Molecular Trajectory of BRCA1 and BRCA2 Mutations

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Every cancer carries genomic mutations. Although almost all these mutations arise after fertilization, a minimal count of cancer predisposition mutations are already present at the time of genesis of germ cells. Of the cancer predisposition genes identified to date, BRCA1 and BRCA2 have been determined to be associated with hereditary breast and ovarian cancer syndrome. Such cancer predisposition genes have recently been attracting attention owing to the emergence of molecular genetics, thus, affecting the strategy of cancer prevention, diagnostics, and therapeutics. In this review, we summarize the molecular significance of these two BRCA genes. First, we provide a brief history of BRCA1 and BRCA2, including their identification as cancer predisposition genes and recognition as members in the Fanconi anemia pathway. Next, we describe the molecular function and interaction of BRCA proteins, and thereafter, describe the patterns of BRCA dysfunction. Subsequently, we present emerging evidence on mutational signatures to determine the effects of BRCA disorders on the mutational process in cancer cells. Currently, BRCA genes serve as principal targets for clinical molecular oncology, be they germline or sporadic mutations. Moreover, comprehensive cancer genome analyses enable us to not only recognize the current status of the known cancer driver gene mutations but also divulge the past mutational processes and predict the future biological behavior of cancer through the molecular trajectory of genomic alterations.

Keywords: breast, ovary, pancreas, prostate, BRCA1, BRCA2, cancer predisposition gene, mutational signature

INTRODUCTION

Cancer cells harbor several genetic mutations and epigenetic modifications, which are believed to have arisen from sequential and multistage neoplastic processes (1). However, the mechanism of cellular transformation remains unclear because each oncogenic event is broken down into a molecular reaction, which seems to occur stochastically and independently during oncogenic events in each cancer case. Even if comprehensive genomic data are available, it is still difficult to determine the correct order of genomic alteration.

A possible breakthrough in the understanding of the evolutional process of cancer cells in vivo was provided by studies conducted on the hereditary cancer syndrome, which is due to a germline mutation of the cancer predisposition gene (2, 3). Before the establishment of molecular evidence, clinicians had insights into the familial breast cancer (4). Subsequently, genetic and reverse-genetic research revealed the initial and the following steps in the neoplastic process, which has contributed to novel strategies for cancer prevention, diagnostics, and therapeutics.

The main purpose of this review is to summarize the molecular biology associated with the representative cancer predisposition genes, BRCA1 and BRCA2, and to speculate on the missing link between normal and cancer cells.
DISCOVERY OF BRCA1 AND BRCA2

Cancer predisposition genes, BRCA1 and BRCA2, were first discovered in the genetic study on familial breast cancer (5) (Table 1). At that time, linkage analyses with DNA polymorphic markers were detecting the causal relationships between certain genetic diseases and specific genomic loci (6). Similarly, a variable number tandem repeat marker known as D17S74, revealed that the candidate familial breast cancer gene is located at chromosome 17q21 (7). Thereafter, this locus, also called the “breast cancer, early onset,” or BRCA1, was indexed for the comprehensive genetic disease database, Mendelian inheritance in Man (MIM), and was given the reference number 113705 (8). After the inter-laboratory competition over 4 years (9), positional cloning of BRCA1 was first achieved using an emerging technique which required the use of bacterial artificial chromosomes (10). In contrast, the second breast cancer predisposition gene, BRCA2, was discovered at chromosome 13q12 by other DNA polymorphic markers, D13S260, and DS13S263 (11), and registered with the MIM number 600185. The discovery of the second breast cancer predisposing gene was followed by the BRCA1 cloning, and subsequently, the race to clone BRCA2 was completed the following year by the same research team (12).

