care needs.

Although the effect of cancer risk of hysterectomy has been thought to be minimal for *BRCA1/2* mutation carriers, recent evidence linking genetic mutations to high grade endometrial cancer may, over time, lead more women to concurrent hysterectomy with RRSO. Within a cohort of 1083 *BRCA1/2* positive women an increase of serous endometrial cancers with an observed to expected ratio of 22 (95% CI, 6.1-56.9) has been demonstrated. As uterine serous carcinoma is a rare, albeit aggressive, form of uterine malignancy, the small numbers make this result difficult to interpret as only 5 cancers were observed (125).

Medical prevention for women at high risk of ovarian Cancer

Although prophylactic surgery is the most effective means to prevent ovarian cancer in a high risk patients, the risk associated with surgery and the associated premature menopause leads some women to seek alternative risk reduction strategies. For women who have not completed childbearing, medical prevention may provide an active path to cancer prevention until they are ready to undergo RRSO. The heterogeneity of ovarian cancer as well as the historic difficulty in identifying a precursor lesion have made the investigation of chemoprevention models in this disease challenging. Recently, however, potential animal models have emerged that are improving the ability to appropriately study ovarian cancer progression, treatment and chemoprevention (126). Examples include the genetically engineered “mogp-TAg” mouse (expressing the SV40 large T-antigen under the control of the mouse Müllerian-specific Ovgp-1 promoter) (90) and the *Pax8-Cre* driven *Brca/Tp53/Pten* deficient mouse (Cre recombinase driven from the *Pax8* promoter, which is a marker of secretory cell lineage) (127), which develop STICs in the fallopian tube that progress to ovarian cancer; and the laying hen model, which requires no genetic or chemical manipulation to induce ovarian carcinogenesis due to the high rates of spontaneous ovarian cancer in this species including peritoneal metastatic disease and ascites (126).

Oral Contraceptives

The use of oral contraceptives has been associated with a reduced risk of ovarian carcinoma in the general population. This risk reduction appears to persist for up to 30 years after

cessation of OCP use (47, 128). Observational studies have shown associations between the use of oral contraceptives and a reduced risk of ovarian cancer among *BRCA1/2* carriers, with odds ratios suggesting a 40 to 50% reduction in risk (124, 129-131). This risk reduction mirrors that seen in the general population making OCP use an attractive prevention strategy for women at high risk of ovarian cancer who are not yet ready to undergo prophylactic surgery. Although an increased risk of breast cancer with OCPs had been previously postulated, with modern, low dose formulations this does not appear to be relevant (131).

Other hormonal agents

A role for progesterone in ovarian cancer prevention has been suggested by population level studies. When progesterone is added to hormone replacement therapy the increased risk of ovarian cancer from estrogen is mitigated (45). Progesterone-only OCPs have been associated with a reduced risk of ovarian carcinoma supporting the hypothesis that incessant menstruation contributes to ovarian carcinogenesis (47). If this is the case, other contraceptive methods that modify menstrual patterns, such as the levo-norgestral intrauterine devices may also prove beneficial in ovarian cancer risk reduction although at this time evidence is lacking (132). Animal studies have strengthened the evidence of a protective effect of progestins against reproductive tract cancers. In a laying hen ovarian cancer model, birds receiving progestins had significantly fewer reproductive tract cancers (OR, 0.61; CI 0.39–0.95; $P=0.03$). The mechanism of this effect has not been fully explained but appears to be independent of suppression of ovulation (46). The application of this protection to the high risk patient has not yet been explored.

Although Tamoxifen and aromatase inhibitors are suggested as chemopreventative options for women with *BRCA2* mutations to reduce breast cancer risk, there is no known role of either of these agents in ovarian cancer prevention (18).

Non-hormonal medical prevention

A small trial of fenretinide, a synthetic vitamin A analogue, in a high risk patient population suggested a role for this drug in chemoprevention of ovarian cancer (133). A clinical trial studying whether fenretinide can lower breast and ovarian cancer risk in women with *BRCA1/2* mutations completed accrual and results are pending.

Other medical prevention strategies including non-steroidal anti-inflammatory drugs (NSAIDs) are under investigation for women at normal risk of ovarian cancer but whether these will benefit the high risk patient remains to be seen (134). A risk reduction for the development of ovarian cancer for daily users of low-dose aspirin has been observed in the general population in a pooled prospective cohort study as well as in a Danish case-control study (135, 136). The observed risk reduction was most pronounced in the serous subtype – because of the correlation between *BRCA1/2* mutation carriers and serous histology aspirin use in a high risk population has been postulated as a means of reducing risk (134, 135).

Reports that statins may reduce ovarian cancer risk have been mixed. Although a Danish case-control study showed no impact of statin use on ovarian cancer risk, a meta-analysis demonstrated a decrease risk of ovarian cancer with long term use (>5 years) (RR 0.49; 95% CI 0.28-0.80)(137, 138). Preclinical evidence for a possible use of statins as

chemoprevention for high risk patients includes a decrease in STIC formation among mogp-TAg mice with lovastatin administration(139).

