

Risk-reducing surgery in hereditary gynecological cancer: Clinical applications in Lynch syndrome and hereditary breast and ovarian cancer (Review)

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Abstract. Risk-reducing surgery (RRS) is defined as a prophylactic approach with removal of organs at high risk of developing cancer, which is performed in cases without lesions or absence of clinically significant lesions. Hereditary gynecological cancers for which RRS is performed include hereditary breast and ovarian cancer (HBOC) and Lynch syndrome. For HBOC, RRS in the United States (US) is recommended for women with mutations in the breast cancer susceptibility (*BRCA1*) and *BRCA2* genes and bilateral salpingo-oophorectomy (BSO) is generally performed. This procedure may reduce the risk of breast, ovarian, Fallopian tube and primary peritoneal cancer, although ovarian deficiency symptoms occur postoperatively. For Lynch syndrome, RRS in the US is considered for postmenopausal women or for women who do not desire to bear children and BSO and hysterectomy are usually performed. This approach may reduce the risk of endometrial and ovarian cancer, although ovarian deficiency symptoms also occur. For RRS, there are several issues that must be addressed to reduce the risk of cancer development in patients with HBOC or Lynch syndrome. To the best of our knowledge, this is the first review to discuss RRS with a focus on hereditary gynecological cancer.

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1. Introduction

Hereditary gynecological cancers include ovarian cancer associated with hereditary breast and ovarian cancer (HBOC); endometrial and ovarian cancer associated with Lynch syndrome; endometrial, cervical and ovarian cancer associated with Peutz-Jeghers syndrome; and ovarian cancer associated with Cowden disease. HBOC is an autosomal dominant hereditary disease that may cause breast, ovarian, Fallopian tube and peritoneal cancer.

Mutations of the breast cancer susceptibility (*BRCA1*) and *BRCA2* genes have been identified in ~8-13% of patients with ovarian cancer (1,2). By the age of 70 years, the estimated risks of developing ovarian cancer are 35-60 and 10-27% in *BRCA1* and *BRCA2* mutation carriers, respectively (2). The mean ages at diagnosis of ovarian cancer are 54, 62 and 63 years for *BRCA1* and *BRCA2* mutation carriers and non-carriers, respectively, indicating that *BRCA1* mutation carriers are more likely to be affected by ovarian cancer at a younger age (3). Clinicopathologically, the majority of ovarian cancers that are *BRCA1/2* mutation-positive are of serous histology and are poorly differentiated (grade 3) stage III-IV tumors, according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria, as defined in 1988 (4,5). In *BRCA1/2* mutation-positive and -negative cases, the rates of serous adenocarcinoma are 63-86 and 57-58%, those of poorly differentiated tumors 68-87 and 48-58% and those of stage III-IV tumors 72-88 and 62-70%, respectively.

Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer, is an autosomal dominant hereditary disease that may lead to colorectal, endometrial, gastric and ovarian cancer. Lynch syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes, which include mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), *MSH3*, *MSH6*, postmeiotic segregation increased 1 (*PMS1*) and *PMS2*. High mutation rates of *MLH1*, *MSH2*, or *MSH6* have been

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identified in Lynch syndrome (6), with 50% of women in families with Lynch syndrome carrying a *MLH1* mutation, 39% a *MSH2* mutation and 7% a *MSH6* mutation. The majority of the cases of endometrial cancer associated with Lynch syndrome have germline mutations of *MSH6* and *MLH1* (7). However, Lynch syndrome may also occur without a pathogenic mutation in MMR genes (8) and may instead be due to an epimutation in the promoter region of *MLH1* or *MSH2*, with different levels among family members and tissues (9). For patients with MMR gene mutations, the estimated risk of developing endometrial, colorectal and ovarian cancer at the age of 70 years is 42-60, 30-54 and 12%, respectively (10,11). Compared to sporadic endometrial cancer, the histological characteristics of endometrial cancer in Lynch syndrome include a lower rate of endometrioid tumors (86.0 vs. 97.6%) that are more often found in FIGO stage I-II disease (88.0 vs. 73.8%) (12) and are more commonly surface epithelial stromal tumors (95.9 vs. 83.6%), including endometrioid (18.3 vs. 9.6%) and clear cell tumors (18.3 vs. 3.6%) (13).

