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BRCA1 ve BRCA2 Mutasyonlu Hastalarda Risk Azaltıcı Bilateral Salpingo-Ooferektomi

Risk-Reducing Bilateral Salpingo-Oophorectomy in Patients With BRCA1 and BRCA2 Mutations

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ÖZET

Amaç: BRCA1/BRCA2 mutasyonu olan kadınlar meme ve jinekolojik kanserler için yüksek risk altındadır. Bu çalışmanın amacı, risk azaltıcı salpingo-ooferektomi (RRSO) uygulanan BRCA mutasyon taşıyıcıları olan hastalarda klinik ve cerrahi sonuçları değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışma Kartal Dr. Lütfi Kırdar Şehir Hastanesi'nde 2012-2022 yılları arasında yapıldı. Profilaktik RRSO uygulanan BRCA1/BRCA2 mutasyonlu hastaların tıbbi kayıtları incelendi. Sosyodemografik özellikler, klinik özellikler, histopatolojik bulgular ve cerrahi veriler toplandı.

Bulgular: 10 yıllık süre içinde BRCA mutasyonları olan (7 BRCA1 ve 4 BRCA2) toplam 11 hasta tespit edildi. Genetik danışma sonrasında tüm hastalara RRSO uygulandı. Yedi BRCA1 taşıyıcısından birine yüksek dereceli seröz yumurtalık kanseri teşhisi kondu. Bu hastalardan sekizinde meme kanseri öyküsü vardı. Kalan bir BRCA mutasyon taşıyıcısına RRSO uygulandı, ancak profilaktik mastektomi yapılmadı.

Sonuçlar: Bulgularımız, BRCA1 veya 2 mutasyon taşıyıcılarının yaşam boyu meme ve yumurtalık kanseri geliştirme riskinin arttığını desteklemektedir. Meme ve jinekolojik kanserlerin önlenmesi için profesyonel genetik danışmanlık, gözetim ve risk azaltıcı bilateral mastektomi ve RRSO'dan BRCA mutasyon taşıyıcılarına verilmesi büyük önem taşımaktadır.

ABSTRACT

Aim: Women with mutations in BRCA1/BRCA2 are at increased risk for breast and gynecologic cancers. The aim of the study to evaluate the clinical and surgical outcomes in patients with BRCA mutation carriers undergoing risk-reducing salpingo-oophorectomy (RRSO).

Methods: This retrospective observational study was conducted at Kartal Dr. Lütfi Kırdar City Hospital, between 2012 and 2022. The medical records of patients with BRCA1/BRCA2 mutations who had undergone prophylactic RRSO, were reviewed. The socio-demographic characteristics, clinical features, histopathological findings and surgical data were collected.

Results: A total of eleven patients with deleterious mutations (7 BRCA1 and 4 BRCA2) were identified during 10-year period. Following genetic counselling, all patients underwent RRSO. One of seven BRCA1 carriers were diagnosed with high grade serous ovarian carcinoma. Of these patients, eight had history of breast cancer. The remaining one BRCA mutation carriers underwent RRSO, but did not undergo prophylactic mastectomy.

Conclusions: Our findings support that BRCA1 or 2 mutation carriers have an increased lifetime risk of developing breast and ovarian cancer. For the prevention of breast and gynecological cancers, it is of great importance to provide professional genetic counseling, surveillance, and risk-reducing bilateral mastectomy and RRSO to BRCA mutation carriers.

Keywords: BRCA1, BRCA2, BRCA mutation carriers, breast cancer, risk-reducing surgery, risk-reducing oophorectomy, risk-reducing mastectomy, ovarian cancer

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Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in women, in general (1). About 70% of women with ovarian cancer are diagnosed with metastatic or locally advanced disease (stages III and IV), with five-year survival rates of nearly 30%. Despite high response rates to chemotherapy in early-stage disease, approximately 80% of women with advanced-stage disease relapse within two years of initial treatment (2).

The most important risk factor for the development of ovarian cancer is the family history of breast or ovarian cancer, especially in two or more first-degree relatives (3). Mutations in DNA repair pathways and BRCA 1/2 genes predispose to an increased risk of breast and ovarian cancer. Women harboring inherited germline mutations have a higher lifetime risk of developing ovarian cancer (15-56%) and breast cancer (45-80%) compared to the general population (4). However, some studies have shown that the risk of developing ovarian cancer is different in those with BRCA1 mutations (45-60%) and BRCA2 mutations (11-35%) (4).

