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# Risk-Reducing Surgeries in Gynecological Cancers: A Review of the Current State

# Jinekolojik Kanserlerde Risk Azaltıcı Cerrahiler: Güncel Duruma Bakış

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## Abstract

Risk-reducing surgery has an important role to play in the prevention of gynecological cancers, particularly in women who are at high risk of these cancers. Risk-reducing bilateral salpingo-oophorectomy (rrBSO) has been shown to significantly reduce the risk of ovarian and fallopian tube cancers and all-cause mortality in women with BRCA1/2 mutations. Combined prophylactic hysterectomy and bilateral salpingo-oophorectomy is recommended for patients with Lynch syndrome and has been shown to reduce the risk of endometrial and ovarian cancer. Although long-term data are needed, opportunistic salpingectomy is considered to be an effective method of reducing the risk of epithelial ovarian cancer. Based on genetic mutations and individual risk factors, risk-reducing surgery for gynecological cancers is an important component of personalised treatment plans. The aim of this review is to provide a comprehensive analysis of the different surgical strategies associated with BRCA1/2 mutations, Lynch syndrome and other hereditary conditions. It evaluates the role and potential benefits of surgical interventions such as risk-reducing bilateral salpingo-oophorectomy (rrBSO), prophylactic hysterectomy and opportunistic salpingectomy in clinical practice, and asses their efficacy and feasibility.

**Keywords:** Risk-reducing surgery, endometrial cancer, bilateral salpingo-oophorectomy, hereditary cancer syndromes, ovarian cancer

## Özet

Risk azaltıcı cerrahi, özellikle yüksek risk altındaki kadınlarda jinekolojik kanserlerin önlenmesinde önemli bir rol oynamaktadır. Risk azaltıcı bilateral salpingo-ooferektomi (rrBSO), BRCA1/2 mutasyonları taşıyan kadınlarda over ve fallop tüpü kanserlerine bağlı mortalite riskini anlamlı şekilde azaltmaktadır. Lynch sendromu olan hastalarda kombine profilaktik histerektomi ve bilateral salpingo-ooferektomi önerilmektedir ve bu yaklaşımın endometriyal ve over kanseri riskini azalttığı gösterilmiştir. Uzun dönem verilerine ihtiyaç duyulmasına rağmen, fırsatçı salpenjektomi, epitelyal over kanseri riskini azaltmada etkili bir yöntem olarak değerlendirilmektedir. Genetik mutasyonlar ve bireysel risk faktörlerine dayanarak, jinekolojik kanserler için risk azaltıcı cerrahi, kişiselleştirilmiş tedavi planlarının önemli bir bileşeni olarak kabul edilmektedir. Bu derleme, BRCA1/2 mutasyonları, Lynch sendromu ve diğer kalıtsal durumlarla ilişkili çeşitli cerrahi stratejileri kapsamlı bir şekilde analiz etmeyi amaçlamaktadır. rrBSO, profilaktik histerektomi ve fırsatçı salpenjektomi gibi cerrahi müdahalelerin etkinliğini ve uygulanabilirliğini değerlendirerek, bu prosedürlerin klinik pratikteki rolünü ve potansiyel yararlarını incelemeyi amaçlamaktadır.

**Anahtar Kelimeler:** Risk azaltıcı cerrahi, endometriyum kanseri, bilateral salpingo-ooferektomi, kalıtsal kanser sendromları, yumurtalık kanseri

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## 1. Introduction

Significant advances have been made in cancer screening, prevention and treatment, but gynecological cancers remain a major global health challenge. According to GLOBOCAN 2022 data, cervical cancer is the second most common cancer worldwide, while endometrial cancer ranks 6th and ovarian cancer ranks 7th.[1] Although modern gynecological cancer screening programmes are effective in cancer prevention, the prevalence of hereditary cancers remains a major concern. Technological advances and comprehensive data from the Human Genome Atlas Project highlight the continued risk of gynecological cancers in patients with hereditary predisposition.[2] Based on the evaluation of family history, genetic counselling and individualised risk analysis in cases of suspected individual risk are current and evolving approaches to cancer prevention.[3] Tailored risk-reduction strategies are gaining in importance and continuing to evolve in cancer prevention. For gynecological cancers, risk-reduction approaches include medical, surgical and lifestyle modifications. The use of oral contraceptives, breastfeeding and a healthy lifestyle can reduce the risk of cancer. However, for women at high risk, the main treatment option is risk-reducing surgery.[4]

The term "risk-reducing" has replaced "prophylactic" in current usage because even surgical procedures such as salpingo-oophorectomy cannot completely prevent peritoneal cancer in women with BRCA1-2 mutations. Choosing risk-reducing surgical options is a complex decision involving ethical considerations, quality of life, patients' fertility wishes, preferences for medical treatment, the increased risk of gynecological malignancies with delayed surgery, the potential risks of surgery and the side effects of drugs.[5]

This review aims to analyse the current state of risk-reducing surgical practices for gynecological cancers, including risk-reducing bilateral salpingo-oophorectomy (rrBSO), prophylactic hysterectomy and opportunistic salpingectomy, and to assess their effectiveness in preventing hereditary cancer.