Genetic tests may be used to determine whether an individual is at high risk of developing cancer; however, screening methods for ovarian cancer and Lynch syndrome have not been established. Therefore, risk-reducing surgery (RRS) may be an important approach to such cases. RRS was originally defined as an operation performed in cases without lesions or absence of clinically significant lesions to remove organs at high risk of developing cancer, for the purpose of reducing the mortality risk from cancer or from the side effects of treatment. The benefits of RRS for gynecological cancers associated with Peutz-Jeghers syndrome or Cowden disease have not been investigated. In this review, we examined the conditions for performing RRS for HBOC and Lynch syndrome, the methods and outcomes of surgery, postoperative management and the current status of RRS for these diseases worldwide.

2. Indications for RRS

The indications for RRS in HBOC are summarized in the guidelines published by the National Comprehensive Cancer Network (NCCN) (14). Due to the absence of a reliable method for early detection and the poor prognosis associated with advanced ovarian cancer, these guidelines recommend 'risk-reducing bilateral salpingo-oophorectomy (RRSO) for women with known *BRCA1/2* mutations, ideally aged 35-40 years and upon completion of child bearing or at an individualized age based on earliest age of ovarian cancer diagnosed in the family' (14). Since 95% [95% confidence interval (CI): 0-16%] of women in hereditary breast cancer families, including patients with ovarian cancer, carry *BRCA* mutations (15), the majority of women in such families are eligible for RRS. King *et al* (16) observed that the risk of developing ovarian and breast cancer at the age of 40, 50 and 60 years was 3, 21 and 40%, respectively, in *BRCA1* mutation carriers and 2, 2 and 6%, respectively, in *BRCA2* mutation carriers; they also reported that the risk of developing breast cancer at these ages was 21, 39 and 58%, respectively, in *BRCA1* mutation carriers and 17, 34 and 48%, respectively, in *BRCA2* mutation carriers. Finch *et al* (17) reported that the prevalence of occult carcinoma was 1.5% for *BRCA1* mutation carriers who underwent oophorectomy at <40 years of age and 3.8%

for women who underwent surgery between 40 and 49 years. This led to the recommendation that *BRCA1* mutation carriers should undergo RRSO by the age of 35 years. Finch *et al* (17) also observed that the rate of diagnosis of ovarian cancer was 4.0% if a *BRCA1* mutation carrier chose to delay RRSO until the age of 40 years and that this rate increased to 14.2% with a delay until the age of 50 years.

Regarding the indications for women without gene mutations in hereditary breast cancer families, the Breast Cancer Linkage Consortium in 1998 collected data on 237 families, each with ≥ 4 cases of breast cancer diagnosed by the age of 60 years (15). A case of ovarian cancer was found to be associated with mutations of *BRCA1* or *BRCA2* in 90% of the families. These results indicated that a woman in a family with at least 1 case of ovarian cancer should be managed in a manner similar to women with *BRCA1/2* mutations. In a study of 165 *BRCA* mutation-negative hereditary breast cancer families at the Memorial Sloan-Kettering Cancer Center (18), the risk of breast cancer in women in these families was 3.13 (95% CI: 1.88-4.89) compared to that in the general population. However, those families did not exhibit a significantly increased risk for ovarian cancer. This suggests that RRSO for the prevention of ovarian cancer may be unnecessary in patients with *BRCA* mutation-negative hereditary breast cancer.

The NCCN guidelines also include an indication for RRS in Lynch syndrome and state that 'when postmenopausal or not desiring to bear children, total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO) should be considered' (19). In patients with Lynch syndrome, Schmeler *et al* (20) found that the median age at diagnosis of endometrial and ovarian cancer was 46 and 42 years, respectively, with diagnosis at ≥ 35 years in 94 and 83% of the cases, respectively. These findings suggested that the more appropriate indication for RRS is 'a woman aged 35 years or older not desiring to bear children, or a postmenopausal woman with suspected Lynch syndrome from family history or known DNA mismatch repair gene mutation' (21). Moreover, since endometrial cancer in Lynch syndrome is mainly detected at an early stage (12), treatment initiated following early detection may be curative (22). Therefore, further studies are required to elucidate the appropriate indications for RRS (23). Of note, performing an RRSO in Japan requires approval from an Ethics Committee, as symptoms have not yet developed; in addition, the patient must have sufficient financial resources, as RRSO is not covered by public health insurance in Japan (24).

