Experience with Bilateral Risk-Reducing Mastectomy for an Unaffected BRCA Mutation Carrier

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Women with BRCA1/2 mutations have a high risk of breast cancer and may opt for risk-reducing mastectomy (RRM). We report a 38-year-old Japanese woman who was diagnosed as a BRCA2 mutation carrier. She underwent prophylactic bilateral skin-sparing mastectomy (SSM) with excision of the nipple and preservation of the areola skin. It is unclear whether a bilateral RRM leads to better survival compared with intensive surveillance. The oncological risk associated with the presence of remnant breast glandular tissue after SSM or nipple-sparing mastectomy has been obscure. We report the first case of RRM for a Japanese BRCA mutation carrier and provide a literature review on risk management for BRCA mutation carriers with a focus on the concepts and procedures of RRM.

Key Words: Genes, BRCA2, Prophylactic surgical procedure, Subcutaneous mastectomy

INTRODUCTION

Germline mutations in the tumor suppressor genes BRCA1 and BRCA2 account for 3% to 5% of all breast cancer cases and 10% to 15% of ovarian cancer cases [1]. The lifetime risk of breast cancer in BRCA1 and BRCA2 mutation carriers is estimated at 47% to 66% and 40% to 57%, respectively. The ovarian cancer risk in BRCA1 and BRCA2 mutation carriers is estimated at 35% to 46% and 13% to 23%, respectively [2]. The median onset age for breast cancer in BRCA mutation carriers is 40 to 50 years, while that for sporadic cases is 60 to 70 years [2]. Previous studies conducted in unaffected BRCA mutation carriers have indicated that prophylactic mastectomy effectively reduces the residual lifetime risk of breast cancer to < 5% [1,3-5]. However, this evidence was derived from retrospective and short-term follow-up prospective studies, so it is not clear whether a bilateral risk-reducing mastectomy (RRM) provides better survival when compared with intensive surveillance. Risk-reducing salpingo-oophorectomy (RRSO) has been demonstrated to reduce risk of ovarian cancer to 85%, also derived from retrospective and short-term follow-up. They recommend RRSO for BRCA mutation carriers especially upon completion of child-bearing in the National Cancer Center Network guidelines because of the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer [6], although they hold RRM to an option for BRCA mutation carriers.

In Japan, risk-reducing surgery as well as genetic counseling or genetic test is outside the health insurance, so we perform risk-reducing surgery for BRCA mutation carriers in the limited hospital facilities after the Ethics Committee granted permission. The safety and feasibility of nipple-sparing mastectomy (NSM) or skin-sparing mastectomy (SSM) in BRCA mutation carriers is debatable, and a consensus of which procedure should be performed has not yet been reached. We report a 38-year-old Japanese women diagnosed with BRCA2 mutation that underwent prophylactic bilateral SSM with excision of the nipple to preserve the areola skin. Furthermore, we provide a review of the literature on the risk management of BRCA mutation carriers, especially the concepts and procedures of RRM.

CASE REPORT

A 38-year-old Japanese woman was diagnosed as a BRCA2 mutation carrier after genetic counseling and testing and was referred to Kitano Hospital in April 2014 to undergo risk-reducing surgery. She had no past medical history and was in
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Although the American Society of Clinical Oncology has previously recommended that BRCA mutation testing should be conducted only for those with at least a 10% likelihood of carrying a mutation, it is currently recommended for any individual with a suggestive family history if the result would affect the magnitude of medical management [1].

Risk management for BRCA mutation carriers includes frequent mammography, breast MRI, clinical breast examinations, chemoprevention, and prophylactic surgery. Previous studies conducted in unaffected BRCA mutation carriers have indicated that prophylactic mastectomy effectively reduces the residual lifetime risk of breast cancer to <5% [1,3-5]. Meijers-heijboer et al. [3] conducted a prospective study of 139 pathogenic BRCA1/2 carriers, among whom, 76 underwent prophylactic mastectomy and 63 were followed by regular surveillance. They showed that there were no cases of breast cancer after RRM with a mean follow-up 2.9 ± 1.4 years, whereas there were eight cases of breast cancers in the surveillance group after a mean follow-up of 3 ± 1.5 years. Hartmann et al. [4] conducted a retrospective study of 639 women with a family history of breast cancer that underwent prophylactic mastectomy. With a median follow-up of 14 years, they reported that prophylactic mastectomy was associated with a 90% reduction in the incidence of breast cancer, with only seven women developing breast cancer. However, randomized controlled trials to evaluate the potential impact of RRM on survival have not been conducted, and it remains unclear whether bilateral RRM improves survival compared with intensive surveillance. The only available data is derived from risk estimates assessed using mathematical models of risk-reducing interventions. Kurian et al. [7] developed a Monte Carlo model of breast screening with annual mammography plus MRI in subjects aged 25 to 69 years; RRSO was performed in those aged 40 to 50 years and RRM was performed in those aged 25 to 50 years. They reported that RRM at age 25 plus RRSO at age 40 years maximizes survival probability, substituting mammography plus MRI screening for RRM seemed to offer comparable survival. As far as chemoprevention is concerned, tamoxifen reduced breast cancer incidence among healthy BRCA2 carriers by 62% [8].