FUNCTIONAL SIMILARITIES AND DIFFERENCES BETWEEN BRCA1 AND BRCA2

Both BRCA1 and BRCA2 are large genes, which consist of ∼100 and 70 kb, respectively; the largest exon of both the BRCA genes is exon 11. Although these genetic features resemble the proof of breast and ovarian cancer predisposing gene family at the first glance, there is no homology between BRCA1 and BRCA2 (13). BRCA1 contains a nuclear localization sequence (NLS) and three functional domains; RING, coiled coil, and BRCT domains interact with the BRCA1-associated RING domain protein (BARD1), the partner and localizer of BRCA2 (PALB2), and several other proteins that include abraxas (ABRA1), CtIP, and BRCA1-interacting protein C-terminal helicase 1 (BRIP1), respectively (13). These interactions lead to versatile functions of BRCA1: DNA damage sensing, cell cycling regulation, E3 ubiquitin ligase activity, chromatin remodeling, and homologous recombination (HR). In contrast, BRCA2 has NLS, eight BRC repeats (14), and a DNA binding domain. Unlike BRCA1, the functional domains of BRCA2 are principally associated with the HR-related proteins, including RAD51 and deleted in split-hand/split foot protein 1 (DSS1) (15, 16). Therefore, the unique molecular traits of each BRCA protein create a difference between BRCA1- and BRCA2-mutated cancers.

As a common function between BRCA1 and BRCA2, HR is an essential DNA repair system that enables the error-free recovery of double strand breaks (DSBs) (17). DSBs are the most severe DNA damage, the accumulation of which results in genetic translocation and cell death (18). In the condition of homologous recombination deficiency (HRD) by BRCA dysfunction, restoration of DSBs depends on an error-prone repair machinery, known as non-homologous end joining (NHEJ). Such an HRD, also called genomic instability, is advantageous for the progression of BRCA-associated cancer to effectively gain sequence and structural variance, especially in the early phase.

OTHER INHERITED BREAST AND OVARIAN CANCER GENES ASIDE FROM BRCA1 AND BRCA2

Because BRCA1 and BRCA2 account for ∼25% of the familial breast and ovarian cancers (19), this section describes other breast and ovarian cancer predisposition genes. A linkage analysis study revealed that the third candidate hereditary breast cancer gene, BRCA3, was suspected at the BRCA2 neighboring locus, 13q21-22, in intact BRCA1/BRCA2 Nordic cohorts (20); however, the replication study failed to demonstrate the cancer susceptibility (21). These findings suggest that the current genetics-based research has been unable to identify the next cancer predisposition gene or that all BRCA genes have already been found.

TABLE 1 | Summary of BRCA1 and BRCA2.

| BRCA1 | BRCA2 |
|---|---|
| Location | Chromosome 17q21 | Chromosome 13q12 |
| Functional domains (their main binding partners) | RING domain (BARD1) | Eight BRC repeats (RAD51) |
| | Coiled coil domain (PALB2) | DNA binding domain (DSS1) |
| | BRCT domain (ABRA1, CtIP, and BRIP1) | |
| Synonym as FA genes | FANCs | FANCD1 |
| Cardinal function as a cancer predisposition gene | Homologous recombination | Homologous recombination |
| Association between promoter methylation and silencing | Established | Not established |
| Reversion of the mutated gene | Sometimes | Sometimes |
| Mutation signatures associated | Signature 3 or SBS3/ID6 | Signature 3 or SBS3/ID6 |
| Association with breast cancer | Basal-like and/or triple negative breast tumor, high grade histology | Lobular neoplasia, moderate to high grade histology |
| Association with ovarian cancer | High-grade serous carcinoma, SET-type | High-grade serous carcinoma, SET-type |
| | Possibly clear cell carcinoma | |
| Association with pancreatic cancer | Not established | Rarely, high grade histology |
| Association with prostate cancer | Not established | Rarely, high grade histology |