Conclusions

Improved understanding of the development of ovarian cancer has accelerated prevention strategies in high risk women and potentially, the general population. Many women have a risk of ovarian cancer that is difficult to define. Known mutations in *BRCA1/2* confer the highest known risk and surgical removal of the tubes and ovaries is recommended in these women. With increased availability of molecular and genetic testing, new low and moderate penetrance genetic abnormalities are being identified and increasing the numbers of women who may be at risk for the development of ovarian cancer. However, decision making has become increasingly complex as technology has advanced more rapidly than our understanding of the clinical consequences of these genetic mutations. Further research is needed to understand the risk of lower penetrance genes, the interactions between genetic and environmental risk and the additive or synergistic risks of multiple risk factors in combination. The long-term clinical effects from the surgical interventions to reduce the development of ovarian cancer as well as an understanding of the clinical outcomes from the genetic and environmental risks are needed to better quantify and individual woman's risk of ovarian cancer. Looking forward, personalization of surgical and medical prophylaxis strategies based upon an individual's risk factors will be possible in order to maximize ovarian cancer prevention and minimize toxicity associated with surgical removal of the ovaries.

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Figure 1.
A Schema for ovarian cancer prevention in the high risk patient.

Table 1
Histologic subtypes of ovarian cancer, molecular genetic changes and precursor lesions

	Type I ovarian cancer				Type II ovarian cancer	
	Clear cell	Endometrioid	Mucinous	Low-grade serous	High-grade serous	
Prevalence of histologic subtype	12%	11%	3%	3%	70%	
Mutations identified	PIK3CA ARID1A PPP2R1A ZNF217	CTNNB-1 PTEN PIK3A ARID1A PPP2P1A	KRAS	KRAS BRAF ERBB2 PIK3CA	P53 BRCA1 BRCA2	
Precursor lesions						
• STIC					X	
• Borderline tumors	X	X	X	X		
• Endometriosis	X	X	X	X		
• Benign ovarian tumors (Brenners tumor, teratoma, etc)				X		

Table 2

Mutations with known and suspected links to ovarian cancer risk and recommended management.

Gene	Role in Genomic Stability	Ovarian Cancer Risk	Recommended Management
<i>ATM</i>	Homologous recombination DNA damage checkpoint control	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>BRCA1</i>	Homologous recombination DNA damage checkpoint control Replication fork stability	20-45% lifetime risk	Recommend RRSO at age 35-40 and upon completion of childbearing
<i>BRCA2</i>	Homologous recombination DNA damage checkpoint control Replication fork stability	10-20% lifetime risk	May consider delaying RRSO until age 40-45 if have already maximized breast cancer risk reduction (bilateral mastectomy) and detailed family history does not show earlier onset ovarian cancer
<i>BRIP1</i>	Homologous recombination	6% risk by age 80	Consider RRSO at age 45-50. Based upon available studies lifetime risk of ovarian cancer appears to be sufficient to justify consideration of RRSO but evidence is insufficient to make a firm recommendation as to optimal age for procedure. Discussion about surgery should be held around 45-50 years of age or earlier based upon specific family history
<i>CDH1</i>	Encodes for a transmembrane glycoprotein involved in calcium-dependent cell-cell adhesion	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>CHECK2</i>	DNA damage checkpoint control	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>MMR Genes: (MSH2, MLH1, MSH6, PMS2, EPCAM)</i>	DNA mismatch repair	Overall lifetime risk for all MMR genes: 8-12% MSH2: 24% risk by age 70 MLH1: 20% risk by age 70 MSH6: 1% risk by age 70	Hysterectomy (given increased risk of endometrial cancer) and BSO once childbearing complete
<i>NBN</i>	Homologous recombination	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>NF1</i>	Encodes GAP neurofibromin which regulates RAS signaling pathway	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>PALB2</i>	Homologous recombination DNA damage checkpoint control	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>PTEN</i>	Phosphatase regulating the PI3K-AKT-mTOR pathway	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery
<i>RAD51C</i>	Homologous recombination	5-15% lifetime risk	Consider RRSO at age 45-50 Based upon available studies lifetime risk of ovarian cancer appears to be sufficient to justify consideration of RRSO but evidence is insufficient to make a firm recommendation as to optimal age for procedure. Discussion about surgery should be held around 45-50 years of age or earlier based upon specific family history
<i>RAD51D</i>	Homologous recombination	5-15% lifetime risk	Consider RRSO at age 45-50 Based upon available studies lifetime risk of ovarian cancer appears to be sufficient to justify consideration of RRSO but evidence is insufficient to make a firm recommendation as to optimal age for procedure. Discussion about surgery should be held around 45-50 years of age or earlier based upon specific family history
<i>STK11</i>	Serine/threonine kinase that targets AMPK pathway involved in cell metabolism, growth and survival	Increased risk of non-epithelial ovarian carcinomas	Insufficient evidence to recommend risk-reducing surgery

Gene	Role in Genomic Stability	Ovarian Cancer Risk	Recommended Management
<i>TP53</i>	DNA damage checkpoint control	Risk not yet quantified	Insufficient evidence to recommend risk-reducing surgery

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