3. Techniques of RRS

RRS performed in HBOC is basically BSO. The benefits of laparoscopic RRSO are reduced invasiveness, a lower rate of postoperative complications and a shorter median hospital stay compared to laparotomy, although laparoscopy may be converted to laparotomy in case of a major intraoperative complication, such as adhesion or perforation (25). Over the last few years, laparoscopic single-port RRSO has been introduced and this procedure has the advantage of further decreased invasiveness compared to conventional laparoscopy (26). Occult cancers are detected at a frequency of 1-4% in cases in which RRSO is performed; thus, both the ovaries and Fallopian tubes should be removed (27,28). In HBOC, the

risk for developing endometrial cancer in *BRCA1* mutation carriers is 2.6-fold higher compared to that in non-carriers (29) and the relative risk for endometrial cancer is 11.6 following tamoxifen treatment in *BRCA1/2* mutation carriers (30). Since the uterus is non-functional following BSO, a hysterectomy should be performed at the same time as BSO (31). However, with regard to prevention of malignant transformation, the incidence of gynecological malignancies was not found to differ significantly between women who did and those who did not undergo hysterectomy with BSO (2.8 vs. 0%) (32). Based on those results, the benefits and risk of simultaneous hysterectomy must be discussed with the patient prior to RRSO.

The NCCN guidelines state that the RRS performed in Lynch syndrome is TAH/BSO (19); however, laparoscopic assisted vaginal hysterectomy (LAVH) and BSO are also occasionally performed (30). Care must be taken when performing LAVH due to the higher risk of injuring the urinary tract during this procedure (odds ratio = 3.13; 95% CI: 1.06-9.28) compared to abdominal hysterectomy (33). Among women with Lynch syndrome, 13% are diagnosed with endometrial/ovarian cancer and colon cancer synchronously or metachronously (20): endometrial/ovarian cancer is diagnosed first in 41-43%, endometrial and ovarian cancer are diagnosed synchronously in 7-14% and colon cancer is diagnosed first in 42-51% of the cases (20,34). If colon cancer is diagnosed first, the next tumor to develop is endometrial and ovarian cancer in 84 and 14% of the cases, respectively (34). Based on those results, RRS following initial diagnosis of colon cancer may prevent the onset of endometrial or ovarian cancer (20). Thus, in patients with Lynch syndrome, TAH/BSO may be performed at the same time as surgery for colon cancer (32).

4. Effects of RRS

Over a mean follow-up of 24.2 months following RRSO for HBOC, the hazard ratio for breast or gynecological cancers, such as ovarian, Fallopian tube and primary peritoneal cancer, was found to be 0.25 (95% CI: 0.08-0.74) (28). A meta-analysis of 10 studies on the efficacy of RRSO reported hazard ratios of 0.21 (95% CI: 0.12-0.39) for onset of ovarian and Fallopian tube cancer and 0.49 (95% CI: 0.37-0.65) for onset of breast cancer, indicating that the risk of developing these cancers was reduced following RRSO (35). Over a mean follow-up period of 3 years, the overall mortality was also found to be reduced in patients who underwent RRSO compared to those who did not (3 vs. 10%, respectively) (36). Finch *et al* (17) observed 5,783 women with a *BRCA1* or *BRCA2* mutation prospectively for an average of 5.6 years and reported hazard ratios for all-cause mortality following RRSO of 0.30 (95% CI: 0.24-0.38) and 0.33 (95% CI: 0.22-0.50) for *BRCA1* and *BRCA2* mutation carriers, respectively.

In patients with Lynch syndrome, Schmeler *et al* (20) observed a significantly decreased incidence of endometrial cancer over a mean follow-up period of 13.3 years following RRS compared to that over a follow-up of 7.4 years in non-RRS patients (0.000 vs. 0.045 per woman-year; $P < 0.001$). For ovarian cancer, the incidence did not differ significantly in a follow-up of 11.2 years following RRS compared to that in a follow-up of 10.6 years in non-RRS patients (0.000 vs. 0.005 per woman-year; $P = 0.09$). Those results indicated that RRS

significantly reduced the risk of endometrial cancer in Lynch syndrome, but did not affect the risk of ovarian cancer. In a study of RRS at the age 30 years for women with Lynch syndrome with an annual gynecological examination, Chen *et al* (37) observed that surgical management increased survival by 2.5 years. When comparing RRS with annual screening (transvaginal ultrasound + endometrial biopsy + measuring serum CA125 levels), it was estimated that 75 surgeries were required to save one life and that 28 and 6 RRS procedures were required to prevent one case of ovarian cancer and endometrial cancer, respectively (37).