RRSO in women with BRCA 1/2 mutations may reduce the risk of ovarian cancer and breast cancer, and related mortality (5). The indication for RRSO should take into account several factors, including the patient's age, current and desired parity, and current risk of malignancy development (6). The National Comprehensive Cancer Network (NCCN) guideline recommends RRSO in BRCA1 mutation carriers between the ages of 35-40 and for those with BRCA2 mutation carriers between the ages of 40-45 (6). The risk of occult malignancy in these patients is between 2% and 10% at the time of risk-reducing salpingo-oophorectomy and lesions are often microscopic (7).

The aim of this study is to evaluate the clinical and surgical outcomes of patients with BRCA 1/2 mutations who underwent prophylactic salpingo-oophorectomy in our clinic.

Methods

The medical records of women who were referred to the outpatient clinic of the Department of Gynecologic Oncology at Kartal Dr. Lütfi Kırdar City Hospital between 2012 and 2022 as BRCA 1/2 mutation carriers were retrospectively analyzed. Ethical approval was obtained by the Research Ethics Committee (Approval number: 2022/514/228/36, 30.06.2022).

Women who had BRCA 1 or BRCA germline mutations, had undergone RRSO, and had complete data were included in the study. Those who had missing data were excluded from the final analysis. Medical records were reviewed for age, marital status, parity, comorbidities, body mass index (BMI), type of BRCA mutation, personal and family history of cancer, previous risk-reducing mastectomy, surgical data, histopathologic results, postoperative hormone replacement therapy (HRT).

Gynecological examinations were performed in each woman diagnosed with BRCA germline mutations. In addition, all women were evaluated by cervical cytology, transvaginal ultrasonography (TVUSG), and CA 125 test. All patients received genetic counseling from the department of medical genetics and medical oncology. After obtaining an informed consent form, RRSO was performed by laparoscopy or laparotomy. Although endometrial sampling is not routinely performed in all patients, histological examination of endometrial samples was performed to exclude concurrent endometrial pathology after the surgery.

Results

A total of eleven BRCA mutation carriers were included in the study. Of the patients with BRCA mutations, seven had BRCA1 mutations and had BRCA2 mutations. The mean age of the study sample was 39.0±2.6 years. Two of eleven women were nullipara. Of those, seven women had a family history of breast cancer, three had a family history of breast and ovarian cancer, and further analysis revealed a BRCA1 mutation. In all patients, no pathological findings were detected in the preoperative ultrasonographic examination. Characteristics of the study sample are shown in Table 1.

Abdominal hysterectomy + bilateral salpingo-oophorectomy was performed in six patients, laparoscopic hysterectomy + bilateral salpingo-oophorectomy in four patients, and laparoscopic bilateral salpingo-oophorectomy in one patient. Ten of the eleven patients underwent a prophylactic mastectomy. Yet, one patient with no history of breast cancer did not prefer a prophylactic mastectomy.

Gynecologic malignancy was not detected in nine (9/11;81.8%) patients. Of the eleven patients, one patient (1/11; 9%) with a BRCA1 mutation was diagnosed with borderline serous ovarian cancer, and one patient (1/11; 9%) with a BRCA1 mutation was diagnosed with a high-grade serous ovarian cancer.

Among patients with BRCA mutations, four of eleven had an elevated preoperative CA125 level. Of those, one patient with an elevated CA125 level (85 u/mL; normal range: 0-35 u/mL) was diagnosed with high-grade serous ovarian cancer and one patient (48 u/mL; normal range: 0-35 u/mL) was diagnosed with a borderline ovarian cancer.

Table 1 • Participant characteristics

ID	Age	Parity	Carrier status	Personal history of BC	Number of relatives with OC	Number of relatives with BC	Gynecological surgery	Ovarian pathology
ID-1	41	3	BRCA1	1	0	1FDR	TAH+BSO	Benign
ID-2	40	2	BRCA1	1	1FDR 1SDR	0	TLH+BSO	High-grade serous ovarian cancer
ID-3	38	0	BRCA1	1	0	1FDR	TLH+BSO	Borderline serous ovarian cancer
ID-4	43	4	BRCA2	1	1FDR	1SDR	TAH+BSO	Benign
ID-5	42	1	BRCA1	1	0	0	TAH+BSO	Benign
ID-6	37	1	BRCA1	0	1FDR	1FDR	L/S BSO	Benign
ID-7	35	3	BRCA2	1	0	1SDR	TAH+BSO	Benign
ID-8	41	3	BRCA2	1	0	0	TAH+BSO	Benign
ID-9	37	0	BRCA1	1	0	1FDR	TAH+BSO	Benign
ID-10	39	2	BRCA2	1	0	0	TLH+BSO	Benign
ID-11	36	2	BRCA1	0	1SDR	2FDR	TLH+BSO	Benign

BC, breast cancer; FDR, first degree relative; OC, ovarian cancer; SDR, second degree relative; TAH+BSO, total abdominal hysterectomy bilateral salpingoophorectomy; TLH+BSO, total laparoscopic hysterectomy bilateral salpingoophorectomy; L/S BSO, laparoscopic bilateral salpingoophorectomy

None of the patients receive post-surgical hormone replacement therapy.