RING, really interesting new gene; BARD1, BRCA1-associated RING domain protein; PALB2, partner and localizer of BRCA2; BRCT, BRCA1 C terminus; ABRA1, abraxas; CtIP, CtBP interactive protein; CtBP, C-terminal binding protein; BRIP1, BRCA1-interacting protein C-terminal helicase 1; DSS1, deleted in split-hand/split foot protein 1; FA, Fanconi anemia; SBS, Single base substitution; ID, Small insertion and deletion; SET, solid, pseudoendometrioid, and transitional cell carcinoma-like histology.
Another technique to identify novel breast and ovarian cancer genes is to identify a gene cluster, such as BRCA genes, that play a role in the DNA repair system. Remarkably, HR is related to the Fanconi anemia (FA) pathway, which mediates repair of the interstrand crosslink (ICL) (22). FA is an inherited hematopoietic disorder that gives rise to myelodysplastic syndrome and leukemia. To date, over 20 genes have been identified as FA predisposing genes, and the germline mutation of the FANCA gene accounts for approximately two-thirds of FA cases (23). Most of the FA genes play an important role in the formation of the FA core complex, which binds at the ICL site and then activates the downstream signaling to repair this severely damaged DNA. Finally, the damaged sequence is removed by HR. Therefore, the defective FA pathway leads to cancer predisposition through genetic instability, such as BRCA1 and BRCA2 dysfunction.

Considering the functional significance of HR in the FA pathway, BRCA1 and BRCA2 have been refocused as FA susceptibility genes. Of the eight FA genes detected, FANCD1 was identified as BRCA2 (24). In contrast, BRCA1 has been recently recognized as FANCS (25). However, germline mutations of BRCA genes lead to bone marrow failure less frequently than mutations in other FA genes, likely because they are absent from the FA core complex.

Individuals with germline mutations of the FA genes are susceptible not only to hematopoietic but also to solid malignancies. Multiple gene panel studies have revealed that inherited breast and ovarian cancers rarely harbor germline mutations of FA genes, including BRIP1/FANCJ, PALB2/FANCN, and RAD51C/FANCO (26). Based on the latest National Comprehensive Cancer Network Guideline (27), PALB2 is categorized as a gene associated with breast cancer risk, whereas BRIP1 and RAD51C are categorized as genes associated with ovarian cancer risk.

The remaining clinically significant, inherited breast and ovarian cancer genes are the so-called cancer predisposition genes: ATM, CDH1, CHEK2, mismatch repair genes, NBN, NF1, PTEN, RAD51D, STK11, and TP53 (27). Therefore, an investigation of these cancer predisposition genes is effective in detecting the pathogenic allele in the case of the non-BRCA inherited breast and ovarian cancer.

**SIGNIFICANCE OF BRCA MUTATIONS**

Although numerous germline BRCA mutations, also called sequence variants, have been reported to date, not all the variants lead to predisposition to cancer. Therefore, interpretation of the clinical significance of the detected mutation is a challenge in medical practice. To determine whether the detected sequence variant is pathogenic or not, the American College of Medical Genetics and Genomics (ACMG), together with the Association for Molecular Pathology and the College of American Pathologist, issued the revised universal guidelines for the interpretation of sequence variants (28). Based on the evidence of pathogenicity or benignity, this guideline classifies the sequence variants into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. In practice, pathogenic and likely pathogenic variants require further medical management, whereas other variants do not require such intervention. Nevertheless, variants of uncertain significance, which are found in up to 20% of BRCA1/BRCA2 genetic tests (29), need follow-up to monitor the manifestation of the true nature of the variants; e.g., variant reclassification programs. The major databases and platforms that contain information on BRCA1 and BRCA2 variants are as follows: BRCA Exchange (30), ClinVar (31), the Human Gene Mutation Database (HGMD) (32), the Leiden Open Variation Database (LOVD) (33), the Consortium of Investigators of Modifiers of BRCA (CIMBA) (34), and the Evidence-based Network for the Interpretation of Germline Mutant Allele (ENIGMA) (35).

Recently, the international collaboration study conducted by CIMBA clarified different cancer risks related to BRCA genes (36). Consistent with the previous studies (37–39), both BRCA1 and BRCA2 genes contain several cancer risk regions. The ovarian cancer cluster region (OCCR) of both BRCA1 and BRCA2 largely overlaps with exon 11, whereas the breast cancer cluster regions (BCCRs) are located on the exterior of exon 11. The mutation in these cancer cluster regions leads to increased cancer risk of the corresponding organ. Additionally, the mutational type of the BRCA genes also affects the breast and ovarian cancer risk. Collectively, the diversity of the BRCA sequence variants implies not only the general cancer risk but also the specific susceptible organ, and, therefore, the detailed classification of the pathogenic variants would be effective to determine the optimal medical management.

