

REVIEW

Exploring Breast Cancer Risk Management in HBOC Patients: Image Surveillance Versus Risk-reducing Surgery

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In Japan, the rising incidence of hereditary breast and ovarian cancer syndrome (HBOC) follows partial insurance coverage introduced in 2020. Compared with the general population (~11% lifetime risk), individuals with HBOC face a significantly higher lifetime risk of breast cancer (48%–76%), often presenting at younger ages. *BRCA1* mutations are linked to triple-negative breast cancer, whereas *BRCA2* mutations typically result in luminal-type disease. Key risk management strategies include surveillance and prophylactic surgery. Annual magnetic resonance imaging and mammography are recommended at younger ages than in the general population, despite concerns regarding contrast agents, radiation exposure, and examination-related burdens. Although risk-reducing mastectomy lowers breast cancer risk by over 90%, it remains underutilized because of cosmetic and psychological considerations. Nipple-sparing or skin-sparing mastectomy combined with immediate or delayed reconstruction offers a balance between risk reduction and postoperative outcomes, although safety and procedure details still warrant careful evaluation. Managing the high breast cancer risk associated with HBOC requires ongoing efforts to refine current strategies while minimizing patient burden. (DOI: 10.2302/kjm.2024-0021-RE)

Keywords: hereditary breast and ovarian cancer syndrome, breast cancer, surveillance, risk-reducing surgery, *BRCA1/2*

Introduction

In Japan, partial health insurance coverage for hereditary breast and ovarian cancer syndrome (HBOC) treatment was introduced in April 2020. Since then, the number of breast cancer patients diagnosed with HBOC has increased each year. For individuals diagnosed with HBOC, appropriate lifelong cancer risk management is

essential. Currently, two primary strategies are employed for managing breast cancer risk: prophylactic (risk-reducing) surgery and surveillance to facilitate early detection. However, insurance coverage for these interventions is available only to patients who have already developed an associated malignancy, leaving those without a history of cancer to pay entirely out of pocket and thereby facing a substantial financial burden.

Although risk-reducing surgery is currently the most effective method for preventing breast cancer, it has not been widely adopted in Japan. Concerns include the physical stress of surgery, postoperative discomfort, and changes in appearance even after reconstruction. Imaging-based surveillance for early detection is seen as particularly valuable for breast cancer risk management, yet the potential anxiety about cancer development and the physical demands of repeated examinations remain as significant issues for patients.

In this study, we review the literature on HBOC-related breast cancer risk management, including publications from Japan and international sources. This review summarizes the current status of HBOC care in Japan.

Breast Cancer Risk in Patients with HBOC

Over the 40 years from 1975 to 2015, breast cancer incidence by age group has shown a fivefold increase in Japan. According to data published by the National Cancer Center,¹ the incidence of breast cancer in Japan is 1 in 9, with a lifetime risk of 11.2%. However, the estimated lifetime risk of breast cancer in patients with HBOC is 48%–76%, indicating a high risk of developing the disease.^{2,3}

Momozawa *et al.*⁴ reported pathogenic variants of genes in Japanese patients with breast cancer, the most frequent of them being *BRCA1* and *BRCA2*. In addition, they stated that individuals with hereditary breast cancer account for 5.7% of all patients with breast cancer, and the lifetime risk of developing breast cancer in Japanese individuals with *BRCA1* and *BRCA2* pathological variants is 72.5% and 58.3%, respectively.

Age-specific breast cancer incidence rates among Japanese with *BRCA1/2* pathological variants were reported by Yamauchi *et al.*⁵ The peak risks for *BRCA1*- and *BRCA2*-induced breast cancer are in the 30s and early 40s, respectively, which are clearly younger than the peak of 40–60 years in the general population. These data are consistent with values reported overseas, suggesting that preventive measures should be tailored for the lifetime risk period of disease onset.²

Characteristics of HBOC Breast Cancer

Characteristics of HBOC-related breast cancer differ between *BRCA1* and *BRCA2*. *BRCA1*-associated breast cancer tends to exhibit a higher frequency of triple-negative breast cancer, whereas *BRCA2*-related breast cancer is predominantly luminal breast cancer. Triple-negative breast cancer, prevalent in *BRCA1*-related cases, represents a relatively high-grade malignancy among the breast cancer subtypes, often necessitating chemotherapy as the primary treatment modality even when diagnosed early. Conversely, hormone receptor-positive breast cancer, prevalent in *BRCA2*-related cases, is considered less

aggressive than triple-negative breast cancer. However, there is some concern regarding its tendency for late recurrence, often requiring extended adjuvant therapy for 5 years or more.