Discussion

The last two decades have seen a growing trend towards the utilization of BRCA1/2 mutation due to reduced cost, increased numbers of laboratories offering BRCA1/BRCA2 sequence testing, and studies showing the clinical benefit of reporting mutation status before surgery (8). An overwhelming body of evidence accumulated over tens of years recognizes the effectiveness of risk-reducing mastectomy and risk-reducing salpingo-oophorectomy in patients with BRCA mutations (9). Since Angelina Jolie announced her BRCA mutation test result and her preference for conservative surgery in 2013, genetic testing and prophylactic surgery have been attracting a lot of interest (10).

BRCA1/2 mutation in the study population was evaluated in accordance with NCCN BRCA1/2 genetic test selection criteria (6). In our research, BRCA1/BRCA2 mutation analyses were performed because eight patients under the age of 45 years were diagnosed with breast cancer and three patients had a strong family history of breast or ovarian cancer.

Prophylactic mastectomy can reduce the risk of developing breast cancer by 90 percent, but these procedures are considered "aggressive" by many women (11). In our research, a patient with a BRCA1 mutation accepted RRSO after genetic counseling, but unwilling to accept prophylactic mastectomy. Cosmetic concerns and early detection of breast cancer may have an effect in patient's decision about declining the surgical treatment of breast cancer. On the other hand, women preferred to undergo RRSO, despite the menopausal effects. This might be explained by the difficulty of detecting ovarian cancer and its poor prognosis.

BRCA1/2 mutation-associated ovarian cancers are mostly diagnosed at an advanced stage, and high-grade serous adenocarcinoma is the most common histology (12). In our research, the option of RRSO was explained to a 38-year-old patient who was diagnosed with breast cancer and BRCA 1 mutation. However, the RRSO was delayed until the age of 40 years due to the patient's fertility desire. Preoperative workup showed that the patient had elevated CA125 levels and a normal ultrasonographic examination. Subsequently, the final histopathological result revealed high-grade serous ovarian cancer.

In contrast to serous ovarian cancer, mucinous and borderline histology have not shown BRCA mutations (13). In our research, risk-reducing mastectomy and RRSO were planned for a 38-year-old patient with BRCA 1 mutation. In the preoperative examination, TVUSG was normal but CA125 levels were elevated. The final pathology resulted in borderline ovarian cancer. It can be concluded that in BRCA mutation carriers, the most effective strategy to reduce the risk of developing breast and ovarian cancer is bilateral salpingo-oophorectomy with or without risk-reducing mastectomy.

Much uncertainty still exists about the necessity of performing a hysterectomy along with a risk-reducing oophorectomy (14). Hysterectomy combined with RRSO may simplify future hormonal therapy to reduce breast cancer risk or relieve menopausal symptoms, as tamoxifen and estrogen replacements are associated with an increased risk of endometrial cancer (14-15). However, the risks of hysterectomy should be borne in mind since the rates of infection, hematoma, and blood loss are higher when hysterectomy is combined with salpingo-oophorectomy (16). We performed only RRSO in a BRCA mutation carrier due to the concerns for sexual function and the potential complications of the combined hysterectomy/salpingo-oophorectomy.

There is little published data on the use of HRT for BRCA 2 mutation carriers . Therefore, HRT should be administered with caution in this group. Adoption of an estrogen-only HRT after RRSO does not increase the risk of breast cancer in BRCA1 mutation carriers (17). In our study, none of the patients who underwent risk-reducing oophorectomy received HRT. One explanation for this might be that the concerns of BRCA mutation carriers and clinicians involved HRT.

In conclusion, BRCA1 or 2 mutation carriers have an increased lifetime risk of developing breast and ovarian cancer. It is recommended that genetic counseling, surveillance, and prophylactic surgeries with regard to BRCA mutation carriers should be provided in a multi-disciplinary team approach. Risk-reducing bilateral mastectomy and risk-reducing bilateral salpingo-oophorectomy are the most effective strategies for BRCA mutation carriers.

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