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Targeted therapy of BRCA2 hypermethylation of breast cancer tumorigenesis in carrier females: A Review

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Abstract

The widespread tumorigenesis among the descendants of females who have a history of breast cancer in their pedigree is also anticipated earlier. The genes carried have a certain probability of activating cancer cells in an advanced stage. Although breast cancer is prone to be diagnosed in female offspring, it is necessary to detect the certainty of inheritance of the most common biomarker gene BRCA2. The effects of tumorigenesis can be in a dormant phase in carrier females. This needs to be watched out for, especially for females who are young and are still growing. The unexpressed BRCA2 gene for breast cancer needs to be predicted for its hypermethylation activity transcriptionally. The initial prognosis is estimated to be seen using multigene therapy. This therapy can target BRCA2 hypermethylation and appropriate treatment before increasing the tumorigenesis in carriers.

Keywords: BRCA2 Hypermethylation, Breast Cancer, Mastectomy, Mutation, Targeted Therapy.

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1. Introduction

BRCA2 is inseparable from the history of strains that are inherited in the family tree. In general, breast cancer biomarkers are found as BRCA1, BRCA2, or TP53 [1-3]. However, BRCA2 is often associated with the highest percentage if it is inherited from an ancestor who has a history of breast cancer. In a pedigree, the filial offspring of crosses are divided into probabilities related to the inheritance of the BRCA2 cancer gene. Usually, based on gender, breast cancer is more common in females than in males [2]. Females with a family history of carrying the BRCA2 gene have not fully expressed breast cancer tumorigenesis [3]. Most of the impact of this family history can allow the activation of tumor cells into malignant breast cancer. Families that are free from the detection of breast cancer are also inseparable from the small prognosis of the BRCA2 gene in increasing tumorigenesis in female patients [4]. In the manifestation of breast cancer, female patients can be categorized as carrier patients and non-carrier patients. Apart from the known appearance of visible symptoms in breast cancer sufferers, career females can contribute to tumorigenesis due to various specific factors [7]. The factor can be caused by exposure to radioisotopes, a certain age, or type of activity, the most common may be carried genetically [4]. This needs to be known from the start in young females, under 40 years old so that they have protection and earlier prevention to anticipate and reduce the prevalences of breast cancer. Besides that, the importance of communication in the family is to educate the impact of breast cancer which is caused by genetic family history [6]. However, the oral communication has not been optimized from the family environment. An understanding of literacy related to breast cancer is finally needed by a geneticist, including communication counselors. Genealogical history on the possibility of developing breast cancer [7]. Less is known about this breast cancer activated BRCA2 hypermethylation in the early stages [4]. However, a BRCA2 gene driver can harm the transcription factors necessary to produce the finished protein [8]. By inhibiting DNA repair activity, this step that increases hypermethylation of the BRCA2 gene makes it simpler to regulate the progression of breast cancer [9]. Later the coding protein will be influenced by BRCA2 and take the proper source of nutrition for cells around the mammary epithelial. Expression of the BRCA2 gene for the active tumorigenesis of breast cancer takes 10

years period [4]. The growth of tumorigenesis in female patients will develop significantly to reach the highest stage [11]. Carrier females need to detect the possibility of BRCA2 tumorigenesis with multigene therapy. Usually, cancer therapy is quite expensive provided in developing countries [12]. This is also confirmed by gene therapy that suppresses tumorigenesis has not been encouraged in all countries and has received little attention [13]. However, multigene therapy tends to be cost-friendly and affordable because it links breast cancer epigenetic factors widely [13]. This review is aimly to compare and choose the effective mastectomy alternatives and the risk for BRCA2-affected females. The discussion will potentially detect tumorigenesis early both in family history and sporadic breast cancer. Besides that, youngest age-determined option will be important to target gene therapy more successful.