5. Complications and surveillance following RRS

There are few complications associated with RRSO for HBOC. Kauff *et al* (28) reported complications in 4 of 98 women following RRSO, including 1 case each of infection; perforation of the bladder, from which the patient recovered in 5 days; distal obstruction of the small bowel, which developed 8 weeks following RRSO; and perforation of the uterus by a uterine manipulator. All these events were caused by BSO alone and no complications occurred in the 11 women who underwent hysterectomy at the time of RRSO. Postoperative follow-up commonly includes bone densitometry with dual-energy X-ray absorptiometry, yearly CA125 serum testing and yearly pelvic examination; however, there is no consensus on the optimal approach and standardized postoperative methods for follow-up are required (38). Tumors may develop following RRSO, with a particular residual risk of breast, ovarian and Fallopian tube cancer (35). The cumulative incidence of primary peritoneal cancer has been estimated to be 4.3% at 20 years following RRSO, including 4 of 7 women who succumbed to their disease, with an average survival of 3 years (39). A mean of 5.3 years had elapsed between RRSO and cancer diagnosis (median, 3 years). Finch *et al* (17) estimated the risk of peritoneal cancer in the 20 years following RRSO to be 3.9% for *BRCA1* and 1.9% for *BRCA2* mutation carriers. A proportion of these cases were metastases of subclinical disease present at the time of surgery and, thus, the authors recommended earlier RRSO to prevent peritoneal cancer.

Complications of TAH/BSO in Lynch syndrome are also rare. Schmeler *et al* (20) reported only one case of ureteral injury following creation of a Hartmann pouch, together with a ureterovaginal fistula and a ureteroenteral fistula to the pouch. The common complications associated with hysterectomy and BSO are bleeding, infection and injuries to the urinary tract and bowel, with complication rates of 1-9% associated with hysterectomy and BSO for benign conditions (20). There is no report of follow-up after RRS in Lynch syndrome; however, surveillance for patients with Lynch syndrome with or without RRS is recommended as follows (40): For colorectal cancer, lower gastrointestinal endoscopy should be performed every 1-2 years with removal of precancerous polyps, beginning at 20-25 years, or at an age 10 years younger compared to the youngest age of diagnosis in the family; for gynecological diseases, annual cytology and histological examinations of the endometrium, transvaginal ultrasound and serum CA125 measurement are recommended; and for urinary system diseases, routine urinalysis with cytology should be performed. Recurrence of endometrial and ovarian cancer has not been

reported following RRS in Lynch syndrome (20). Primary peritoneal cancer has been reported following hysterectomy and BSO in 2 patients with Lynch syndrome (41); however, in those cases the procedures were performed following occurrence of benign disease and endometrial cancer, respectively; thus, no case of primary peritoneal cancer following RRS has been reported. In a study of 223 patients with Lynch syndrome, a digestive system tumor developed after the initial diagnosis of endometrial cancer and ovarian cancer in 46 and 6 cases, respectively (34); however, no case with a digestive system tumor following RRS has been reported.

BSO is commonly performed in RRS for HBOC as well as Lynch syndrome. Ovarian deficiency symptoms may develop and they present a major concern, particularly in premenopausal women (24). These symptoms begin with vasomotor effects and mood disorders caused by menopausal symptoms and lead to atrophic vaginitis, incontinence, osteoporosis, dyslipidemia and associated arteriosclerotic diseases. Therapeutic methods for ovarian failure syndrome include hormone replacement therapies (HRTs), such as estrogen therapy (ET) and estrogen/progesterone therapy (EPT) (42). Bone density should be measured within 1 year following surgery to evaluate the risk of osteoporosis; risk factors for cardiovascular diseases, such as hypercholesterolemia, hypertension, diabetes mellitus and smoking history, should also be evaluated (43).

