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Basic knowledge for counseling patients undergoing risk-reducing salpingo-oophorectomy

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Significant progress has been made in the molecular diagnosis of cancer. It provides personalized medicine, including cancer diagnosis, prognosis, targeted therapy, and risk detection. These advances allow physicians to identify patients at risk for cancer before it develops and offer them an opportunity to prevent its development. Mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and 2) are one of the most well-known cancer-related gene mutations since actor Angelina Jolie shared her experience with genetic mutations and risk-reducing surgery in the media. In Korea, tests for germline BRCA1/2 mutations have been covered by insurance since May 2012 and the number of women of BRCA1/2 mutations has continued to increase over the past decade. Most carriers of BRCA1/2 mutations consider risk-reducing salpingo-oophorectomy (RRSO) resulting in early menopause and want to know the lifetime risks and benefits of RRSO. However, despite the increasing number of carriers of BRCA1/2 mutations, the counseling and management of patients requiring RRSO varies among physicians. This article provides basic knowledge on RRSO to help physicians comprehensively assess its risks and benefits and manage at-risk women.

Keywords: BRCA mutation; Breast cancer; Epithelial ovarian cancer; Menopause; Risk-reducing salpingo-oophorectomy

Introduction

Disease prevention is of paramount importance for maintaining health. There are three categories of disease prevention: primary prevention, which is practiced before disease occurrence (e.g., regular exercise, healthy diet, and vaccinations); secondary prevention, which is practiced after a disease is diagnosed but before causing morbidity (e.g., early detection of asymptomatic cancer); and tertiary prevention, and which is practiced after some morbidity but intended to prevent further deterioration. Primary and secondary preventions are the cornerstones of avoiding mortality or morbidity due to cancer [1].

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer worldwide, causing an estimated 207,752 deaths in 2020 [2]. In Korea, EOC is the most common cause of gynecological cancer deaths, with 1,349 deaths in 2022, the 5-year survival rate of EOC has not improved substantially from 60% in 2000 to 64.7% in 2020 [3,4]. To improve the survival outcomes of patients with EOC, early detection is important. However, in the absence of an effective screening method, more than 70% of patients are still diagnosed at an advanced stage [5-8].

In the era of precise medicine, genetic testing can identify individuals at a high risk of developing cancer [9]. Pathogenic germline mutations associated with inherited cancer syndromes account for 20% of cases of EOC [10,11]. Mutations in DNA repair pathways, including breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2), predispose women to an increased lifetime risk for EOC and breast cancer (BC) [12]. Therefore, for women with pathogenic germline BRCA1 or BRCA2 (BRCA1/2) mutations,

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prophylactic removal of the ovaries and fallopian tubes (called risk-reducing salpingo-oophorectomy, RRSO) is considered primary prevention, with an estimated cancer risk reduction of up to 95% [13-17]. Currently, RRSO is considered a relatively simple and safe minimally invasive surgical procedure [18]. However, surgical removal of the ovaries results in a sudden onset of permanent menopause, which leads to chronic medical problems, including cardiovascular disease, osteoporosis, and neurocognitive impairment [19].

In Korea, tests for germline BRCA1/2 mutations have been covered by insurance since May 2012, and the number of carriers of BRCA1/2 mutations and those undergoing RRSO has continued to increase over the past decade. However, counseling and management of patients requiring RRSO varies by physician or hospital [20,21]. This article reviews the published research on RRSO and provides clinical guidance to help physicians comprehensively assess the risks and benefits of RRSO and manage at-risk women.

Method

The EMBASE, PubMed, Web of Science, and Cochrane databases up to October 2023 were searched for relevant publications. The comprehensive search strings were "BRCA1", "BRCA2", "epithelial ovarian cancer", "ovarian cancer", "breast cancer", "oophorectomy", "salpingectomy", "risk-reducing salpingo-oophorectomy", "RRSO", "risk-reducing surgery", "hereditary breast ovarian cancer", and "HBOC". Only English language articles were included. Studies were included if the full text was available. The abstracts were reviewed for relevance, and all potentially relevant articles were reviewed for inclusion. Manual searches for other potential studies were conducted using the reference lists of selected articles. Approximately 100 articles were reviewed.