## 2. BRCA Mutations and Risk-Reducing Bilateral Salpingo-Oophorectomy

The BRCA1 and BRCA2 tumor suppressor genes play a critical role in the homologous recombination repair (HRR) of double-stranded DNA breaks. Hereditary breast and ovarian cancers associated with pathogenic variants of the BRCA1/2 are characterised by an autosomal dominant inheritance pattern. These genetic mutations significantly increase susceptibility to breast and ovarian cancer, often at a younger age than sporadic tumors. In the general population, the prevalence of carriers of BRCA1/2 mutations is estimated to be between 1 in 500 and 1 in 800.[6] BRCA1 and BRCA2 mutated women have an increased overall risk of developing 22 different types of cancer. The risk is much higher for women with a BRCA1 mutation, with a cumulative lifetime risk of 72% for breast cancer and 44% for ovarian cancer. However, women with a BRCA2 mutation have a cumulative lifetime risk of 69% for breast cancer and 17% for ovarian cancer.[7]

Risk-reducing bilateral salpingo-oophorectomy (rrBSO) is used to reduce the risk of developing epithelial cancer of the ovaries and fallopian tubes in patients with hereditary cancer syndrome. A 2014 meta-analysis showed that rrBSO in BRCA1/2 carriers reduced the risk of ovarian cancer by 80% (risk ratio [RR] 0.19, 95% CI 0.13-0.27) and all-cause mortality by 68% (RR 0.32, 95% CI 0.27-0.38).[8]

The risk for ovarian cancer in women with BRCA 1 mutations increases substantially from age 35, with 2-3% developing ovarian cancer by age 40, and the average age at diagnosis is 50. The increased risk of ovarian cancer increases significantly from the age of 35, with 2-3% developing ovarian cancer by the age of 40, with an average age of diagnosis of 50, a decade later, with an average age of diagnosis of 60, similar to the general population, as BRCA2s tend to present with ovarian cancer 8-10 years after the onset of symptoms compared to BRCA1s.[9-11] Therefore, international guidelines recommend rrBSO for women with known or likely pathogenic BRCA1/2 variants, typically between the ages of 35 and 40.[12] In the context of women who test positive for pathogenic or likely pathogenic BRCA2 variants, it may be reasonable to delay rrBSO until the age of 40-45, as their risk of ovarian cancer tends to develop later. However, if family history indicates an earlier age of diagnosis, it may be necessary to consider this prophylactic surgery earlier.[13,14] Patients should be referred to a gynecological oncologist for discussion of this surgery, and specific protocols have been recommended for pathological review and follow-up of abnormal findings.

Alternative approaches such as risk-reducing salpingectomy followed by delayed oophorectomy have been considered because of concerns about the risks of bone and heart disease following surgical menopause after oophorectomy, and the challenges of managing hormone replacement therapy (HRT). This strategy is being considered because of the potential tubal origin of ovarian cancer, the presence of serous tubal intraepithelial carcinoma (STIC) in risk-reducing surgery, and the role of endosalpingiosis in female pelvic serous tumors.[15] If salpingectomy is omitted, it is unclear whether the surgeon can completely remove the fimbriated end of the fallopian tube, as the surface of the ovary and the mesovarium may harbor tubal epithelium, which may be a potential source of epithelial ovarian cancer. Furthermore, the function of the ovaries and the potential benefits of ovarian salvage may be reduced because the bipolar cautery device used for salpingectomy may inadvertently damage the ovarian cortex and collateral vessels.[16] The development of stage 4 ovarian cancer in patients with BRCA mutations who have undergone salpingectomy has been reported in population-based studies.[17] However, it is known that new ovarian neoplasms can develop not only after salpingectomy but also after rrSO. The clinical practice statement from the Society of Gynaecologic Oncology (SGO) states that salpingectomy may be an appropriate and achievable strategy to reduce the risk of ovarian cancer, but emphasises that further studies are needed to determine the safety of this practice.[18] For this reason, the National Comprehensive Cancer Network (NCCN) guidelines state salpingectomy alone is not the usual treatment. With regard to the ongoing trials of salpingectomy, the analysis of effectiveness in terms of risk reduction is a long-term assessment. The completion dates for these trials are beyond 2030.[19]