2. Review

2.1. BRCA2 hypermethylation in tumorigenesis development

BRCA2 gene oncosuppressor biomarkers may play a role in breast cancer tumorigenesis. BRCA2 hypermethylation involves inactivation and is more at risk for the development of tumorigenesis. BRCA2 is an array of 26 coding exons on the long arm of chromosome 13 (13q12.3). BRCA2 can synthesize a protein code of up to 3418 amino acids [14]. Based on the large size of BRCA2, it is associated with the role of this gene as a structural element in DNA repair in suppressing breast cancer tumorigenesis [15,16]. Important roles in the composition of BRCA2 include BRC repeats having 8 conserved motifs of 35 amino acids; there is a DNA-binding domain (DBD) composed of a long helix domain (HD) and there are 3 oligonucleotide/oligosaccharide-binding (OB) folds and a TR2 C-terminal domain is formed. BRCA2 subcellular location is controlled by 2 NLSs (nuclear localization signals) and 1 NES (nuclear export signal). In addition, several BRCA2 regulatory proteins such as RAD51, (PALB2)/FANCN, and FANCD2 [14]. The composition of the BRCA2 domain includes multifunctional proteins in the biological pathways of breast cancer development. Concern for the effects of BRCA2 hypermethylation affects the genomic stability of target cells [42]. Regarding genome stability which can suppress the prognosis of tumorigenesis, its function is to focus on repairing DNA lesions including DNA double-strand breaks (DSBs) and intrastrand crosslinks (ICLs) (Figure 1) [17]. This repair function is non-dependent. The function of BRCA2 targets the cell cycle, namely inhibiting nucleolytic degradation of the central chain of DNA replication [14]. Directly or indirectly, BRCA2 hypermethylation maintains the telomerase cycle of breast cancer-inducing cells without the progress of multigene therapy [18]. Females with a large prognosis for breast cancer are likely to interfere with the mechanism of DNA replication, even to thwart the process of dividing chromosomes during mitosis [9]. Furthermore, BRCA2 hypermethylation results in a stalled transcriptional stage and results in nonfunctional protein products. The potential for mutations in breast cancer activating genes causes genome rearrangements for specific cell tumor colony markers affected [20]. BRCA2's N-terminal domain is implicated in various protein-protein interactions, including those with PALB2 and EMSY. BRCA2 has eight BRC repeats in the protein's core region; they are largely engaged in binding to monomeric RAD51, but they are also involved in other protein-protein interactions (PDS5B/APRIN and Polη). A helical domain (HD), three oligonucleotide/oligosaccharide-binding (OB) folds, and a Tower domain (T) comprise the BRCA2 DNA-binding domain (DBD). They help BRCA2 bind to single-stranded DNA (ssDNA) and poly (ADP-ribose) (

Figure **1**) [21]. Disruption of protein synthesis from the detection of BRCA2 hypermethylation can incoordinate DSB (double-strand break) repair resulting in the level of cell death. The detected DSB is caused by the loss of a segment and a chromosomal translocation occurs [22]. Instead, changes to the genome sequence are required for DNA repair. However, this contributes to the spread of tumorigenesis and a higher risk of breast cancer for female patients [28]. Even if the problem of synthesis error can be corrected, the detection of BRCA2 for regulation of cancer cell growth results in allowing gene mutations to inhibit this repair. Once accumulated, tumorigenesis occurs which persists throughout the life of the affected patient [19,22].