Murakami *et al.*⁶ reported the characteristics of breast cancer in 30 Japanese *BRCA1* mutation carriers and 29 *BRCA2* mutation carriers; 86.7% of the *BRCA1* cases were triple-negative breast cancers and 69.0% of the *BRCA2* cases were luminal breast cancers. In addition, they analyzed the imaging characteristics of each type of breast cancer and found that *BRCA2*-related tumors were usually detected as calcifications on mammography, whereas *BRCA1*-related tumors were detected as masses in the posterior part of the breast.

Treatment of HBOC Breast Cancer

The therapeutic strategies for HBOC-associated breast cancer are no different from those of other types of breast cancer. Surgical intervention is imperative for achieving a cure, with adjuvant systemic therapy administered in cases of invasive cancer. Points of differentiation between the treatment approaches for HBOC-related breast cancer and other breast cancers include the recommendation for total mastectomy during surgical planning and the inclusion of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as an option in adjuvant therapy in HBOC-related breast cancer because of their high risk of developing breast cancer. Additionally, prophylactic contralateral mastectomy may be considered an option.

Oral consumption of PARP inhibitor for 1 year as post-operative adjuvant therapy for HBOC-related breast cancer under certain conditions has been covered by insurance since October 2022. Furthermore, PARP inhibitor taken 1 year postoperatively notably improved the 3-year invasive cancer recurrence-free survival [hazard ratio (HR), 0.57; 99.5% confidence interval (CI), 0.39–0.83; $P < 0.001$] and overall survival (HR, 0.68; 98.5% CI, 0.47–0.97; $P = 0.009$) with 3.5 years of median follow-up.^{7,8}

Surveillance

According to the National Comprehensive Cancer Network (NCCN) guidelines 2023, breast awareness or self-palpation is recommended from the age of 18 years for patients with HBOC.⁹ In addition, breast palpation by a specialist every 6–12 months is recommended from the age of 25 years. Given that the mammary glands change with the menstrual cycle, it is important to know when it is appropriate to perform an examination. It should be noted that the premenstrual period is not favored for self-palpation because breast tautness makes it difficult to distinguish between masses and mammary gland tissue. During this stage of the menstrual cycle, abnormalities are also less noticeable by magnetic resonance imaging (MRI) and other imaging studies, making it unsuitable

Table 1 Schedule of breast surveillance at our institute for HBOC syndrome

	Initial examination	6 months	12 months	18 months	24 months
Breast palpation	●	●	●	●	●
MMG	●		● ^a		● ^a
MUS	○	○	○	○	○
CE-MRI	● ^b		● ^b		● ^b

^a Omitted for those under 30 years of age; ^b Recommended timing for examination is during days 7–15 of the menstrual cycle. MMG; mammography, MUS; mammary ultrasound test, CE-MRI; contrast-enhanced breast magnetic resonance imaging.

for screening. The recommended timing for examination is during days 7–15 of the menstrual cycle.

The NCCN guidelines recommend annual contrast-enhanced breast MRI for breast cancer surveillance for ages 25–29 years. For those aged 30–75 years, the recommendation includes annual contrast-enhanced breast MRI and mammography with tomosynthesis. Previous studies have consistently reported that the sensitivity of MRI screening (77%–94%) is higher than that of mammography (33%–59%) in detecting breast cancers.^{10–17} The combination of mammography and contrast-enhanced MRI is considered the most effective method for detecting breast cancer.¹⁸ Mammography is extremely useful in detecting early-stage breast cancer, which is detected as calcified lesions within the breast, and some of these lesions can only be detected by mammography. Nevertheless, some argue that mammography is not useful in detecting masses in relatively young women owing to the high concentration of dense tissue. The usefulness of mammography is controversial because of its sensitivity and exposure to radiation. Contrast-enhanced MRI is considered the imaging test with the highest sensitivity and specificity for detecting breast cancer, but some are concerned about the effects of the use of gadolinium-based contrast agents. The use of gadolinium contrast media is contraindicated in patients with bronchial asthma or renal dysfunction. The safety of multiple uses of gadolinium contrast media remains debatable, even for general cases. Although the United States Food and Drug Administration has indicated that there is no clear evidence that gadolinium contrast media accumulates in the brain, the use of gadolinium contrast media should be carefully monitored.^{19–21} Moreover, the long time required for acquisition of the image in the prone position during the examination is burdensome for patients.

Although screening ultrasonography often detects breast cancers missed by mammography, particularly in women with dense breasts, ultrasonography is not recommended as a surveillance tool in many guidelines around the world. Invasive carcinoma in patients with HBOC is often detected on ultrasonography as a benign mass with well-defined borders. Furthermore, many of them occur relatively deep in the mammary gland and are difficult to detect by ultrasonography. Moreover, noninvasive carci-

noma is difficult to distinguish from mastopathy changes in ultrasonography. Therefore, the detection rate of ultrasonography is clearly inferior to that of MRI. However, ultrasonography is a harmless test, and its effective use in the Japanese population should be verified. **Table 1** summarizes the surveillance policy at our institute.