Thorough examination of the abdomen (including the liver, diaphragm, omentum, appendix, bowel, and paracolic ducts), pelvis (including the uterus, ovaries, fallopian tubes, and posterior pelvic cavity) and the entire peritoneum is essential in performing rrBSO. To ensure that no ovarian cells remain on the peritoneal surface, if adhesions are present between peritoneal structures during rrBSO, all adhesions together with the ovary must be resected.[20] The aim should be to remove as much of the fallopian tube as possible. Special care should be taken to ensure that the fimbriae are completely removed.[21] Complete removal of the fallopian tube is recommended, although the interstitium is usually left after rrBSO and there are no documented cases reported of malignant transformation from this part.[22]

The literature shows that occult gynecological neoplasia, including both invasive neoplasia and epithelial lesions, has been found in 4.5% to 9% of cases with a pathogenic BRCA1/2 variant who have undergone rigorous pathological evaluation of the ovaries and fallopian tubes by rrBSO.[23] Occult disease is more likely to be diagnosed in women with a BRCA1 mutation, at a rate of 4.2%, compared with a rate of 0.6% in women with a BRCA2 mutation.[24] Peritoneal carcinomatosis should be considered as a phenotypic variant of ovarian cancer. Women undergoing rrBSO are still at risk of developing this malignancy, with an incidence of approximately 1.7%.[25] There is a lack of evidence on the optimal surveillance methods for peritoneal cancer after rrBSO. However, patients can be followed for up to 10 years using a combination of annual pelvic examinations, transvaginal ultrasound and serum CA 125 testing. STIC was identified in 5% to 8% of women with BRCA1/2 variants undergoing rrBSO. The incidence and significance of these early lesions in the general population remains to be clarified, as STIC has been identified in individuals who have undergone surgery for risk reduction or other gynecological reasons.[26]

Historically, rrBSO has been shown to have an approximately 50% reduction in breast cancer risk in patients with BRCA1/2 mutations.[27] However, some prospective studies in the literature suggest that this effect may not be present. [28] Consequently, there is evidence that rrBSO may also have a beneficial effect on the risk of breast cancer in premenopausal women.

The SEE-FIM (Sectioning and Extensively Examining the Fımbriated End) protocol is highly recommended for patients undergoing risk-reducing salpingo-oophorectomy (rrBSO) because of its effectiveness in detecting early malignancy. This detailed evaluation of the fallopian tubes, particularly the fimbriated end, is critical for those with BRCA1/2 mutations or other high-risk profiles. The implementation of the SEE-FIM protocol in rrBSO procedures will improve the detection of pre-cancerous lesions such as serous tubal intraepithelial carcinoma (STIC), ensuring early intervention and better outcomes for the patient. [29]

The SEE-FIM protocol involves serial sectioning of the fallopian tubes at 2-3 mm intervals, with particular attention to the fimbriated end. Microscopic precancerous lesions, such as STIC, can be identified through this meticulous examination. The implementation of the SEE-FIM protocol in rrBSO procedures improves the detection of these precancerous lesions. This allows for early intervention and better patient outcomes.[30]

In addition to BRCA1/2, many other genes are now known to contribute to the development of breast and ovarian cancer. These genes include PALB2, MSH2, CDH1, BARD1, NF1, BRIP1, RAD51D, STK11, CHEK2, ATM, MSH6, PMS2, MLH1, EPCAM, and RAD51C. The efficacy of rrBSO in individuals with these gene mutations is also being investigated. Recommendations for rrBSO based on genetic analysis are given in Table 1. This includes genes for which rrBSO is recommended, as well as those for which rrBSO is not recommended alone, but should be considered in conjunction with family history for risk analysis and decision making.

