CASE REPORT

Five screening-detected breast cancer cases in initially disease-free BRCA1 or BRCA2 mutation carriers

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Abstract
Individuals carrying pathogenic BRCA1 or BRCA2 mutations have an increased lifetime risk of breast and/or ovarian cancer. The incidence of breast cancer amongst disease-free BRCA mutation carriers under surveillance and the clinical and pathological characteristics of those who subsequently develop the disease remain unclear in Japan. We reviewed the records of 155 individuals with BRCA1 or BRCA2 mutations identified by genetic testing between January 2000 and December 2016. At the time of genetic testing, 26 individuals with one of these mutations had no history of breast cancer and were therefore enrolled in a surveillance program that included biannual ultrasonography, clinical breast examination, annual mammography, and conditional magnetic resonance imaging for the early detection of primary breast cancer. During the surveillance period, 5 individuals with BRCA1 or BRCA2 mutations were diagnosed with primary breast cancer. The mean surveillance duration until breast cancer diagnosis was 48 months. The incidence of primary breast cancer during surveillance in initially disease-free BRCA mutation carriers was 4.23%/year. In two cases, the tumors were only detectable on MRI. The case 5 patient who presented with a tumor that was detected by self-examination, which then grew rapidly, had stage IIB triple-negative breast cancer. In conclusion, our results show that some challenges exist in the early detection of breast cancers in BRCA1 or BRCA2 mutation carriers. There are also some difficulties in approaching those individuals in Japanese society.

Keywords BRCA1 mutation carrier · BRCA2 mutation carrier · Screening-detected breast cancer · Breast cancer incidence

Introduction
Clinical management of hereditary breast and ovarian cancer (HBOC) is important as these women are at higher risk of developing breast cancer. The breast cancer incidence rate peaks at an earlier age, i.e., in the late 40s, in Japan than in western countries. Women with HBOC are diagnosed at an even younger age and often during important phases of their lives, such as the period of childbirth and rearing. The implementation of early detection and prevention strategies thus plays an important societal role. Risk-reduction mastectomy has not only reduced the incidence of contralateral breast cancer but has also improved the overall survival rate. In a clinical setting, the identification of BRCA1 or BRCA2 mutations has gained significance as a tool for the implementation of cancer risk-reducing strategies. We describe herein the clinicopathological characteristics in surveillance-detected breast cancers among unaffected BRCA mutation carriers.
Patients and methods

Between January 2000 and December 2016, 776 probands visited the outpatient division of the clinical genetic oncology department at the Cancer Institute Hospital (CIH) in Tokyo. Of these, 550 (464 probands and 86 family members) underwent genetic testing. BRCA1 or BRCA2 mutation was detected in 155 individuals, including suspected deleterious mutations identified by genetic testing. At the time of receiving their genetic test results, 26 individuals with one of these mutations were disease-free, but had a family history of at least breast cancer or ovarian cancer. Those 26 individuals were enrolled in an intensive surveillance protocol that included biannual ultrasonography and clinical breast examination (CBE), annual mammography (MMG), and conditional contrast-enhanced magnetic resonance imaging (MRI) for the early detection of primary breast cancer in the CIH in Tokyo. Observation of these individuals started from the day of the release of genetic testing results until either the day of primary breast cancer diagnosis or the end of 2017. This study was approved by the Institutional Review Board of CIH (2016-1151), and informed consent was obtained from all subjects.

Table 1 Baseline and clinical characteristics of the subjects included in this study

| Characteristics                                      | Breast cancer patients (n = 5) | Subjects without breast cancer (n = 21) |
|------------------------------------------------------|-------------------------------|----------------------------------------|
| Mean age at diagnosis/end of 2017 (years)            | 41.4 (35–48)                  | 48 (28–76)                              |
| Mean age at genetic testing (years)                  | 37.5 (23–46)                  | 46.1 (25–71)                            |
| Mean duration of surveillance until cancer diagnosis/end of 2017 (months) | 48 (4–145)                  | 56 (19–100)                            |
| Mutation                                             |                               |                                        |
| BRCA1                                                | 2 (40)                       | 16 (76.2)                               |
| BRCA2                                                | 3 (60)                       | 5 (23.8)                                |
| Salpingo-oophorectomy                                |                               |                                        |
| Yes                                                  | 0                            | 8 (38.1)                                |
| No                                                   | 5 (100)                      | 13 (61.9)                               |
| Family history of breast cancer                       |                               |                                        |
| Yes                                                  | 5 (100)                      | 18 (85.7)                               |
| No                                                   | 0                            | 3 (14.3)                                |
| Age of the youngest family member at breast cancer diagnosis (years) | 30                           | 25                                      |
| Family history of ovarian cancer                      |                               |                                        |
| Yes                                                  | 1 (20)                       | 15 (71.4)                               |
| No                                                   | 4 (80)                       | 6 (28.6)                                |
| Age of the youngest family at ovarian cancer diagnosis (years) | 33                           | 40                                      |
| Ovarian cancer diagnosis                              |                               |                                        |
| Yes                                                  | 0                            | 3 (14.3)                                |
| No                                                   | 5 (100)                      | 18 (85.7)                               |

Data are given as mean values (range) or n (%). Mean age was calculated using age at diagnosis for those with breast cancer, or age on 31/12/2017 for those without.