Results

1. How to perform RRSO?

Timely RRSO increases survival in women at high risk of developing EOC [16]. Risk-reducing salpingo-oophorectomy has been performed in 50-78% women with BRCA1/2 mutations [21,22]. Recently, germline BRCA mutation testing has been widely implemented in Korea for patients with breast cancer with a personal or family history suggesting a genetic predisposition, and RRSO is increasingly being offered to women with BRCA mutations [20]. Best practices for RRSO can maximize the prophylactic effect of EOC. Herein, we present the detailed surgical procedure for RRSO by summarizing published guidelines [8,23-25]. 1) Minimally invasive surgery such as laparoscopy is recommended to minimize surgical morbidity. 2) After entering the abdominal cavity, the entire abdomen and the pelvic cavity should be thoroughly examined. If a suspicious lesion is detected, excision and biopsy should be performed. Routine, random omental, or peritoneal biopsies are no longer recommended. 3) Ascitic fluid cytology should be performed. If there are no ascites, peritoneal washing cytology using approximately 50 mL of normal saline should be performed. 4) Surgeons should perform RRSO by opening the peritoneum and dissecting the ovarian vessels in the retroperitoneal space to completely remove the ovaries, thereby avoiding ovarian remnants. 5) Surgeons should remove adhesions, endometriosis, or other inflammatory lesions that may cause incomplete ovarian resection. 6) If a hysterectomy is not performed, the fallopian tubes should be amputated as close to the uterine cornua as possible. And 7) to detect microscopically invasive cancer, the entire ovary and fallopian tubes should be serially sectioned at 2-3 mm intervals and examined by an experienced gynecologic pathologist [26].

2. Who needs RRSO?

1) Carriers of germline BRCA1/2 mutations

BRCA1 and BRCA2 are tumor suppressor genes involved in DNA repair. Loss of BRCA function results in the development of chromosomal instability, leading to cancer [27]. Women with germline BRCA1/2 mutations have a substantially increased lifetime risk for developing certain cancers, including breast, epithelial ovarian, fallopian tube, peritoneal, pancreatic, and prostate cancer [12,27]. They have a 10% to 65% cumulative lifetime risk of EOC (39-65% for women with a BRCA1 and 11-23% for women with a BRCA2) compared to women in the general population who have a lifetime risk of 1-2% [12,28,29].

In Cochrane reviews, RRSO at the recommended age increases survival outcome, including a 68% reduction (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.19-0.54; $P<0.001$) in overall mortality, 94% reduction (HR, 0.06; 95% CI, 0.02-0.17; $I^2=69\%$; $P<0.0001$) in high-grade serous

carcinoma-associated mortality, and 42% reduction (HR, 0.58; 95% CI, 0.39-0.88; I^2=65%; *P*=0.009) in BC-associated mortality. Furthermore, RRSO reduces the risk of EOC (relative risks [RR], 0.17; 95% CI, 0.04-0.75; *P*=0.02) and also reduces BC risk (RR, 0.64; 95% CI, 0.43-0.96; *P*=0.03) [16].

Women with BRCA1/2 mutations account for 10-15% of patients with EOC [30]. RRSO is recommended for women with BRCA1/2 mutations, particularly after childbearing. Because the increased risk of EOC manifests 8-10 years later in those with BRCA2 mutations than in BRCA1 mutations, women with BRCA1 and BRCA2 mutations are advised to undergo RRSO at 35-40 and 40-45 years of age, respectively. However, the age at which RRSO is performed should be adjusted based on family history [31,32].

In Korea, the number of germline BRCA1/2 genetic tests increased 10-fold, from 578 in 2010 to 5,880 in 2017, and 9.2% were diagnosed as carriers of BRCA1/2 mutations. Among carriers of BRCA1/2 mutations, RRSO was performed in 34.6% and 11.9% of patients with and without breast cancer, respectively [20].

