Experience of Risk-reducing Salpingo-oophorectomy for a BRCA1 Mutation Carrier and Establishment of a System Performing a Preventive Surgery for Hereditary Breast and Ovarian Cancer Syndrome in Japan: Our Challenges for the Future

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Background: Risk-reducing salpingo-oophorectomy is currently regarded as the most certain primary method for preventing ovarian cancer among BRCA1/2 mutation carriers with hereditary breast and ovarian cancer syndrome. However, risk-reducing salpingo-oophorectomy has rarely been performed in Japan.

Methods: We developed the first system in Japan for performing risk-reducing salpingo-oophorectomy for BRCA1/2 mutation carriers at our university hospital in 2008.

Results: The indication for risk-reducing salpingo-oophorectomy for patients with hereditary breast/ovarian cancer syndrome is currently limited in Japan. This situation may be because of the limited number of genetic counseling units, the limited number of facilities that can perform BRCA1/2 genetic testing and the fact that prophylactic surgery is not covered by health insurance in Japan.

Conclusions: Recent treatment guidelines for breast cancer in Japan recommended risk-reducing salpingo-oophorectomy for BRCA1/2 mutation carriers. Risk-reducing salpingo-oophorectomy should be performed in the framework of the standard therapeutic modality for BRCA1/2 mutation carriers in the near future.

Key words: hereditary breast and ovarian cancer syndrome — risk-reducing salpingo-oophorectomy — BRCA1 — BRCA2 — mutation carrier

INTRODUCTION

Hereditary breast and ovarian cancer syndrome (HBOC) is a hereditary autosomal-dominant disorder characterized by the existence of cancers, such as breast cancer (BC) and ovarian cancer (OC, including fallopian tube cancer and primary peritoneal cancer), in multiple relatives. Miki et al. identified BRCA1 in 1994, and Wooster et al. later identified BRCA2 in the same year (1,2). In total, 35–60% of female BRCA1 mutation carriers are at risk for developing BRCA1-related gynecologic cancers (OC, fallopian tube cancer or primary peritoneal cancer) by the age of 70. The incidence rate of OC in women is 1.4%; however, the incidence rate of
female \( BRCA1 \) and/or \( BRCA2 \) (\( BRCA1/2 \)) mutation carriers is 35- to 40-fold higher than that of the general female population (3–5).

The preoperative diagnosis of ovarian tumors as benign or malignant is sometimes difficult. No effective surveillance technique has been reported for OC. OC screening techniques such as transvaginal ultrasonography and serum CA-125 testing have limited sensitivity and specificity, and they have not contributed to reducing mortality rates (6). The preoperative diagnosis of early-stage OC is particularly difficult. Therefore, risk-reducing salpingo-oophorectomy (RRSO) is the most certain modality for the primary prevention of OC among \( BRCA1/2 \) mutation carriers (7).

However, RRSO had not been performed in Japan until recently. Oophorectomy had been performed as the endocrine therapy for breast cancer aiming at reducing breast cancer recurrence. Surgical ablation of the ovary has rarely been performed in Japan after the approval of tamoxifen as the drug of endocrine therapy for the breast cancer in 1981.

We performed RRSO for \( BRCA1/2 \) mutation carriers after obtaining approval from the ethics committee of School of Medicine, Keio University (Tokyo, Japan). We report an overview of the procedure and issues related to performing RRSO in Japan.

**METHODS AND RESULTS**

A genetic counseling clinic for hereditary cancer was launched at Keio University Hospital (Tokyo, Japan) in January 2002. In cooperation with the Department of Surgery and the Department of Obstetrics and Gynecology, multi-institutional study was performed to elucidate the prevalence of \( BRCA1/2 \) mutations among Japanese kindred suspicious of HBOC (8). The protocol was approved by the ethics committee of School of Medicine, Keio University (approval number: 20030097) (8). Twenty-nine patients with the past medical history of BC and/or OC, and family history of BC and/or OC within their second-degree relatives, were referred to the genetic counseling clinics in Keio University Hospital from January 2005 through May 2006, and 10 deleterious mutations (5 in \( BRCA1 \) and 5 in \( BRCA2 \)) were detected (8).