Results

Five of the 26 individuals with BRCA1 or BRCA2 mutations were diagnosed with primary breast cancer while undergoing surveillance. Table 1 shows the baseline and clinical characteristics of the subjects included in this study. The mean age at genetic testing of the five patients who were diagnosed with breast cancer was lower than that of those who remained breast cancer-free (37.5 years vs 46.1 years). The mean duration of surveillance until breast cancer diagnosis was 48 months. Regarding genotype, two cases had a BRCA1 mutation and three had a BRCA2 mutation. Three out of five cases had only ductal carcinoma in situ (DCIS); one of these cases had irregular calcifications detected on MMG, and the other two had tumors that were detectable only by MRI. The five cases of breast cancer in previously unaffected BRCA mutation carriers are described below in further detail.

Case 1

A 42-year-old woman with a BRCA1 mutation developed DCIS as a primary breast cancer during surveillance only 4 months after genetic testing. She had received regular...
check-ups every year for 7 years. She had a positive family history of breast cancer: her sisters were diagnosed with breast cancer at 38 and 45 years of age, and her paternal grandmother was diagnosed at 70 years of age. Cancer was detected by MMG examination. She underwent total mastectomy and sentinel lymph node biopsy, and the tumor was shown to be pathological stage 0.

**Case 2**

A 35-year-old woman with a *BRCA1* mutation developed DCIS as a primary breast cancer during surveillance, 12 years after genetic testing was performed. She had a strong positive family history of breast cancer: her mother had bilateral breast cancer, with one tumor diagnosed at 45 years of age and the other at 48 years of age; her maternal grandmother had been diagnosed with breast cancer at age 90 years of age; and her maternal aunt’s daughter had breast and ovarian cancer at 33 years of age. Furthermore, the patient’s mother was diagnosed with ovarian cancer at 62 years of age. This patient had undergone breast screening examination every 6 months. Her cancer was detected only on MRI screening. The lesion was described as a non-mass with high signal on diffusion-weighed imaging (DWI). The apparent diffusion coefficient (ADC) level was slightly reduced. She underwent a total mastectomy and sentinel lymph node biopsy. The tumor was pathological stage 0 (Table 2).

**Case 3**

A 47-year-old woman with a *BRCA2* mutation developed a 4-mm-sized invasive ductal carcinoma (IDC) that was estrogen receptor (ER)-positive and human epidermal growth factor receptor (HER2)-negative. The carcinoma developed as a primary breast cancer during the surveillance period 7 months after undergoing genetic testing. Her cancer was first detected by ultrasonography. She had a positive family history of breast cancer: her monozygotic twin sister had breast cancer at 44 years of age, and her paternal grandmother had been diagnosed in her 50s. The patient underwent total mastectomy and sentinel lymph node biopsy; the tumor was pathological stage I.

**Case 4**

A 48-year-old woman with a *BRCA2* mutation developed DCIS as a primary breast cancer during surveillance 3 years after genetic testing. She had a strong positive family history of breast cancer: her mother had been diagnosed with breast cancer at 53 years of age, her maternal aunt at 52 years of age, one of her sisters at 30 years of age, and her youngest sister at 36 years of age. This patient had undergone breast examinations every 6 months. Her cancer was detected only on MRI. The lesion was also described as a non-mass-like enhancement in contrast-enhanced medium but was not detectable on DWI. She underwent a total mastectomy and sentinel lymph node biopsy. The tumor was pathological stage 0.

**Case 5**

A 35-year-old woman with a *BRCA2* mutation developed IDC that was ER-, progesterone receptor (PgR)-negative, and HER2-negative, as a primary breast cancer during surveillance, 2 years after receiving her genetic testing results. She had a strong positive family history of breast cancer: her mother had bilateral breast cancer, with one tumor diagnosed at 47 years of age and the other at 49 years of age; her maternal aunt also had bilateral breast cancer, with one tumor diagnosed at 45 years of age and the other at 47 years of age. The patient presented with a tumor that had been