2) Other genetic mutations

In addition to the well-established benefits of RRSO in patients with BRCA 1/2 mutations, other mutations increase the risk of EOC and patients benefit from RRSO (Table 1). Mutations in BRCA1- interacting protein C-terminal helicase 1 (BRIP1), RAD51 homolog C (RAD51C), RAD51 paralog D (RAD51D), and mismatch repair (MMR) genes increase the risk of EOC and patients benefit from RRSO for mutation status alone, whereas partner and localizer of BRCA2 (PALB2) and ataxia telangiectasia mutated (ATM) genes increase the risk of EOC in patients with a family history [8,9,31].

BRIP1, RAD51C, and RAD51D are involved in homologous recombination of DNA repair pathways. Several recent studies demonstrate that the BRIP1, RAD51C, and RAD51D genes may be the most important genes for EOC predisposition after BRCA1 and BRCA2 [31,33-35]. Germline mutations in these three genes account for 2% of patients with EOC and they seem to increase the lifetime risk of EOC [36,37]. Mutations in BRIP1 account for 1% of patients with EOC. BRIP1 increases the risk of EOC with estimated RRs of 2.62-11.2, and the cumulative lifetime risk of developing EOC for patients with BRIP1 mutations is 3-4% [31,34]. Mutations in RAD51C and RAD51D are present in 0.4% and 0.6% of patients with EOC, respectively [34]. The lifetime cumulative risk of EOC is estimated to be 4-18% for patients with mutations in both genes, with a recent segregation analysis of families with RAD51C/RAD51D mutations estimating the cumulative risk of EOC to be 11% for RAD51C and 13% for RAD51D [33,34,38]. This risk appears to increase from the baseline risk at approximately 50 years of age in carriers of these three genes. Therefore, carriers of BRIP1, RAD51C, and RAD51D mutations should undergo RRSO between the ages of 45 and 50 years [31].

Table 1. Genetic mutations that benefit from risk-reducing salpingo-oophorectomy

Gene	Life time risk (%)	Age (yr)	Hysterectomy	Breast cancer risk (%)
BRCA1	39-65	35-40	Slightly increased risk of serous carcinoma	>60
BRCA2	11-29	40-45	Not recommended	>60
BRIP1	4-15	45-50	Not recommended	Insufficient data
RAD51C	10-15	45-50	Not recommended	17-30
RAD51D	10-20	45-50	Not recommended	17-30
MSH2	8-38	After child bearing	Recommended	Insufficient data
MLH1	4-20	After child bearing	Recommended	Insufficient data
MSH6	1-13	After child bearing	Recommended	Insufficient data
PMS2	1.3-3	Insufficient evidence	Can be considered	Insufficient data
PALB2	3-5	45-50	Not recommended	41-60
ATM	2-3	Based on family history	Not recommended	20-30

BRCA1, breast cancer susceptibility gene 1; BRCA2, breast cancer susceptibility gene 2; BRIP1, BRCA1 interacting helicase 1; RAD51C, RAD51 homolog C; RAD51D, RAD51 paralog D; MSH2, mutS homolog 2; MLH1, mutL homolog 1; MSH6, mutS homolog 6; PMS2, postmeiotic segregation increased 2; PALB2, partner and localizer of BRCA2; ATM, ataxia telangiectasia mutated.

Other ovarian cancer susceptibility genes include the MMR genes (mutL protein homolog [MLH] 1, MSH2, MSH6, and postmeiotic segregation increased 2 [PMS2]) associated with Lynch syndrome, which predisposes to colorectal and endometrial cancers [31,39]. Estimates of the cumulative lifetime risk of EOC are from 4-20% for MLH1 mutations, 8-38% for MSH2 mutations, and 1-13% for MSH6 mutations [9,31]. The National Comprehensive Cancer Network (NCCN) guidelines recommend RRSO for patients with mutations in these three genes after completion of childbearing, but not earlier than 35-40 years of age [31]. However, the risk is lower for women with PMS2 mutations than for the other MMR genes. Therefore, limited data support RRSO for carriers of PMS2 mutations [31,40].