Figure 1 shows the pedigree of the family in which the proband (III-3) underwent surgery for breast cancer at 46 years old. Her mother and aunt suffered from contralateral breast cancer and ovarian cancer, respectively. The proband underwent \( BRCA1/2 \) DNA testing, and a deleterious mutation of R1443X in \( BRCA1 \) was detected. She was referred to the clinic of the Department of Obstetrics and Gynecology for the surveillance of gynecological cancer. At that time, her elder sister (57Y) developed a peritoneal cancer and underwent the chemotherapy (III-1). She had a past history of the esophageal cancer at the age of 41. After genetic counseling and subsequent DNA testing, she was found to share the same \( BRCA1 \) mutation (R1443X) as her sister. This result prompted the proband eagerly to undergo preventive surgery, and we set out to apply the protocol of RRSO to the ethics committee of School of Medicine, Keio University (approval number: 20070090).

The results of \( BRCA1/2 \) genetic testing should ideally be used to secondarily prevent cancer, that is, to prevent cancer deaths through early detection and treatment. However, no suitable surveillance system has been established for OC. Currently, RRSO is the most certain method for preventing OC in \( BRCA1/2 \) mutation carriers. Clinical trials have revealed that prophylactic mastectomy and RRSO for women with \( BRCA1/2 \) mutation carriers are correlated with a reduced risk of BC and OC development and a reduced risk of death due to BC and OC (7,9–11). Secondary prevention with surveillance for early detection and treatment is opted when women with \( BRCA1/2 \) mutations do not wish to undergo RRSO. Unlike the breasts, the ovaries are intraperitoneal organs; therefore, in many cases, it is difficult to diagnose ovarian tumors as benign or malignant without performing surgery. The following clinical characteristics are related to the detection and diagnosis of OC: (i) the preoperative pathological diagnosis is difficult because the ovaries are intraperitoneal organs, (ii) the early stage is associated with few subjective symptoms, and thus, OC is often detected at stage III or IV, (iii) OC is difficult to detect in early stages through physical findings, (iv) tumor markers such as CA-125 often yield false-positive results and (v) determining whether ovarian tumors are benign or malignant is often difficult. In addition, chemical prevention via oral contraceptives may reduce the overall risk of OC (12,13). However, although some reports observed primary preventive effects in \( BRCA1/2 \) mutation carriers, these findings have been inconsistent (14,15).

The basic procedure for RRSO is bilateral salpingooophorectomy (BSO). The uterus loses its function after BSO; therefore, simultaneous total hysterectomy (TH) is recommended. In cases in which RRSO is not performed for \( BRCA1/2 \) mutation carriers and OC later develops, radical surgery including retroperitoneal lymphadenectomy and omentectomy is often indicated in addition to the TH and BSO performed in RRSO. The complications of radical operations for OC generally include excessive bleeding, organ injury, pulmonary thromboembolism, lymphedema, intestinal obstruction, infection, wound dehiscence and peripheral nerve palsy. Such complications occur more frequently in radical operations for OC than in TH + BSO, and these complications reduce patients’ quality of life (QOL). Furthermore, RRSO is economically more effective when compared with the costs regarding pre- and post-operative tests, repeated courses of anticancer treatment and the number of days spent visiting hospitals for palliative care for the patients with OC.

Frequent detection of occult fallopian tube cancer in samples obtained during RRSO has been reported, necessitating a pathologic diagnosis based on serial sections (16).
Peritoneal cancer occasionally develops after RRSO. This is believed to occur because peritoneal cells and ovarian epithelial cells have the same developmental properties. For BRCA1/2 mutation carriers, the possibility of developing peritoneal cancer within 10 years after RRSO is reported to be 3% or higher (17). Therefore, regular surveillance is necessary following RRSO.

Rapid decreases in estrogen levels following RRSO cause ovarian dysfunction and represent a long-term risk factor for dyslipidemia and osteoporosis. Patients with dyslipidemia and osteoporosis are at high risk for cerebrovascular disease, cardiovascular disease, bone fractures and an accompanying bedridden state. Health care accompanying reduced ovarian function in women following RRSO is important. An environment must be created in which the counseling for sexual problems can also be conducted.