2.2. Multitarget factors related on breast cancer reduced risks

Gene therapy for this is targeted routinely to carrier females with a family history of affection who have a breast cancer prognosis [26]. As a result of decreasing heredity in the genealogy of parents who insert tumor mutation genes in their offspring, the effects of breast cancer can spread aggressively during the active stage that is running [28]. This anticipation needs to be activated earlier, especially for females, including at the youngest age between 15-39 years old [29, 30]. The introduction of therapeutic methods that target cancer cells is detected by looking at multitarget factors because carrier females also get cancer gene variants of other subtypes or types than breast cancer which can attack normal body tissues [31]. Carrier females get the BRCA2 gene transfer from their parents on one of the chromosomal alleles. This can be watched out for by planning multigene therapy in the future [30]. BRCA2 hypermethylation targeted therapy inhibits actively growth of the BRCA2 genes as a breast cancer biomarker. In addition, this therapy can stop the spread of other cells originating from mammary cells [4]. Related to the effectiveness of multigene therapy on carrier women, BRCA2 hypermethylation still adapts to inhibition of achieving growth needs such as breast cancer. Based on , BRCA2 contributes to a life span of 41-90%. The determination of the breast cancer survey was carried out through the MRI check prevention method at the age of 25 while using a 3D mammogram at the age of 30 [33]. The risk of suppressing the effects of breast cancer can be considered when using a mastectomy. In addition, the BRCA2 gene can be selected according to methods regarding chemoprevention [34]. Intensive target breast surveillance for carrier females at high risk of breast cancer involves clinical breast examination using yearly mammograms with tomosynthesis (3D) and annual breast MRI with contrast starting before the age of 40 years [35]. The age of initiation of breast cancer screening depends on the variant or type of pathogen mutation. Meanwhile, breast cancer risk detection begins more quickly for early adolescence age in the family history [36]. When testing for mutations in cancer-associated genes, a high index

of suspicion must be used based on each patient's clinical circumstances [37]. When there is a family history of cancer, it is best to test the person with the cancer diagnosis to increase the likelihood of a positive test result. Sanger sequencing and PCR amplification have traditionally been used in clinical BRCA1 and BRCA2 testing protocols [38]. If a mutation is discovered, other family members may be subjected to targeted testing to determine their risk [39]. Possible outcomes include a true positive, a true negative (a person in a family with a known mutation testing negative for that mutation), and an uninformative result (a negative test in a family where a mutation has yet to be identified). Genetic testing could result in a variant with unknown significance (VUS). A VUS is a genetic change discovered without a clear explanation of any clinical risk [8]. BRCA1 and BRCA2 mutations were previously the primary focus of testing for patients with a suspected genetic risk, with additional testing based on the patient's family history [40]. There have been more options for evaluation with the development of multiplex gene tests in recent years. Using next-generation sequencing, numerous genes can be examined for mutations at a fraction of the cost of sequencing each gene individually [41]. Furthermore, this method may detect mutational changes that traditional sequencing techniques missed, such as significant rearrangements [42]. Multiplex genes test amplify more than one gene and across the genome in a single run sequencing simultaneously. This method may benefit to patients with a less common underlying cause for their hereditary proclivity to develop cancer or women with a less obvious family history, those with fewer female relatives or paternal inheritance of the genes [37]. Future research will most likely provide a better understanding of the function of modifier genes. It may facilitate an understanding of how various gene mutations or polymorphisms interact to produce additive or synergistic effects [20]. More in-depth genetic analysis, as well as the availability of multiplex assays, frequently result in more ambiguous data [43]. Furthermore, for next-generation sequencing test, rigorous VUS analysis and interpretation will be required. Several in silico models speculate on the functional significance of these variations [17]. It is currently recommended to treat these mutations as VUS until they are identified as harmful. Furthermore, as the cost of genomic assays has decreased, the number of commercially available tests marketed as personal genomic testing (PGT) has increased significantly [26]. In any case, the researcher is still not very good at interpreting the results of these tests. Because a few tests are purchased directly from consumers, it is difficult for handling therapists to know the versatility of testing [29]. A major issue with this new method of medical risk management is that patients and doctors regularly feel unprepared to analyze data.