**DNA METHYLATION STATUS OF THE BRCA GENES**

The dysregulation of the BRCA genes arises not only from genetic alternations but also from epigenetic modifications. At the transcriptional level, BRCA1 is regulated by the DNA methylation status at its upstream CpG island (40–42). Consistent with the promoter hypermethylation, BRCA1 is silenced in sporadic breast and ovarian cancer (43, 44). The aberrant BRCA1 promoter methylation is found in approximately one-ninth of ovarian cancer tumors (45–47) and in one-fourth of breast basal-like tumors (48), suggesting that BRCA1 silencing is considered a leading non-genetic case of BRCA1 inactivation in sporadic wild-type BRCA cancer. The comprehensive ovarian cancer genomic studies revealed that hypermethylated-BRCA1 ovarian cancer with platinum therapy had a similar prognosis as the intact BRCA cancer, whereas BRCA1/BRCA2-mutated ovarian cancer showed better prognosis than the wild-type cancer (46, 47). On the other hand, cancer with homologous BRCA1 hypermethylation showed a good response to an emerging therapeutic agent (described in a later section), the PARP inhibitor, which was same as the response of cancer with BRCA germline mutation (49). These evidences suggest that quantitative methylation analysis of BRCA1 promoter would be needed to predict the clinical behavior of hypermethylated BRCA1 cancer.
Conversely, the functional significance of the nearest CpG islands of BRCA2 still remains unclear. Unlike BRCA1, BRCA2 promoter methylation is not considered a leading cause of BRCA2 dysfunction (45–48, 50). However, the specific CpG site methylation is a possible marker of germline BRCA mutations (51). Because functional significance of the aberrant methylation still remains unclear, further investigations would be needed.

**REVERSION OF THE BRCA MUTATION**

Reversion is defined as the secondary mutation of an inherited mutant gene, which restores normal function in somatic cells (52). For example, the pathogenic BRCA allele sometimes reverts to the wild-type sequence via an additional point mutation (back mutation) (53, 54). Conversely, additional insertion/deletion of BRCA genes amends the altered reading frame normally (in-frame mutations), thus, converting it to the non-pathogenic allele. These genetic alterations are considered to be a late stage oncogenic event to reactivate the HR pathway, and it consequently renders the cancer cells resistance to lethal DNA damage. Interestingly, approximately a quarter to half of ovarian cancers with germline BRCA1/BRCA2 mutations exhibit the reversion of the inherited mutation and chemoresistance after chemotherapy (47, 55, 56), suggesting that in vivo retrieval of BRCA function is a potent oncogenic event to resist unwanted DNA damage.

**MUTATIONAL SIGNATURE OF BRCA DYSFUNCTION**

The forthcoming breakthrough in carcinogenesis research is the “mutation signature,” which stands for a unique pattern of genetic alterations in somatic cells. Given that every mutation arises from a specific molecular reaction, the characteristic sets of the genetic alterations are good evidence for mutational processes in cancer cells. This concept enables researchers to convert the vast genomic data on cancer cells into evidence on the current status of cancer-related genes and sheds light on the history of cancer progression.

Owing to the emerging technology, such as next-generation sequencing (57), the first series of comprehensive somatic mutation research successfully demonstrated the close relationship between a certain type of cancer and mutational signatures. Briefly, the melanoma cell line frequently carried C>T and/or CC>TT transition, which is consistent with the effect of ultraviolet light exposure on pyrimidine bases (58). Conversely, the small-cell lung cancer cell line harbored predominantly G>T, G>A, and A>G transitions, which are interpreted as the modification of purine bases by tobacco smoke carcinogens (59). Interestingly, both studies also highlighted the presence of other mutational signatures, suggesting that somatic cells experience multiple mutational processes in vivo.