PALB2 encodes a protein that binds BRCA1/2 at sites of DNA damage, and pathogenic germline variants of PALB2 are found in 0.5% of all patients with EOC [41]. Several recent studies have demonstrated an increased risk of EOC of 1.22-4.4 and a lifetime cumulative risk of EOC of 4.8%, which was estimated to be higher (up to 10%) in those with a significant family history of EOC in carriers of PALB2 mutations [9]. ATM encodes a protein involved in the repair of double-stranded DNA breaks [31]. The cumulative lifetime risk of EOC is 3-4%, which may be higher in people with a significant family history of EOC in ATM mutation carriers [9]. Therefore, the NCCN guidelines recommend RRSO for patient with mutations in these two genes at ages near natural menopause, with a discussion of the risks and benefits based on family history and individual risk factors, not just mutational status [31].

3) Family history of EOC

RRSO should be considered earlier than the recommended age for patients with a significant family history of EOC because several studies have shown that a positive family history may increase the risk of EOC. Therefore, RRSO should be performed 5-10 years before the earliest diagnosis of EOC in patients with a significant family history [9,31].

3. What should the physician consider before and after RRSO?

Premature menopause has been associated with deleterious effects on a woman's health, including decreased quality of life (QoL) and sexual activity, bone loss, cardiovascular disease, cognitive impairment, and increased overall lifetime mortality [42-45]. Given that the recommended age for RRSO is approximately 40 years, most patients undergo RRSO before natural menopause.

Several prospective studies have demonstrated that the short-term health effects of RRSO in premenopausal women reduce QoL compared with those in women with natural menopause, such as vasomotor symptoms, vaginal dryness, sexual dysfunction, and sleep and mood disturbances [46-48]. Although no prospective studies have investigated the long-term health effects of RRSO, there is ample evidence that early menopause due to oophorectomy is associated with osteoporosis, cardiovascular disease, cognitive dysfunction, and increased overall mortality in the general population [49-53].

Women who undergo RRSO typically have a genetic predisposition for development of BC [31]. Hormone replacement therapy (HRT) increases the risk of breast cancer development in postmenopausal women. These two well-publicized findings may lead women with RRSO to hesitate in using HRT [54-56]. However, the clinical scenario in women who undergo surgically induced menopause at a young age is completely different from the results of HRT trials in postmenopausal women. HRT is contraindicated in women with a history of BC, particularly hormone receptor-positive BC [57,58]. However, HRT may be a reasonable option for women who have a BRCA mutation and no history of BC. The prevention and observation of surgical endpoints (PROSE) prospective cohort study followed 462 carriers of BRCA1/2 mutations without a history of BC for an average of 3.6 years to evaluate BC risk with or without HRT. In the PROSE study, RRSO was associated with BC risk reduction (HR, 0.40; 95% CI, 0.18-0.92) and BC risk was not changed by the use of HRT (HR, 0.37; 95% CI, 0.14-0.96) [59]. In addition, several studies have evaluated the effects of HRT on carriers of BRCA1/2 mutations and have shown that estrogen-only HRT does not increase the risk of BC [60-62]. Based on the available data, a 2022 position statement from the North American Menopause Society stated that short-term use of HRT does not increase the risk of BC in a high-risk population without a history of BC, and recommended short-term use of HRT [50].