It should be stressed that surveillance is an examination to detect breast cancer at an early stage, not to prevent its occurrence. Whenever there is the slightest suspicion of malignancy on imaging studies, a needle biopsy under local anesthesia should be performed for diagnosis.

A less burdensome, cheaper, and more accurate inspection method for surveillance is desirable. Non-contrast MRI, short contrast-enhanced MRI (abbreviated MRI),^{22–25} and contrast-enhanced mammography¹² have been reported in recent years. Currently, the appropriate imaging modalities and examination intervals are still under investigation.

Risk-reducing Surgery

Risk-reducing surgery involves the removal of an organ not yet affected by disease. In patients with HBOC, prophylactic mastectomy has been shown to reduce the risk of breast cancer by over 90%,^{26–29} making it the most effective preventive intervention. However, because the breast is a superficial organ, changes in appearance following surgery pose a significant concern.

There are three primary methods of mastectomy: (1) simple mastectomy, (2) nipple-sparing mastectomy (NSM), and (3) skin-sparing mastectomy (**Fig. 1**). NSM and skin-sparing mastectomy are most often employed when simultaneous breast reconstruction is planned. Among these procedures, NSM retains the greatest volume of residual breast tissue, necessitating ongoing evaluation of its safety. At present, the probability of cancer arising from the nipple–areolar complex is considered to be very low. Several studies have concluded that NSM is an appropriate option for risk-reducing mastectomy in HBOC patients.^{30–32} In Japan, Yamauchi et al.⁵ reported that 11.3% of HBOC patients undergoing risk-reducing surgery were found to have occult breast cancer on post-operative pathological examination.

A flowchart of breast reconstruction surgery is shown

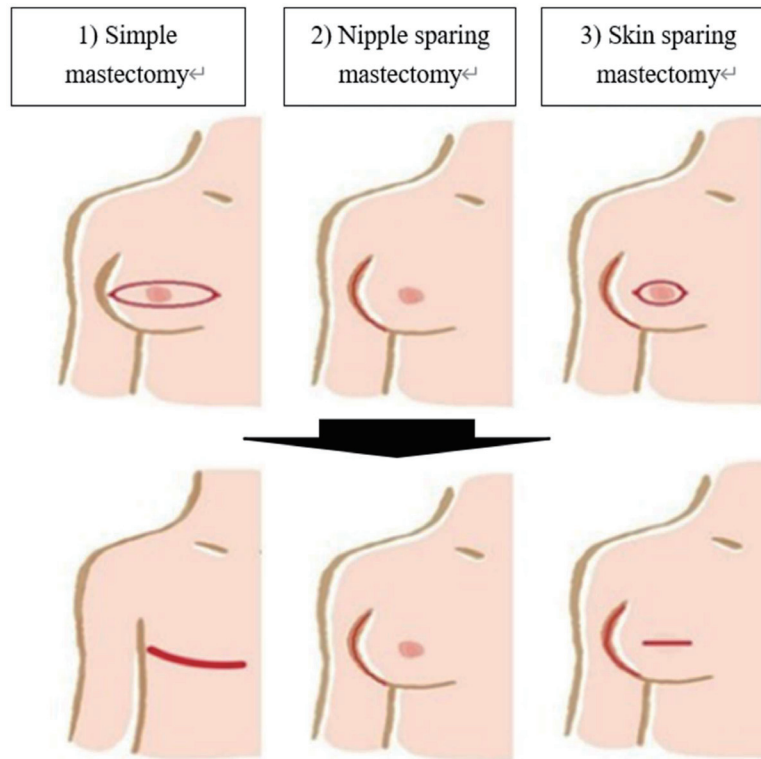


Fig. 1 Three options of risk-reducing mastectomy.

The most effective method of preventing breast cancer is risk-reducing mastectomy. There are three options for risk-reducing mastectomy. The choice of surgical technique depends on the difference in appearance and whether reconstruction is desired.

in **Figure 2**. Breast reconstruction can be divided into primary reconstruction, in which reconstruction is performed simultaneously with mastectomy, and secondary reconstruction, in which reconstruction is performed later in another surgery after mastectomy. In primary reconstruction, two methods can be used. One method involves reconstructing the breast with implants or autologous tissue in a single surgery to complete the final shape (primary one-stage reconstruction); the second method entails inserting a tissue expander during the first surgery and formation of the final shape with implants or autologous tissue in a second surgery at a later date (primary two-stage reconstruction).