In the last decade, the classification of mutational signatures has rapidly progressed (Figure 1). The classification of mutational signatures was first initiated in a whole-genome study of human breast cancers (60). Owing to the complementation between pyrimidine and purine nucleobases in the double helices, all single base substitutions (also known as point mutations) can be summarized into the following six patterns: C>A/G>T, C>G/G>C, C>T>G>A, T>A/A>A>T, T>C/A>G, and T>G/A>C transitions. Additionally, to consider the sequence context of the mutated base, these six mutation classes are further subdivided into 96 trinucleotides patterns by referring to the neighboring bases: the 5′- and 3′-base (each base has four types). By analyzing these 96 trinucleotides patterns in 21 different types of breast cancers with mathematical models, five distinctive molecular signatures were extracted. The mutational spectrum of these signatures possibly reflected either aging (spontaneous deamination of 5-methyl-cytosine: Signature A), overexpression of cytidine deaminase belonging to the APOBEC family (Signatures B and E), or BRCA1/BRCA2 mutations (Signatures C and D). Unlike the other mutational signatures, the BRCA1/BRCA2 mutation-associated signatures were unique in regard to the relatively equal distribution of the 96 trinucleotides patterns. Additionally, BRCA1/BRCA2-mutated cancer carried microhomology-mediated deletions more frequently compared with the wild-type cancers. These genomic abnormalities are likely due to the dysfunction of HR when double strand breaks occur. Subsequently, the additional breast cancer genome study failed to reproduce the Signature C-like pattern; thus, the BRCA1/BRCA2 mutation associated Signatures C and D was combined into Signature 3 (61).

Thereafter, the international collaborative research group analyzed the large collection of somatic mutations for various cancer types to identify further detailed classes of mutational signatures (62). Although this study identified the 21 distinctive patterns of mutational signatures, the etiology remained unknown for approximately half of the mutational signatures. The mutational signature for BRCA1/BRCA2 mutations, or Signature 3, was reconfirmed in this study, and documented in version 2 of the Catalog of Somatic Mutations in Cancer (COSMIC) mutational signatures (63).

To date, the classification of mutational signatures continues to evolve. Version 3 of COSMIC mutational signatures is composed of three conceptual sets: Single Base Substitution (SBS), Double Base Substitution (DBS), and Small Insertion and Deletion (ID) Signatures (64). This detailed scheme sorts the BRCA1/BRCA2-associated mutational signature into SBS and ID. In other words, the relatively equal SBS distribution and microhomology-mediated deletions of Signature 3 are interpreted as SBS3 and ID6, respectively.

The analysis of mutational signatures reveals the DNA damage and repair processes of the cancer genome, which arise from the specific molecular reaction. Given the close relationship between Signature 3 and BRCA mutations, this genome-wide mutational pattern would be applied to the analysis of cancer genome (50, 65). Increased Signature 3 activity was observed not only in the dysfunction of BRCA1 and BRCA2 but also in the inactivation of other HR-related genes, including the PALB2 germline mutation and RAD51C hypermethylation. Remarkably, the increased Signature 3 activity is significantly associated with biallelic mutation, loss of heterozygosity, or epigenetic silencing of the HR-related genes. In contrast, HR-related incomplete
inactivation of the gene, e.g., a monoallelic mutation, did not achieve significant Signature 3 enrichment. Therefore, Signature 3 is the circumstantial evidence of HRD, and a good predictor of pathogenic variants of HR-related genes.

**CHARACTERISTICS OF CANCER WITH BRCA DYSFUNCTIONS**

The link between BRCA mutations and specific types of cancer has been emerging. The recent TCGA study addressed the molecular classification of gynecologic and breast cancers, and acknowledged the existence of a subset of cancers with BRCA-associated mutational signatures (66). In breast cancer, BRCA1-mutated carcinoma is significantly associated with the basal-like subtype that exhibits negative expression of the estrogen receptor (ER), progesterone receptor (PGR), and ERBB2/HER2 (67–69). Additionally, BRCA1-mutated and basal-like breast cancer are high grade carcinomas with frequent TP53 mutations (70, 71), indicating that coexisting BRCA1 and TP53 mutations facilitate breast cancer progression. In comparison with BRCA1-mutated cancer, BRCA2-mutated breast carcinomas frequently express ER and PGR; additionally, HER2 is expressed at the same frequency (69). Furthermore, the histological grade of BRCA2-mutated breast carcinoma is generally lower than that of BRCA1-mutated breast carcinoma. Regarding the histological type, lobular carcinoma is typically prevalent in the BRCA2-carriers, whereas medullary carcinoma is more common in BRCA1-carriers. Lately, in the breast surgical specimens of BRCA-carriers, the dedicated histological examination revealed a distinctive pathologic condition known as “hyaline fibrous involution” (72). Lee et al. reported that hyaline fibrous involution was frequently