In this case, after we discussed all of the risk management options for BRCA mutation carriers recommended by the National Comprehensive Cancer Network (NCCN) guidelines, she has finally chosen to have RRM, because she has believed RRM might release from the fear of future cancer more than other cancer preventive options. She made choice to have RRM by her responsibility that 37-year-old widowed mother with three young children, concerning that prophylactic mastectomy effectively reduces the residual lifetime risk of breast cancer to <5% which is superior than chemoprevention, although addressing psychosocial effect of mastectomy, and

good health. Her father had been diagnosed with prostate cancer when he was 49 years old; he had died from the disease 2 years later. Her mother was alive but had a history of arrhythmia that was diagnosed when she was 64 years old. Her paternal grandmother had been diagnosed with breast cancer when she was 54 years old and had died from the disease 10 years later. Although her maternal grandfather died at the age of 72 years because of metastatic cancer, the precise details were not known. There was no family history of ovarian cancer. Her ancestry was Japanese, and she was unaware of any Ashkenazi Jewish heritage. Because of her family history, the fact that she was a widowed mother with three children, and her knowledge of hereditary breast and ovarian cancer, she worried about that, and consulted a genetic counselor to undergo BRCA mutation testing. Genetic testing revealed a BRCA2 mutation. After genetic counselor showed all of the risk management options for BRCA mutation carriers, frequent mammography, breast magnetic resonance imaging (MRI), clinical breast examinations, chemoprevention, and prophylactic surgery including extent of cancer risk reduction, risks associated with surgeries, reconstructive options, management of menopausal symptoms, and reproductive desires, addressing psychosocial, social, and quality of life aspects, she finally desired RRM and RRSO. The Ethics Committee granted permission for the RRM in May 2014, and we provided informed consent prior to the RRM.

The need for RRSO remained to be discussed because of concerns associated with RRSO such as menopausal disorders caused by iatrogenic fertility. Breast MRI showed rapid early enhancement with linear and ductal distribution in both the breasts, and the possibility of ductal carcinoma in situ could not be ruled out. Axillary node enlargement was not observed. In July 2014, to improve aesthetic and psychological outcomes according to her preference, she underwent a bilateral SSM with excision of the nipple to preserve the areola skin. Using indigo carmine, we demarcated the perimeter of the breast tissue preoperatively to ensure complete excision of the mammary gland. Immediate breast reconstruction was performed using the standard prosthetic reconstructive technique of two-stage expander-implant reconstruction. On pathological examination, there was no evidence of malignancy. She was disease-free at a 1-year follow-up and her general condition was good. She has decided to undergo RRSO in near future.

Discussion

Although the American Society of Clinical Oncology has previously recommended that BRCA mutation testing should

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risks associated with surgeries. Bresser et al. [9] reported that 95% of women opted for RRM because of decreased cancer-related psychological distress. Mutation carriers opting for prophylactic mastectomy are most often in their 30s [10]. They tend to have young children and a greater awareness of the genetic nature of cancer in the family compared with those who opt for regular surveillance [9], as well as in this case.

For BRCA1 or BRCA2 mutation carriers at high risk for ovarian cancer, the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have impelled them to the performance bilateral RRSO after completion of childbearing, ideally by age 35 to 40 years. As to the chemoprevention option, oral-contraceptive use protected against ovarian cancer both for carriers of the BRCA1 mutation (odds ratio, 0.5; 95% confidence interval, 0.3–0.9) and for carriers of the BRCA2 mutation (odds ratio, 0.4; 95% confidence interval, 0.2–1.1) [11].