| Patient no. | Age at breast cancer diagnosis (years) | Mutation | Surveillance period (months) | Diagnostic modality | Family history | Pathology | Stage | Outcome |
|-------------|---------------------------------------|----------|-----------------------------|--------------------|---------------|----------|-------|---------|
| 1           | 42                                    | *BRCA1*  | 4                           | MMG                | BC            | DCIS     | TisN0M0 Stage 0 | Alive without metastasis |
| 2           | 35                                    | *BRCA1*  | 145                         | MRI                | BC+OC         | DCIS     | TisN0M0 Stage 0 | Alive without metastasis |
| 3           | 47                                    | *BRCA2*  | 7                           | US                 | BC            | IDC      | T1N0M0 Stage I  | Alive without metastasis |
| 4           | 48                                    | *BRCA2*  | 51                          | MRI                | BC            | DCIS     | TisN0M0 Stage 0 | Alive without metastasis |
| 5           | 35                                    | *BRCA2*  | 35                          | CE (self-palpation)| BC+OC         | IDC      | T2N1M0 Stage IIB | Alive without metastasis |

MMG mammography, US ultrasonography, MRI magnetic resonance imaging, CE clinical examination, BC breast cancer, OC ovarian cancer.
detected by self-examination and which then grew rapidly in the interim. Figures 1 and 2 show the findings on MMG and MRI at the time of tumor detection, respectively. The lesion was described as a mass with high signal intensity in DWI of MRI. The ADC was reduced. However, there were no remarkable findings on MMG, ultrasonography, or CBE at the last evaluation, performed 3 months earlier. MRI was not performed at the last evaluation but had been performed the year before. She underwent a nipple-sparing mastectomy and axillary lymph node dissection; the tumor was pathological stage IIB.

Discussion

According to the National Comprehensive Cancer Network guidelines [1] and the Japanese Breast Cancer Society guidelines [2], annual MRI should be performed as part of regular check-ups for individuals with BRCA1 or BRCA2 mutations. Annual MRI combined with MMG examination has been reported to be more effective than MMG, ultrasonography, or CBE alone for detecting malignancies in BRCA1 and BRCA2 mutation carriers [3–5]. MRI increases the sensitivity of breast cancer detection at earlier stages and facilitates early detection of familial breast cancer regardless of the patient’s age, breast density, or mutation status [6]. It was not possible to perform annual MRI examination in all our patients due to the costs, limited access to the device, or constitutional factors. In fact, cases 1 and 3 were diagnosed with breast cancer within a year from the commencement of intensive surveillance, before scheduled MRI was performed. In the other 3 breast cancer cases, the first MRI examination performed in these patients resulted in detection of DCIS in 2. In agreement with studies from other countries [3–5], the combination of MRI and MMG was associated with a diagnosis of cancer at an earlier stage in women with a BRCA1 or BRCA2 mutation undergoing surveillance.

The Consortium of Investigators of Modifiers of BRCA1/2 stated that ER-negative cancers occurring in both BRCA1 and BRCA2 mutation carriers were associated with a higher histological grade than ER-positive cancers. Sixty-eight percent of breast cancers occurring in BRCA1 carriers were triple-negative, compared to only 16% of breast cancers in BRCA2 carriers [7]. In our study, the patient of case 5, who had a BRCA2 mutation, presented with advanced breast cancer of nuclear grade 3 and a triple-negative subtype. There were no remarkable findings on MMG, ultrasonography, or CBE at the last evaluation, 3 months prior to diagnosis. MRI was not performed at the last evaluation but was performed in the previous year. At the time of breast cancer diagnosis, she had been under surveillance for 2 years. Early detection of breast cancer was difficult in this patient who was of child-bearing age, although she was highly aware of her

Fig. 1 Mammography examination of case 5 revealed a possible focal asymmetric density on the upper area of the right breast with mediolateral oblique (MLO) view. RMLO right mediolateral oblique, LMLO left mediolateral oblique

Fig. 2 Contrast-enhanced magnetic resonance imaging in case 5 revealed a partially enhanced irregular mass of 3.2 cm in the upper-inner area of the right breast
risks. Women with BRCA1 or BRCA2 mutations strongly expressed preferences for breast cancer risk reduction and preservation of fertility [8].

Secondary breast cancers are mostly diagnosed at a more favorable stage than primary tumors [9]. Even when the secondary cancer was detected at a relatively early stage, the survival of patients with sporadic bilateral breast cancer was poorer than that of women with unilateral breast cancer [9–11]. If the interval between the primary surgery and contralateral breast cancer is short, the risk of relapse is greater and the breast cancer-specific and all-cause mortalities are higher [10, 12]. In case 5, the primary diagnosis was made at age 35, and both the patient’s mother and her maternal aunt had developed bilateral breast cancers with a 2-year interval. Contralateral risk-reducing mastectomy (CRRM) was offered to this patient. However, as she was of a child-bearing age, this made the decision to undergo CRRM very difficult.