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**FIGURE 1** | BRCA-associated mutational signature. *(Upper panel)* Classification of the mutational signatures possibly related with BRCA dysfunction. The details of each classification are found in the references 60, 61, 62, and 64. *(Lower panel)* Characteristics of the BRCA-associated mutational signatures. COSMIC, the Catalog of Somatic Mutations in Cancer; v2, version 2; v3, version 3; SBS, Single base substitution; DBS, Double base substitution; ID, Small insertion and deletion; NA, not applicable.
associated with BRCA-mutated perimenopausal women. This unusual histological finding, including diffuse thickening of the fibrous band in the benign breast lobule, likely arises from the abnormal DNA repair state in non-neoplastic breast epithelium. Although this atrophic-like alteration is a promising premalignant lesion that is rarely found in the benign breast disease, we believe that hylane fibrous involution is an unexpected chance to suspect inherited cancer in cases without genetic test and clinical history.

Conversely, ovarian cancer among BRCA-carriers tends to be the most frequent histological type; it is a high-grade serous carcinoma (HGSC) (73). HGSC is a representative type II carcinoma (74), which almost always exhibits high grade nuclear atypia arising from TP53 mutations (46). The prophylactic surgical specimens revealed that the fallopian tube sometimes contained serous intraepithelial carcinoma (STIC) with TP53 mutations even in asymptomatic BRCA-carriers (75, 76). Interestingly, the putative precursor lesion of STIC, or the p53 signature (77), which already carries the TP53 mutation, is also sometimes found in the fallopian tube, regardless of the BRCA genotype. Additionally, the TP53 mutation type of the p53 signature is occasionally discordant with that of HGSC (78). These findings suggest that the functional significance of BRCA mutations is the promotion of neoplastic cells rather than the initiation of minute precursors. Additionally, they suggest that inherited ovarian cancer is most probably an inherited "tubal" cancer, on the basis of the tubal origin theory of HGSC (79).

Notably, HGSC with BRCA dysregulations, including BRCA1/BRCA2 mutations and BRCA1 promoter hypermethylation, are associated with specific morphological “SET” patterns: Solid, pseudoEndometrioid, and Transitional cell carcinoma-like histology (80, 81). Recognition of the SET variant is in line with the recent diagnostic concept for ovarian carcinoma; there are five major histological types that reflect unique molecular characteristics and precursor lesions, and mixed-type ovarian carcinoma accounts for a rare fraction of ovarian epithelial malignancies (82). Although ovarian transitional cell carcinoma was a distinct entity (83), this malignant tumor was incorporated into HGSC in the World Health Organization 2014 classification because of the similarity of the molecular characteristics between the two carcinomas (84). Importantly, SET-type HGSC shows good therapeutic response compared to the conventional-type HGSC, likely due to the HRD arising from BRCA dysregulation. Thus, the SET pattern is a diagnostic and therapeutic predictor for HGSC; therefore, pathological examination still remains important in the era of molecular oncology.

Another possible genetic-pathologic correlation between clear cell carcinoma (CCC) and BRCA2 mutations (85, 86) seems contradictory to the findings of other research groups (87, 88). Because CCC is a type I carcinoma that originates from endometriosis-related cysts or lesions (74), the pathogenesis of CCC is generally unrelated to the above-mentioned high-grade serous carcinogenesis. Nevertheless, three mixed CCC and HGSC cases were reported based on immunohistochemical and genetic analyses (82). The two of the three mixed CCC and HGSC cases were true combined type I and II carcinomas, whereas the remaining case was pure HGSC. These findings suggest that CCC and HGSC might arise from the common precursor cells or that CCC is sometimes misinterpreted as a HGSC by histological assessment only. Therefore, further data are needed to confirm this ovarian genetic-pathologic correlation.