Surgically induced menopause in premenopausal women entails sudden estrogen deprivation, which leads to more severe menopausal symptoms, including vasomotor symptoms, sleep and mood disorders, and sexual dysfunction than in women with natural menopause. Therefore, HRT is

recommended to be started immediately after RRSO and can continue until age 45 or the natural age of menopause to alleviate menopausal symptoms [19,63]. Hormone replacement therapy using estrogen alone or in combination with progestin improves vasomotor symptoms and sexual discomfort in women with RRSO. Estrogen-only HRT appears to be safer than the combination of progestin and estrogen in this population. For women with surgically induced menopause before 45 years of age high doses of estrogen (oral micronized estradiol 2 mg or conjugated equine estrogen 1.25 mg daily) are required to achieve physiological estrogen levels [55,57,60,62]. However, there has been no research on the effects of HRT on the long-term health of women with RRSO. Given these findings, short-term use of estrogen-only HRT is currently recommended for the women without a uterus, whereas estrogen with intermittent progestin withdrawal therapy every 3 months or a progestin-based intrauterine device should be considered for the women with a uterus to minimize systemic progestin exposure [62,64,65]. Furthermore, decreased androgen levels after RRSO may lead to sexual dysfunction. Several studies have demonstrated that the use of transdermal testosterone, androgen pills, tibolone, or topical estrogen cream may improve sexual discomfort in this population [50].

Hormone replacement therapy seems to be a safe therapeutic option for carriers of BRCA1/2 mutations undergoing RRSO. However, the rate of HRT use after an RRSO for carriers of BRCA mutations varies from 44-71% [54,66]. For carriers of BRCA mutations, the decision to use HRT is complex and should be discussed in detail before RRSO. However, HRT should be recommended for premenopausal women with consideration of their desires, BC or hysterectomy history, severity of their menopausal symptoms, and risk factors for chronic diseases, such as osteoporosis and cardiovascular disease.

4. Why do RRSO?-besides EOC

1) Breast cancer

Most genes that increased the risk of EOC were also associated with an increased risk of BC (Table 1). BRCA1 and BRCA2 mutations account for up to 10% of patients with BC, with a lifetime risks of developing BC of 72% and 69%, respectively [67]. Therefore, several options for the prevention of BC have been recommended for carriers of BRCA mutations, including chemoprophylaxis, routine surveillance, and risk-reducing mastectomy [68].

In the Cochrane review in 2018, BC-related mortality (HR, 0.58; 95% CI, 0.39-0.88; P=0.009) and incidence (HR, 0.45; 95% CI, 0.30-0.67; P<0.0001) were decreased in women with BRCA1 or BRCA2 mutations who underwent RRSO [16]. In addition, Wang et al. [68] reported that carriers of BRCA1 and BRCA2 mutations who underwent RRSO exhibited a reduced risk of BC (HR, 0.63; 95% CI, 0.49-0.81; P<0.01 and HR, 0.51; 95% CI, 0.34-0.75; P<0.01, respectively), and these results are consistently observed in women younger than 50 years who are carriers of BRCA1 mutations (HR, 0.48; 95% CI, 0.30-0.77; P<0.01) and BRCA2 mutation carriers (HR, 0.22; 95% CI, 0.08-0.65; P<0.01). Furthermore, there are several other studies where RRSO performed before the age of natural menopause may decrease the risk of BC from 50-68% in patients with BRCA1 and BRCA2 mutations [32,69-71].

A reduction in circulating estrogen and progesterone levels following RRSO in patients with BRCA mutations decreases the risk of hormone-sensitive BC. Breast cancers in women with BRCA1 mutations are more likely to be hormone receptor-negative as part of a triple-negative phenotype. Women with BRCA2 mutations generally have estrogen or progesterone-receptor-expressing BC [38,72]. Mavaddat et al. [73] reported that RRSO was associated with a substantial reduction in the risk of primary breast cancer in patients with BRCA2 mutations, but RRSO did not appear to reduce the risk of primary breast cancer in patients with BRCA1 mutations alone. In addition, there is supporting preclinical evidence indicating that hormones play an important role in the tumorigenesis of BRCA-related cancers [74-76]. However, patients who underwent RRSO without bilateral mastectomy had an increased risk of developing BC. Women at risk should participate in regular breast screening, including mammography, breast ultrasonography, and breast magnetic resonance imaging, regardless of their previous BC history [20].