Currently, RRSO is not covered by the public medical insurance system in Japan; therefore, it is important to inform patients that all charges were covered by their own expense, ~750 000 Japanese yen (cost of surgery only, except for admission fee).

All of the aforementioned issues were explained to BRCA1/2 mutation carriers during genetic counseling; those who understand the explanation and wish to undergo RRSO are considered as candidates for RRSO.

The proband requested to undergo RRSO, so that we applied the RRSO protocol to the ethics committee of School of Medicine, Keio University, where the protocol was thoroughly discussed, especially whether the documents addressing the risks and benefits of RRSO were informative enough and easy to understand. After the twice revision of the protocol, RRSO was finally accepted as the clinical study in 2008.

After a few courses of the counseling sessions regarding these issues, the patient opted to TH + BSO as a risk-reducing surgery. The patient experienced hot flashes and dyslipidemia thereafter due to ovarian dysfunction caused by premenopausal oophorectomy. The client had been administered Toki-shakuyaku-san, a Japanese traditional herbal medicine (Kampo medicine), for hot flashes. This treatment was effective. She was also treated for dyslipidemia, which also might have been due to premenopausal oophorectomy.

This case has been disease free for cancer in 5 years after undergoing RRSO with strict surveillance.

DISCUSSION

RRSO reduces the risk of developing both OC and BC. In addition, RRSO has also been used in the prevention of BC. Schinzinger first proposed salpingo-oophorectomy as a method of treating BC in 1889 (18). A.F. Liber, a pathologist, proposed the concept using oophorectomy to prevent OC (19). He examined a woman and her five daughters, all of them were confirmed pathologically to have developed OC, and stated that oophorectomy should be considered for other relatives before they developed OC. The results from the clinical trials indicate that preventative breast resection and RRSO for BRCA1/2 mutation carriers are correlated with a reduced risk of BC and OC development in addition to the reduced overall mortality rates for both BC and OC (9,20). Domchek et al. reported that RRSO reduced BC mortality, gynecologic cancer-related death and overall mortality rates by 90, 95 and 76%, respectively (9).

The National Comprehensive Cancer Network Guidelines™ Genetic/Familial High-Risk Assessment: Breast and Ovarian...
V.1.2011 recommends RRSO for HBOC as follows: ‘Recommend risk-reducing salpingo-oophorectomy, ideally between 35 and 40 y, and upon completion of child bearing, or individualized based on earliest age of onset of OC in the family. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and OC, management of menopausal symptoms, possible short term hormone replacement therapy (HRT) to a recommended maximum age of natural menopause, and related medical issues’ (21). Furthermore, the 2009 revision of the American Congress of Obstetricians and Gynecologists guidelines also recommend RRSO for patients with a high risk of BRCA1/2 mutations. Kauff et al. reported that RRSO was performed in 98 of 170 women (58%) aged 35 years or older with BRCA1/2 mutations (11). However, RRSO has rarely been performed in Japan.

Review of a patient’s detailed family history is the first and most important step in detecting HBOC. HBOC is a hereditary autosomal-dominant disease that occasionally leads to the creation of a ‘large’ family pedigree. In the United States, the Department of Health and Human Services has begun a nationwide public health campaign called the US Surgeon General’s Family History Initiative, which encourages awareness regarding one’s family history through the internet (22).

Minimally invasive operations have also been performed for RRSO. RRSO is performed using a laparoscope, and single-port laparoscopy has been preferred in recent years (23). However, RRSO is not covered by public health insurance in Japan; therefore, laparoscopic RRSO imposes a much greater financial burden than does laparotomy. We estimated the cost of undergoing RRSO via laparoscopic surgery or laparotomy and determined that laparotomy is less expensive than laparoscopic surgery. However, when the total cost of hospitalization is considered, laparoscopic surgery is more cost effective than laparotomy because it enables short-term hospitalization.

In patients in whom the uterus is preserved, both hormone replacement therapy for ovarian-deficit syndrome following bilateral oophorectomy and tamoxifen therapy for BC are known to increase the risk of developing endometrial cancer. Furthermore, BRCA1 mutation carriers are reported to have a 2.6-fold higher risk of developing endometrial cancer than nonmutation carriers (24). BRCA1 mutation carriers are also reported to have a high frequency of uterine serous carcinoma (25). Operative procedures involving TH result in more complications; therefore, it is necessary to ensure that the patient understands the risks and benefits via counseling before deciding to undergo simultaneous TH.