2.3. Early mastectomy alternatives as breast cancer therapy consideration

Breast-conserving surgery (BCT) is a popular mastectomy alternative for early breast cancer [35]. However, one of the relative comorbidities for BCT with breast illumination is "females with a known or suspected genetic susceptibility to breast cancer," according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN). Problems with breast reconstruction after breast radiation exposure, consideration of prophylactic bilateral mastectomy (BRRM), and an increased risk of anteriorly breast progression in women with HR-related or radiosensitive germline mutations, such as Li-Fraumeni syndrome, are all possible causes [37]. The chances of BRCA1/2 mutation carriers experiencing ipsilateral breast recurrence and contralateral breast cancer (CBC) survival regarding BCT have previously been studied [39]. A recent meta-analysis examined 11 review studies on ipsilateral breast tumor recurrence or IBTR BCT, CBC, distant likelihood, and prognosis. Six retrospective studies on BCT toxicity in BRCA mutation carriers and noncarriers, six retrospective studies on BCT and mastectomy in BRCA mutation carriers, and one meta-analysis report were published [43]. In BRCA mutation carriers, there were no discernible differences in BCT toxicities, distant likelihood, or overall survival between BCT and mastectomy, even though it is unknown whether the risk of long-term IBTR, including new primary IBTR, raises after BCT in BRCA mutation carriers and noncarriers [41]. There are no randomized controlled trials comparing BCT to radiation therapy for breast cancer with BRCA mutations [38]. The data comes from reviews, research reports, and retrospective experiments. Mastectomy is not recommended unless preoperative BRCA mutations are discovered, or the patient heavily prefers breast-conserving surgery compared to the prolonged risk [39]. Most hereditary types of cancer have a[moderate effect of gene mutations [46]. But besides that, BRCA2 is one of the four genes that result in the highest penetration risk associated with tumorigenesis of breast cancer [47]. It is possible to detect BRCA2 hypermethylation more than the BRCA1 subtype gene. These gene mutations are less likely to cause malignancy of breast cancer. However, carrier females aged less than 40 years have unexpected probabilities when multigene therapy is not applied [48]. This can change the target cells for tumorigenesis and spread along with the growth of breast cancer. Multigene therapy can affect epigenetic activating tumor cells and result in more aggressive results than previously prediagnosed. In multigene therapy options, reducing the risk of breast cancer is recommended through the mastectomy method. Mastectomy can reduce the risk of increasing tumorigenesis of breast cancer by more than 90% [34]. Intensive control of breast cancer tumorigenesis detection involves annual breast MRI checks and annual mammograms [49, 50]. Usually, the schedule is set alternately every 6 months. According to clinical sources, provider-recommended breast cancer risk checks every 6 to 12 months [51,53]. Patient carrier females need awareness to space the examination time within the recommended period. Breast MRI was initiated at age 25 and follow-up mammograms were awaited until age 30 due to increased breast density at the age of female growth and concern over cumulative radioisotope effects during multigene therapy. Breast cancer preventive activities will have the greatest impact if they begin at a youngest age and continue throughout females' life. Early-life therapeutic radiation is linked to an increased risk of breast cancer. Faster than that influences anxiety levels, and affects their mental disorders, as well as biopsies that are not guaranteed [40,51].