The side effects of HRT include endometrial, breast and ovarian cancer and ET has been found to cause endometrial cancer with a relative risk of 2.3 (95% CI: 2.1-2.5) with estrogen use compared to non-use (44). However, in a study in which patients were randomly assigned to ET or placebo following hysterectomy for stage I or II endometrial cancer, with or without lymph node dissection, the recurrence rates were 1.9% in the placebo and 2.3% in the ET group, whereas mortality was 0.6% in the placebo and 0.8% in the ET group (45). Based on those results, ET may be administered in stage I or II endometrial cancer under careful observation. EPT does not increase the risk of endometrial cancer, with a relative risk of 0.71 (95% CI: 0.56-0.90) compared to non-HRT patients (46). Therefore, the preferred regimen in these patients is EPT, comprising 0.625 mg of conjugated estrogen daily and 5-10 mg of medroxyprogesterone acetate for ≥ 10 days over 28 days (47). However, EPT may increase the risk of breast cancer and HRT in patients with breast cancer may induce tumor cell proliferation; therefore, its use is contraindicated (24). In a study with a follow-up of 11 years, an increased risk of breast cancer was found with EPT, but not with ET (48), with hazard ratios of 1.25 (95% CI: 1.07-1.46) with EPT and 0.77 (95% CI: 0.62-0.95) with ET. Eden (49) demonstrated that ET did not increase the risk of breast cancer for at least 7-10 years. A study with a short-term follow-up of 3.6 years following RRSO in women with a *BRCA1/2* mutation demonstrated that HRT did not significantly increase breast cancer risk compared to that in non-HRT patients, with a hazard ratio of 1.35 (95% CI: 0.16-11.58) (50). In *BRCA1* mutation carriers, the hazard ratios for breast cancer risk are 0.63 (95% CI: 0.34-1.16) within 3 years after HRT and 0.51 (95% CI: 0.24-1.08) at >3 years after HRT. These results indicate that ET or EPT may reduce breast cancer risk compared to no HRT (51). The hazard ratio for ET was 0.51 (95% CI: 0.27-0.98) and that for EPT was 0.66 (95% CI: 0.34-1.27).

In patients with Lynch syndrome, the risk of developing breast cancer was reportedly 4-fold higher compared to that of sporadic breast cancer (52), although a variation of breast cancer risk following HRT has not been reported. However, in postmenopausal women following hysterectomy, the hazard ratio for breast cancer was found to be 0.77 (95% CI: 0.59-1.01) with HRT compared to placebo (42). Selective estrogen receptor modulator (SERM) treatment reduces the risk of breast cancer by 65% compared to no HRT (53) and the risk of endometrial hyperplasia has been found not to differ between combination therapy with ≥ 20 mg/day bazedoxifene, a third-generation SERM, and 0.625 mg/day conjugated estrogen for 1 year, compared to placebo (54). These results indicated that HRT using a combined regimen may be used without risk of increased breast and endometrial cancer. In patients with HBOC who cannot undergo HRT, selective serotonin reuptake inhibitors or serotonin noradrenaline reuptake inhibitors may be used to improve vasomotor symptoms (55) (Table I).

Pearce *et al* (56) reported that the relative risk (hazard ratio) of developing ovarian cancer was 1.22 (95% CI: 1.18-1.27) with ET and 1.10 (95% CI: 1.04-1.16) with EPT, but remained significantly increased compared to non-users. By contrast, Lacey *et al* (57) observed a risk of developing ovarian cancer of 1.89 (95% CI: 1.22-2.95) with ET for >10 years and a relative risk of 3.09 (95% CI: 1.68-5.68) for EPT therapy with progestin used sequentially (progestin for <15 days per cycle) for >5 years. Those findings led to the conclusion that EPT was significantly associated with the development of ovarian cancer and to a more significant extent compared to ET (57). However, another study reported that ET was associated with a significant relative risk of 2.07 (95% CI: 1.50-2.85), whereas EPT had a relative (and non-significant) risk of 1.18 (95% CI: 0.79-1.76) (58). Therefore, there is currently no consensus on whether ET or EPT is better for reducing the risk of ovarian cancer.

6. Current status of RRS worldwide

The status of RRSO differs in Asia compared to Europe and the United States (US). Miller *et al* (59) reported that the percentage of carriers of *BRCA1/2* mutations who underwent RRSO ranged between 10 and 78% in Europe and the US, but that the overwhelming majority of women were satisfied with their decision to undergo the surgery (86.4-97%). Factors positively associated with undergoing RRSO included demographic variables, such as age, having had children and educational level; medical variables, including family history of ovarian cancer, personal history of ovarian cancer and previous risk-reducing mastectomy; and psychosocial variables, including beliefs, higher perceived ovarian cancer risk and increased cancer-related distress. Regarding costs, in the US, the rate of prophylactic oophorectomy covered by health insurance was 18% in women with an ovarian cancer family history and 20% in women with a known *BRCA* mutation (60). Anderson *et al* (61) reported that the cost of RRSO was 118,605 and 116,213 US\$ per *BRCA1* and *BRCA2* mutation carrier, respectively, which were lower compared to the respective screening costs of 135,858 and 124,016 US\$. The quality-adjusted life years (QALYs) following RRSO were 18.39 and 17.69 in *BRCA1* and *BRCA2* mutation carriers,

Table I. RRS for HBOC and Lynch syndrome.