One report on a 20-year postoperative follow-up of BRCA1/2 mutation carriers who underwent RRSO stated that the cumulative death rate associated with the development of intra-abdominal carcinomatosis was 3.5% or higher. According to this result, it is necessary to inform BRCA1/2 mutation carriers at the counseling stage that surveillance is necessary after RRSO (17).

The Gynecologic Oncology Group is currently conducting prospective research on long-term OC screening methods and risk reduction methods for BRCA1/2 mutation carriers (GOG#199) (26).

Frequent detection of fallopian tube cancer in samples obtained at the time of RRSO has been reported; thus, pathologic diagnosis based on serial sections is necessary to detect such occult cancers (16). Furthermore, in RRSO, tumor cells are occasionally detected in the peritoneal cavity, necessitating a diagnosis using peritoneal cytology. Colgan et al. reported that peritoneal cytology revealed positive findings in 3 of 35 women who underwent RRSO. Moreover, two of these three patients had either occult fallopian tube cancer or occult OC, whereas, in the other patient, primary OC was not detected on any serial sections of surgical samples (27).

Premenopausal bilateral oophorectomy burdens women with the following adverse events: fractures due to osteoporosis, arteriosclerosis arising from dyslipidemia and subsequent cerebrovascular and cardiovascular disease. These issues related to post-RRSO health care, including sexual issues, should be conveyed to patients before performing RRSO. Ovarian dysfunction due to hormone deficiency is inevitable in RRSO, particularly in cases opt for premenopausal oophorectomy. In addition, oophorectomy can have various effects for more than 10 years in some patients. Early-stage menopausal symptoms, such as hot flashes, fatigue, shoulder stiffness and palpitations, can lead to further presentation of symptoms such as coital pain, atrophic (senile) vaginitis, urethritis, urinary incontinence, rough and dull skin accompanying skin atrophy, and obesity. In addition, other problems can easily occur in the long term, such as osteoporosis or osteopenia, dyslipidemia and arteriosclerosis. These illnesses are associated with few early-stage subjective or objective symptoms; however, when these illnesses progress, they have a direct effect on QOL, thus necessitating management from an early stage.

We could administer Kampo medicine, which is approved as the treatment option for menopausal syndrome in Japan. Japanese gynecologists have useful tools for RRSO-treated patients, but HRT is used to treat menopausal syndrome in most other countries. HRT is generally suitable for improving symptoms related to decreased ovarian function; however, it cannot be used in patients with BC, as estrogen contributes to tumor growth. In contrast, there is no established theory regarding HRT administration for BRCA1/2 mutation carriers who have not developed BC. In 2008, the results of the controlled study of 472 postmenopausal women with BRCA1 mutations were published, in which the risk of BC was reduced in patients who were administered hormone therapy (28).

**CONCLUSION**

We have described the efforts involved in introducing RRSO for BRCA1/2 mutation carriers in Japan. RRSO for HBOC in Japan has been rarely performed thus far. The reasons for this rarity are as follows: limited number of medical
institutions with gene diagnostics departments and facilities can perform BRCA1/2 genetic testing; RRSO is not covered by health insurance; and there is a dearth of experience related to gene diagnosis.

Currently, when considering RRSO, appropriate procedures are necessary, such as obtaining approval from the ethics committee of School of Medicine, Keio University, after conducting sufficient counseling from a surgical intervention perspective for patients who have not yet developed symptoms.

More recently, the revised treatment guidelines for BC, as edited by The Japanese Breast Cancer Society, recommend RRSO for BRCA1/2 mutation carriers (29). Moreover, the National Comprehensive Cancer Network guidelines for HBOC have been translated into Japanese (30). RRSO should be performed in the framework of standard medical treatment for BRCA1/2 mutation carriers in the near future in Japan. Same analogy would be applied for carcinomas of endometrium and ovary in women with Lynch syndrome, who develop these gynecological cancers along with colorectal carcinomas (31). Further study is required to accumulate the evidences in this particular field of hereditary cancer syndromes.

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Conflict of interest statement

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