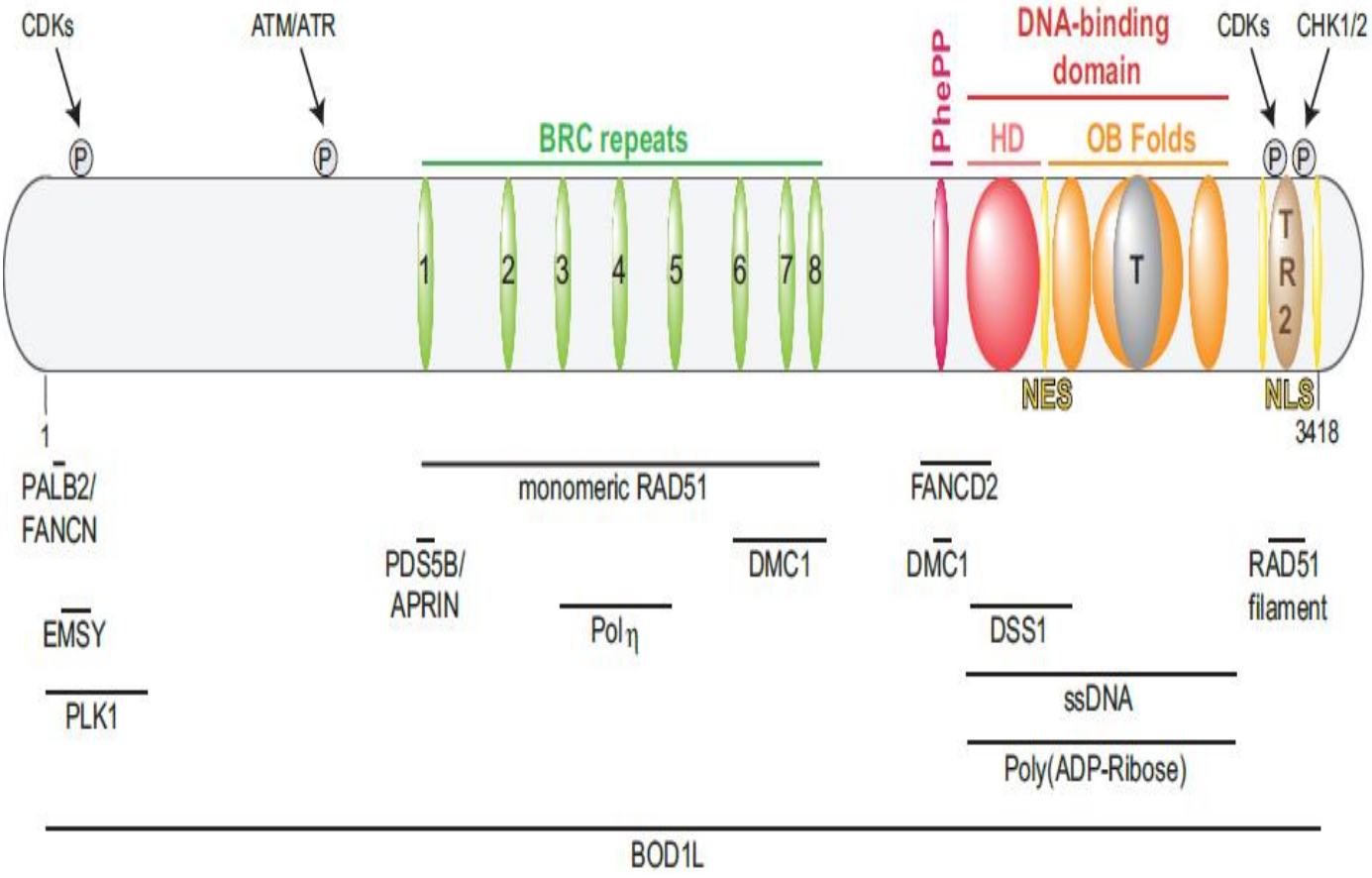

Figure 1: Domain structure of gene BRCA2 [21]

Table 1: Risk-reduction methods of gene BRCA2 towards breast cancer [34]

Gene	Lifetime Risk	Breast Surveillance	Risk Reduction Methods
BRCA1	41-90%	• Breast MRI initiate at age 25. • 3D mammogram is recommended at age 30.	• Consider vulnerability-reducing mastectomies. • Chemoprevention is a possibility, but it is not as effective.
BRCA2	41-90%	• Breast MRI initiate at age 25. • 3D mammogram is recommended at age 30.	• Consider vulnerability-reducing mastectomies. • Chemoprevention is a possibility, but not as thoroughly researched in these inhabitants.
TP53	~54%	• Breast MRI initiate at age 20. • 3D mammogram is recommended at age 30 (due to radioactive risk alert).	• Consider vulnerability-reducing mastectomies. • Chemoprevention is a possibility, but not as thoroughly researched in these inhabitants.

3. Conclusions

BCT is a mastectomy alternative for early breast cancer. This method can reduce the risk of increasing tumorigenesis of breast cancer by more than 90%. To detect BRCA2 tumorigenesis, age 25 and were awaited until age 30 indicate higher breast density by annual breast MRI checks and annual mammograms. During multigene therapy, breast cancer preventive BCT will have the long serious impact if they begin at a youngest age before 25 years old. Earlier BRCA2 targeted gene therapy is linked to an increased risk of breast cancer for females patient. Multigene therapy is necessary for carrier females to screen for the potential development of BRCA2 tumors.

4. Recommendation

From the research review, we recommend that clinicians selectively offer screening for BRCA2 breast cancer in adults aged 25 to 39 years. Evidence indicates that the net benefit of screening all persons in this age group is remarkable. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and other preferences.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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