2) Serous tubal intraepithelial carcinoma (STIC) and peritoneal carcinomatosis

Even if RRSO is performed to reduce the development of EOC, a 3-4% risk of developing peritoneal carcinomatosis (PC) persists in patients with BRCA mutations [77,78]. For patient with BRCA1 and BRCA2 mutations, the estimated cumulative risks of developing metachronous PC in the 20

years after RRSO were 3.9% and 1.9%, respectively [17].

High-grade serous carcinoma accounts for 70% of EOC and appears to originate from STIC, which occurs in the distal third of the fallopian tube or the fimbria [79]. STIC is found in 0.4-11% of patients with BRCA mutations when RRSO is performed [80-82]. Steenbeek et al. [83] reported that women with STIC at the time of RRSO have an increased risk of developing PC compared to women without STIC (HR, 33.9; 95% CI, 15.6-73.9; $P<0.001$). Furthermore, the 5 and 10-year risks of PC, respectively, are 10.5% and 27.5% for women with STIC compared to 0.3% and 0.9% for women without STIC [83]. STIC is more often diagnosed in women with BRCA1 mutations, and women diagnosed with STIC generally are older than those without (52 years vs. 46 years) [80,81]. Given that STIC is strongly associated with the subsequent development of PC in patients with BRCA mutations, timely RRSO not only reduces the risk of EOC development but also reduces the risk of STIC and subsequent PC [81]. Previous studies have reported a wide range (0.6-18.5%) of the incidence of occult cancers, including STIC, at the time of RRSO. This is probably due to differences in surgical techniques and pathological review protocols [80,84-87]. Through the meticulous surgical-pathological protocol described in this article, the ability to detect early neoplastic changes and occult malignancies can be improved at the time of RRSO.

Despite the strong association between STIC and PC, the pathogenesis of PC after RRSO remains unclear. The European Society for Medical Oncology-European Society of Gynecological Oncology recommends that women with STIC should consider staging surgery to detect PC. Women without STIC have a very low risk of developing PC and require regular close monitoring.

5. What is the role of a hysterectomy?

Women with Lynch syndrome are advised to undergo prophylactic hysterectomy to reduce the risk of developing endometrial cancer [88]. Previous studies have reported that carriers of BRCA1 mutations have an increased risk of developing serous endometrial cancer, which has a poor prognosis [89,90]. Havrilesky et al. [91] reported that concurrent hysterectomy and RRSO are cost-effective and can increase the life expectancy of patients with BRCA1 mutations. However, routine hysterectomy is still not recommended for women with BRCA mutations based on mutation status alone [31].

Progesterone-containing HRT increases the risk of endometrial cancer after RRSO, especially in patients with BRCA1 mutations [92]. Hysterectomy at the time of RRSO allows patients with BRCA mutations without BC history to take estrogen alone, which may be more favorable for BC risk compared to combined progestin and estrogen HRT [44,59,62]. Gordhandas et al. [44] noted that patients receiving tamoxifen may benefit from a hysterectomy to avoid the risk of endometrial cancer. Concurrent hysterectomy and RRSO may simplify HRT or tamoxifen administration; however, hysterectomy is also associated with an increased hospital stay, morbidity, and cost [93]. There is no conclusive answer regarding hysterectomy as a risk-reducing surgery for EOC. However, women with other uterine diseases (such as fibroids, adenomyosis, endometriosis, history of uterine or cervical dysplasia, and uterine or cervical cancer) should have a discussion with their surgeon regarding the relative benefits of concurrent hysterectomy prior to surgery [40,94].

6. Future perspectives

Recently, risk-reducing salpingectomy alone or with delayed oophorectomy has been introduced as an emerging alternative preventive strategy for EOC to delay surgically induced menopause in inherited high-risk groups [95,96]. For patients undergoing interval salpingectomy with delayed oophorectomy (ISDO), salpingectomy is performed after the completion of childbearing, and subsequent oophorectomy is recommended at a maximum delay of 5 years beyond the upper limit of the current guidelines. Ongoing trials related to this are described in Table 2. However, salpingectomy alone or ISDO should not be recommended outside clinical trials, and RRSO remains the treatment of choice for EOC prevention [97,98].