Postoperative considerations	HBOC	Lynch syndrome
Surgical complications	Infection Perforation of the bladder Distal obstruction of the small bowel Perforation of the uterus	Ureteral injury Ureterovaginal fistula Ureteroenteral fistula
Treatment of ovarian deficiency symptoms	20 mg/day bazedoxifene + 0.625 mg/day conjugated estrogen, as HRT reduces the risk of breast cancer and endometrial cancer. In cases with breast cancer, an SSRI or SNRI is initiated.	20 mg/day bazedoxifene + 0.625 mg/day conjugated estrogen, as HRT reduces risk of breast and endometrial cancers
Postoperative management	No consensus Bone densitometry Annual measurement of serum CA125 level Annual internal examination Any of the above may be combined	No information. As follow-up for Lynch syndrome with or without RRS, the following are recommended: Lower gastrointestinal endoscopy every 1-2 years and removal of precancerous polyps Annual cytology and histological examination of the endometrium, transvaginal ultrasound and serum CA125 level measurements Routine urinalysis with cytology
Postoperative occurrence of tumors	Breast cancer Ovarian cancer Fallopian tube cancer Primary peritoneal cancer	No information

HBOC, hereditary breast and ovarian cancer; HRT, hormone replacement therapy; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; RRS, risk-reducing surgery.

respectively and QALYs with screening were only 15.64 and 16.42, respectively. Those results indicated that, in patients with HBOC, RRSO is cost-effective compared to annual screening.

Yurgelun *et al* (62) reported that 21-65% of patients with Lynch syndrome selected RRS. The percentage of women who were satisfied with their decision to undergo this type of surgery was not reported. Total hysterectomy and BSO performed as RRS in Lynch syndrome had a cost of 23,422 US\$ per case and the QALY value was 25.71, while annual screening cost 68,392 US\$, with a QALY value of 25.17 and annual examinations cost 100,484 US\$, with a QALY value of 24.60. Those results suggested that RRS in Lynch syndrome is highly cost-effective compared to the other methods.

The findings of Miller *et al* (59) and Yurgelun *et al* (62) clearly support RRS as an option for patients in Europe and the US. By contrast, the number of studies on Asian patients is limited. In Japan, RRS has rarely been performed in HBOC or Lynch syndrome. In 2005, a woman in an HBOC family who did not desire *BRCA1/2* genetic diagnosis underwent RRSO at the Cancer Institute Hospital in Tokyo (63). Reports of RRSO in patients with HBOC include a case at Keio University Hospital in 2008 (24) and a case at the Cancer Institute Hospital in 2011 (64). In Lynch syndrome, modified radical hysterectomy and BSO were performed as an early intervention at the stage of atypical endometrial hyperplasia in a case at Keio University Hospital in 2011 (65). In that case, a woman

aged 46 years with an *MLH1* mutation, who wanted to bear children, did not undergo surgery after endometrial hyperplasia was found in initial screening, but underwent surgery following a histological examination that detected complex endometrial hyperplasia with atypia. RRS is not common in Japan, due to the limited number of genetic counseling units and facilities that perform *BRCA1/2* genetic tests, the lack of coverage of RRS for HBOC and Lynch syndrome by the health insurance system and insufficient knowledge and experience of medical staff regarding genetic diagnosis (24). In China, 12 patients with *BRCA* mutations were treated with RRSO (66), but RRS for Lynch syndrome has not yet been reported. In Asia, RRS is most common in Korea, based on a study on RRSO in 21 patients with HBOC (67).

7. Conclusions

RRS may reduce the risk of ovarian and breast cancer in patients with HBOC and the risk of endometrial and ovarian cancer in patients with Lynch syndrome. The benefits of RRS are a lower rate of complications and higher cost-effectiveness compared to annual screening and routine examinations. However, ovarian deficiency symptoms occur postoperatively and tumors may still develop following surgery. Thus, RRS for patients with HBOC or Lynch syndrome should be performed only after informed consent is obtained, following detailed explanation of the benefits and concerns. There are several

problems associated with RRS that require further investigation, including the indications for Lynch syndrome, whether hysterectomy should be combined with RRSO and follow-up measures after surgery. Addressing these issues is expected to make RRS more common and reduce the risk of cancer development in patients with HBOC or Lynch syndrome.

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