Bilateral risk-reducing mastectomy (BRRM) reportedly reduces the risk of breast cancer significantly, although it does not completely eliminate the risk because of the possibility of residual mammary-gland tissue [13–15]. BRRM has not been proven to show improved survival rates [16]. Moreover, selecting appropriate high-risk cases for BRRM is difficult. Metcalfe et al suggested that women with BRCA1 or BRCA2 mutations who were treated for stage I or II breast cancer with bilateral mastectomy had better outcomes than those undergoing unilateral mastectomy [17]. According to a Dutch study, the overall 10-year contralateral breast cancer risk for unselected BRCA1 or BRCA2 mutation carriers is approximately 18%, whereas that for mutation carriers with a family history of breast cancer is higher, at 25% [18]. This study also emphasized the importance of age when the primary breast cancer is diagnosed, because in patients who were diagnosed with breast cancer before the age of 41 years, the 10-year contralateral breast cancer risk was 23.9%, compared to 12.6% for those aged 41–49 years [12]. The mean age at the primary breast cancer diagnosis in our five cases was 41.4 years, and the approaches to our cases should be carefully reviewed.

The current study has several limitations. First, this was a retrospective study. Additionally, the follow-up period was short, and annual MRI was not performed in all subjects. A longer follow-up period will be necessary in future studies to confirm our current findings.

In conclusion, we presented five cases of primary breast cancer in patients carrying a BRCA1 or BRCA2 mutation, whose tumors were diagnosed during surveillance. During the surveillance period, 5 individuals with BRCA1 or BRCA2 mutations were diagnosed with primary breast cancer. The mean surveillance duration until breast cancer diagnosis was 48 months. The incidence of primary breast cancer during surveillance in initially disease-free BRCA mutation carriers was 4.23%/year. Our results suggest that there are challenges involved in the early detection of breast cancers in BRCA1 or BRCA2 mutation carriers.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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References

1. National Comprehensive Cancer Network. NCCN guidelines. http://www.nccn.org/professionals/physician_gls/. Accessed 19 Dec 2017.
2. Taira N, Arai M, Ikeda M, Iwasaki M, Okamura H, Takamatsu K, et al. The Japanese Breast Cancer Society clinical practice guideline for epidemiology and prevention of breast cancer, 2015 edition. Breast Cancer. 2016;23:343–56.
3. Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol. 2011;29:1664–9.
4. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA. 2004;292:1317–25.
5. Rahkhlina A, Curpen B, Warner E, Betel C, Wright B, Jong R. Breast MRI as an adjunct to mammography for breast cancer screening in high-risk patients: retrospective review. AJR Am J Roentgenol. 2015;204:889–97.
6. Riedl CC, Luft C, Bernhart C, Weber M, Bernathova M, Tea MK, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol. 2015;33:1128–35.
7. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomark Prev. 2012;21:134–47.
8. Liede A, Mansfield CA, Metcalfe KA, Price MA, Snyder C, Lynch HT, et al. Preferences for breast cancer risk reduction among BRCA1/BRCA2 mutation carriers: a discrete-choice experiment. Breast Cancer Res Treat. 2017;165:433–44.
9. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, Ausens MG, Collée JM, Jansen L, et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer. 2015;136:668–77.
10. Evans DGR, Ingham SL, Baildam A, Ross GL, Laloo F, Buchan I, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2013;140:135–42.

11. Fayanju OM, Stoll CRT, Fowler S, Colditz GA, Margenthaler JA. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. Ann Surg. 2014;260:1000–10.

12. Vichapat V, Garmo H, Holmqvist M, Liljegren G, Wärnberg F, Lambe M, et al. Tumor stage affects risk and prognosis of contralateral breast cancer: results from a large Swedish-population-based study. J Clin Oncol. 2012;30:3478–85.

13. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, Van’t Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22:1055–62.

14. De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol. 2015;22:2876–80.

15. Skytte AB, Crüger D, Gerster M, Lænkholm AV, Lang C, Brøndum-Nielsen K, et al. Breast cancer after bilateral risk-reducing mastectomy. Clin Genet. 2011;79:431–7.

16. Ingham SL, Sperrin M, Baildam A, Ross GL, Clayton R, Laloo F, et al. Risk-reducing surgery increases survival in BRCA1/2 mutation carriers unaffected at time of family referral. Breast Cancer Res Treat. 2013;142:611–8.

17. Metcalfe K, Gershman S, Ghadirian P, Lynch HT, Snyder C, Tung N, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ. 2014;348:g226.

18. van den Broek AJ, Van’t Veer LJ, Hooring MJ, Cornelissen S, Broeks A, Rutgers EJ, et al. Impact of age at primary breast cancer on contralateral breast cancer risk in BRCA1/2 mutation carriers. J Clin Oncol. 2016;34:409–18.

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