Conclusion

This review article details the candidate genes for RRSO, the risks and benefits of RRSO, recommended surgical approaches for RRSO, and the management of patients before and after RRSO. In addition to the well-known BRCA mutations, mutations in the BRIP1, RAD51C, RAD51D, and MMR genes may increase the risk of EOC. Timely RRSO can reduce the incidence and mortality of EOC in patients harboring mutations in these genes. Moreover, RRSO reduces the incidence

Table 2. Ongoing trials of risk reducing surgery in inherited high-risk patients

Trial	Title	Procedure	Primary outcome	Secondary outcome
NCT02321228	Early salpingectomy (tubectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 gene mutation carriers [95]	ISDO vs. RRSO	Menopause-related QoL	General QoL, surgery-related complications, histologic findings, cardiovascular risk factors, incidence of cardiovascular diseases, incidence of EOC, incidence of breast cancer, and cost effectiveness
NCT02760849	Surgery in preventing ovarian cancer in patients with genetic mutations (WISP-study)	ISDO vs. RRSO	Female sexual function	Menopausal symptoms, QoL, mental health, patient satisfaction, mental health, and occurrence of malignancy
NCT04294927	TUBectomy with delayed oophorectomy as alternative for risk-reducing salpingo-oophorectomy in high-risk women to assess the safety of prevention: TUBA-WISP II study [96]	ISDO vs. RRSO	Ovarian cancer incidence	Incidence of premalignant lesion, peri-operative morbidity, and mortality, and incidence of breast cancer
NCT05287451	Risk-reducing salpingectomy with delayed oophorectomy as an alternative to risk-reducing salpingo-oophorectomy in high risk-women to assess the safety of prevention-United States cohort study	ISDO vs. RRSO	HGSC incidence	Incidence of premalignant lesion, peri-operative morbidity, and mortality, incidence of breast cancer, HGSC incidence after ISDO or RRSO in patient with BRIP1, RAD51C, and RAD51D
NCT01907789	Prophylactic salpingectomy with delayed oophorectomy, risk-reducing salpingo-oophorectomy, and ovarian cancer screening among BRCA mutation carriers: a proof-of-concept study	ISDO vs. RRSO vs. EOC screening	Patient compliance	Incidence of occult malignancy, and type of complications and QoL
NCT04251052	A study to compare two surgical procedures in individuals with BRCA1 mutations to assess reduced risk of ovarian cancer (SOROCk)	ISDO or bilateral salpingectomy vs. RRSO	Time to development of HGSC	QoL, cancer distress, medical decision making, adverse events, estrogen deprivation symptoms, sexual dysfunction, and menopausal symptoms

BRCA, breast cancer susceptibility gene; ISDO, interval salpingectomy with delayed oophorectomy; RRSO, risk-reducing salpingo-oophorectomy; QoL, quality of life; EOC, epithelial ovarian cancer; WISP, women choosing surgical prevention; HGSC, high-grade serous carcinoma; BRIP1, BRCA1 interacting helicase 1; RAD51C, RAD51 homolog C; RAD51, paralog D.

and mortality rates of breast and peritoneal cancers in carriers of BRCA mutations.

HRT should be offered to patients without a history of breast cancer who have undergone RRSO to prevent health problems caused by surgically induced early menopause. Short-term use of estrogen-only HRT is safer than the combined use of progestin and estrogen in patients after RRSO. Prospective studies are required to elucidate the long-term health effects of HRT in patients after RRSO.

Routine hysterectomy is not recommended for women with BRCA mutations based on mutation status alone. However, physicians may consider hysterectomy in patients with other uterine diseases such as symptomatic uterine fibroids.

As previously mentioned, RRSO should be customized for each patient based on cancer history, mutational status, childbearing status, menopausal status, and patient desire. This article provides basic knowledge of RRSO to allow physicians to comprehensively assess its risks and benefits and provide customized management for women at risk.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

Not applicable.

Patient consent

No patient consent is needed for this review article.

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