In addition to breast and ovarian cancers, pancreatic and prostate cancers rarely harbor BRCA mutations (89, 90) and BRCA-associated signatures (62, 64). The clinical sequence studies reveal that the germline BRCA2 mutation is detected in ~5% of metastatic prostate carcinoma cases (91–93). Histologically, BRCA2-mutated prostate carcinoma is associated with high grade histology (94, 95), including ductal (96) and endocrine (97, 98) differentiation. On the other hand, pancreatic cancer also harbors BRCA2 mutations. Of the common types of cancer, including pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine tumors (PanNET), ~4 and 1% of PDAC and PanNET possess germline BRCA2 mutations, respectively (99, 100). These findings suggest that mutated BRCA2-carriers should exercise caution regarding the development of extra-mammary and uterine adnexal cancers.

## THERAPEUTIC APPROACH TO THE BRCA-MUTATED CANCER

Because breast and ovarian cancer predisposition genes were identified, the principal strategy of hereditary cancer management involves the early detection of cancer by frequent medical checks, including mammogram, breast MRI, transvaginal ultrasound, and serum CA-125 test, frequently referred to as surveillance. In some cases, this entails the surgical removal of the susceptible organs, if deemed medically necessary. Traditionally, pathogenic BRCA-carriers require a prophylactic removal of the susceptible organs to prevent breast and/or ovarian cancer even in their reproductive age (101). The resected breasts and uterine adnexa contain premalignant lesions and/or microscopic carcinomas (102, 103), which imply the presence of candidates for future malignancy. Indeed, BRCA-carriers sometimes suffer from contralateral breast cancer after the first breast cancer. Therefore, bilateral mastectomy is effective to prevent multiple and hererochronous cancer. In addition, in a recent study, it was revealed that oophorectomy slightly assisted in decreasing contralateral breast cancer (104).

Recent molecular and clinical evidence endorses molecular therapy for BRCA-mutated cancer. As described previously, BRCA-mutated cancer generally exhibits high-grade histology and aggressive phenotypes but responds favorably to platinum-containing chemotherapy (105–108). Such platinum sensitivity is probably due to BRCA-associated HRD that fails to recover platinum-induced ICL (109).

A novel molecular treatment using poly (ADP-ribose) polymerase (PARP)-inhibitor is also based on HRD in the BRCA-mutated cancer cells. PARP1 is a cardinal DNA repair molecule in the case of single strand breaks (SSB) (110). Inhibition of PARP1 results in the occurrence of DSBs, which is the failure of the replication fork through SSB repair (111, 112), as well as the disturbance of the NHEJ repair pathway,
by blocking the chromatin remodeler known as CHD2 (113). Together, PARP1 inhibitor and HRD accumulate the critical DSB damage in the BRCA-mutated cancer cells. Consistent with the results of these in vitro studies, PARP inhibitors have the effect of suppressing the BRCA-mutated cancer regardless of the cancer type (114–117). Currently, clinical use of these promising drugs has been approved by the FDA (118). In the future, genetic testing of the BRCA mutation would be necessary to determine the optimal therapeutic plan for individuals with advanced cancer.

CONCLUSION

As the molecular functions of BRCA1 and BRCA2 have been elucidated, the clinical focus on these cancer predisposition genes shifts toward the development of therapeutic strategies. Additionally, comprehensive cancer genome analysis illustrates not only the present status of cancer related genes but also the past and ongoing mutational processes arising from specific molecular reactions. In the future, the prospective biological behavior of cancer will be predicted via the molecular trajectory of genomic alteration.

AUTHOR CONTRIBUTIONS

YH contributed to the conception of the work and wrote the manuscript. MT, MM, and AH contributed to the revisions of the manuscript. All authors have read and approved the submitted manuscript.

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