### 3. Opportunistic Risk-Reducing Surgery

Opportunistic salpingectomy (OS) is the prophylactic removal of the fallopian tubes during pelvic surgery in patients with an average risk of developing epithelial cancer of the ovaries, fallopian tubes or peritoneum. Retrospective studies have consistently shown that tubal ligation reduces the risk of developing epithelial ovarian cancer, particularly endometrioid and clear cell histotypes, possibly by preventing the passage of endometriotic or endosalpingiotic cells.[31] A meta-analysis of three trials with an average follow-up of 18 to 36 years evaluated the effect of bilateral salpingectomy on the prevention of epithelial ovarian cancer (EOC). Patients who underwent prophylactic bilateral salpingectomy were almost 50% less likely to develop EOC than those who did not undergo salpingectomy (odds ratio 0.51, 95% CI 0.35 to 0.75). The absolute rate of EOC was similar in both groups, 0.8% for salpingectomy and 0.7% for no salpingectomy.[32] The evaluation of the role of OS in the prevention of epithelial ovarian cancer requires a large number of patients to undergo OS for primary prevention, with long follow-up periods to observe a reduction in the incidence of ovarian cancer below the expected norms. Opportunistic salpingectomy for primary prevention of ovarian cancer can be recommended in patients who are seeking surgical sterilisation or planning to undergo hysterectomy for other reasons, based on retrospective data. Patients should be informed that spontaneous pregnancy is not possible after bilateral salpingectomy and that the procedure is irreversible.[33]

### 4. Prophylactic Uterine Surgery

A significant association between BRCA mutations and endometrial cancer has been demonstrated in recent studies, with 4.3% of women with endometrial cancer carrying BRCA mutations.[33] A large cohort study of families with BRCA1/2 mutations showed a 2.83-fold increased risk of any endometrial cancer and a 9.77-fold increased risk of serous endometrial cancer compared with the general population.[34]

Prophylactic hysterectomy is therefore a consideration and can be performed by laparotomy, laparoscopy or transvaginal approaches, often in conjunction with rrSO. A population-based Australian study showed that hysterectomy combined with rrSO significantly reduced all-cause mortality (Hazard Ratio (HR) .69; 95% CI .53 to .89; p<0.005), particularly in premenopausal women (HR .45; 95% CI .25 to .79; p<0.006), and breast cancer-specific mortality (HR .43; 95% CI .24 to .79; p<0.006).[35] However, the current evidence is not sufficient to make a general recommendation for prophylactic hysterectomy alone for the prevention of serous endometrial cancer in women with a BRCA mutation. Further trials and long-term data are needed to establish definitive guidelines.

Lynch syndrome, the most common cause of hereditary colorectal cancer (CRC), significantly increases the risk of other malignancies, including endometrial and ovarian tumors. Therefore, prophylactic hysterectomy combined with bilateral salpingo-oophorectomy (BSO) is recommended.[36] There is strong evidence in support of this recommendation. A large prospective cohort study of 315 patients with Lynch syndrome found that none of the patients undergoing prophylactic hysterectomies had endometrial cancer, whereas the rate was 33%. In addition, none of the patients who underwent BSO developed ovarian cancer, compared with an incidence of 5% in the control group.[37] The American College of Obstetrics and Gynaecology, the SGO and the American College of Gastrointestinal Surgeons recommend 40 to 45 years, while the American Society of Clinical Oncology and the European Society for Medical Oncology recommend 35 years.[38-41] NCCN guidelines recommend that total hysterectomy be considered based on individual factors such as desire to have children, comorbid conditions, family history, and genetic mutations, but do not specify a specific age.[42]

Risk-reducing surgery for gynecological cancers can be performed laparoscopically, robotically, abdominally or vaginally. The choice of the most appropriate approach should be an individual one, with consideration of the patient's specific circumstances, and should be discussed in detail with the patient. Minimally invasive techniques, such as laparoscopic and robotic surgery, are preferable for patients who meet the relevant criteria. They tend to offer advantages such as shorter recovery times and lower complication rates. To ensure optimal outcomes, it is important to tailor the surgical approach to each individual patient.

### 5. Conclusion

In the prevention of gynecological cancers, risk-reducing surgeries play a crucial role for high-risk patients, particularly in reducing the incidence of fallopian tube, peritoneal, ovarian, and endometrial cancers. For BRCA1 mutation carriers, risk-reducing bilateral salpingo-oophorectomy (rrBSO) is recommended between the ages of 35-40, and for BRCA2 mutation carriers, between the ages of 40-45. Following these surgical interventions, the onset of early menopause and associated side effects should be considered, and hormone replacement therapy (HRT) should be carefully planned, taking individual risk factors into account. Additionally, other surgical approaches, such as opportunistic salpingectomy, have shown potential benefits in reducing the risk of epithelial ovarian cancer; however, further data are needed to confirm their long-term efficacy.

For individuals with Lynch syndrome mutations, prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) are recommended after childbearing is complete, typically after the age of 35-40. These surgical interventions significantly reduce the risk of endometrial and ovarian cancers.

It is also essential to provide genetic counseling services for patients at high risk for hereditary cancers, ensuring that personalized risk reduction strategies are developed based on the results of genetic testing.

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