In July 2019, the acknowledgment of malignancy caused by breast implants used for breast augmentation (Allergan textured implants) shocked the world. Therefore, although the incidence of breast implant-associated anaplastic large cell lymphoma and squamous cell carcinoma is extremely low, patients should be informed of these risks when provided the option of breast reconstruction.³³

The policy on surveillance after risk-reducing surgery is not well defined. In general, ultrasound and/or con-

trast-enhanced MRI studies should continue, because the risk of developing cancer from a small amount of residual subcutaneous mammary tissue including the accessory breast area after a total mastectomy is not completely eliminated.

Selection of Prophylactic Method

Deciding whether to undergo risk-reducing mastectomy or opt for surveillance in HBOC patients remains a complex process. Multiple factors—including age, marital status, parity, and family history of breast cancer—influence this decision-making process. Although earlier studies have reported lower postoperative physical well-being after risk-reducing surgery, more recent investigations focusing on long-term psychological outcomes suggest a trend toward improved psychological well-being, largely attributable to relief from cancer-related anxiety.^{34–36}

Early detection through screening is feasible for breast cancer, and many early-stage tumors identified in this manner are highly curable with appropriate treatment. According to the literature, 0.5%–11.3% of occult cancers—undetected by imaging but found incidentally on

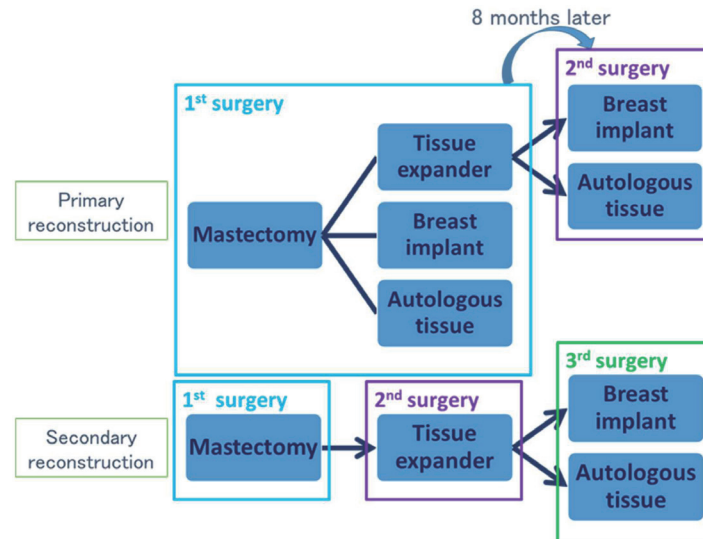


Fig. 2 Flowchart of breast reconstruction.

There are many options for breast reconstruction. Decisions must be made on when to perform reconstruction and whether to use breast implant or autologous tissue.

surgical specimens—have been reported following risk-reducing surgery for HBOC. Most of these lesions are either noninvasive or, if invasive, measure less than 5 mm. Generally, chemotherapy and other potent systemic treatments are not recommended for invasive tumors below 5 mm in size.

Although risk-reducing surgery is highly effective in reducing the risk of breast cancer and offers the advantage of substantially alleviating concern and anxiety regarding the development of breast cancer, its risk-reducing effect is not absolute and does not eliminate the possibility of breast cancer arising from residual breast tissue in the subcutaneous or nipple–areolar complex areas. Moreover, it is imperative to consider the potential for postoperative complications or supplemental surgery. Following surgery, sensation in skin and the nipple–areolar complex is often attenuated after surgery. The lifetime residual breast cancer risk and absolute benefit from risk-reducing surgery or surveillance should be quantified for each individual life stage.

Future Directions

Future challenges for medical professionals include simplifying the screening process and improving the accuracy of examinations. The current 40-min contrast-enhanced MRI examination in the prone position, along with the painful compression of the breast and exposure to radiation for mammography, warrant improvement. Although there are high expectations for the use of abbreviated MRI scans, this modality still involves the burden

of using contrast media. In addition to imaging studies, detection tools using liquid biopsy are also being explored.

Lowering the burden of risk-reducing surgery also poses a significant challenge. In this regard, the use of robotic or robotic-assisted surgery holds promise for achieving cosmetically pleasing outcomes with smaller skin incisions.

For chemoprevention, although this element of cancer therapy is not covered by insurance in Japan, there is significant need for more data in this field. In addition, the enhancement of cancer prediction accuracy for individuals would be highly beneficial.^{37–39}

Conclusion

Managing the high breast cancer risk associated with HBOC requires ongoing efforts to refine current strategies while minimizing patient burden. Simplifying screening protocols, introducing more convenient and safer prevention methods, and advancing surgical options remain pivotal goals. Promising approaches, including abbreviated MRI, liquid biopsy, chemoprevention, and robotic-assisted procedures, may lead to more personalized care that balances optimal risk reduction with quality-of-life considerations. Continued research and interdisciplinary collaboration are essential for achieving these objectives.

Conflicts of Interest

The authors have declared that no conflict of interest exists.

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