In this case, the need for RRSO remained to be discussed in the Ethics Committee, and she underwent RRM at first before RRSO, as following reasons: Firstly, the most important reason is that there is the difference between the risk of breast cancer and of gynecologic cancer in age of 30s in BRCA2 mutation. The timing of RRSO is controversial, while NCCN Guidelines Panel recommends RRSO for women with a known BRCA1 or BRCA2 mutation, typically between ages 35 and 40 years and upon completion of childbearing. It is well established that among women with BRCA2 mutation, the risk of gynecologic cancer is only 2% to 3% by the mean age of 50 years, while it increases in the late 30s in women with BRCA1 mutation [12]. However, the risk of breast cancer is over 20% in 30s in women with BRCA2 mutation. Secondly, mutation carriers who undergo RRSO at a young age face medical problems such as osteoporosis, and cardiovascular disease, as well as quality-of-life issues associated with menopause, hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes. Thirdly, women who undergo bilateral mastectomy but who have ovaries intact can use oral contraceptive safety for protecting against ovarian cancer. oral contraceptive use has been associated with a small increase in the risk of breast cancer in young and old women. In a large meta-analysis, current use of oral contraceptives was associated with a relative risk 1.2 for breast cancer [11].

She has not use oral contraceptive even after RRM, because she desire to have children, but she can take oral contraceptive after she gave up having children. Fourthly, short-term hormone replacement therapy after RRSO may be useful after RRM to improve their quality-of-life for women without increasing the risk of breast cancer, when no history of breast cancer has confirmed pathologically [1,12].

As far as the method of RRM is concerned, SSM and NSM are increasingly performed instead of the conventional total mastectomy to allow for immediate breast reconstruction and to achieve a natural aesthetic outcome. The oncological risk associated with remaining mammary gland is unclear, and there remains a small risk of cancer arising beneath the nipple and areola in NSM. Reynolds et al. [13] evaluated 62 nipple-areolar complex (NAC) tissues from 33 female BRCA1/2 mutation carriers who underwent mastectomy and found that 24% of NACs contained terminal duct lobular units (TDLUs), with only 8% found in the nipple papilla, and they estimated that NSM might be appropriate and oncologically safe for women with BRCA mutation carriers, but TDLUs can be found in the NAC and are more likely at the base of the nipple, so the significance of this for long-term risk is unknown.

However, Hartmann et al. [4] reported that no significant difference in the incidence of breast cancer between women who underwent subcutaneous mastectomy and those who underwent total mastectomy. The PROSE study followed 105 BRCA1/2 mutation carriers who underwent a bilateral prophylactic mastectomy, at least 30% of whom had subcutaneous mastectomies [14]. At 6.4 years of follow-up, two women who underwent subcutaneous mastectomies developed breast cancer, with one developing metastatic breast cancer in the axilla and the other developing breast cancer in residual breast tissue [14]. In a review of the literature, van Verschuier et al. [15] reported that 21 primary breast cancers occurred after 6,044 prophylactic mastectomies, three occurred after a total mastectomy, and 17 occurred after a conservative mastectomy, but that the majority of primary breast cancers did not originate near NAC or skin flap but were found in the chest wall or axilla. They suggested that oncological surgeons should be diligent, ensuring complete removal of all glandular tissue, especially in the axillary tail and chest wall, and that the skin flaps and NAC should be dissected as thin as possible [15]. Current NSM and SSM techniques aim for skin flaps < 5 mm and for a NAC thickness of 2 to 3 mm [15]. SSM and NSM using peri-areolar or inframammary incisions can be challenging, because of difficulty of removal of remaining mammary gland in all quadrants and in the axillary tail.

Detection of BRCA1/2 mutations gave rise to a new concept in prophylactic medicine, although risk management for BRCA1/2 mutation carriers requires further discussion.

It is generally accepted that a randomized controlled study design would allow a better evaluation of risk reducing surgery on cancer risk and mortality reduction, it is generally accepted that randomized approach would not be ethical for the management of these patients and therefore, this field of re-

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The search is limited to undertaking observation studies, which intrinsic methodological limitation. The patient finally described herein chose to undergo bilateral SSM for RRM with the excision of the nipple and preservation of the areola skin. This is the first report of such a case in Japan. The best choice of risk reduction for BRCA mutation is different from each others, so it is important that the decision making should be made with knowledge of risk management options, through receiving counseling about the risks and benefits of each options.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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