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Review Article

Relevance of *BRCA1* and *BRCA2* variants in treating triple negative breast cancer patients

Engku Fatimah Syairah Engku Safruddin[a], Thirumulu Ponnuraj Kannan[b,c]*, Wan Zainira Wan Zain[d], Venkata Murali Krishna Bhavaraju[e]

[a] Department of Nuclear Medicine, Radiotherapy and Oncology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[b] School of Dental Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[c] Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[d] Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[e] Penang Adventist Hospital, 465, Jalan Burma, George Town, 10350 Penang, Malaysia.

* Corresponding author: kannan@usm.my

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Abstract Given that the germline mutations of *BRCA1* and *BRCA2* confer genetic susceptibility to cancer, the genetic variations, polymorphisms or mutations are widely analyzed in Western countries. However, in Asian population, the prevalence of *BRCA1* and *BRCA2* polymorphisms is very limited. In Asia, breast cancer occurs in women early with an age of onset under 50 years. This review comprises the incidence of *BRCA1* and *BRCA2* polymorphisms in the Japanese, Korean and Malaysian population. Founder mutations of *BRCA1* and *BRCA2* were also compared to mark the genetic difference in these populations. The mutational analysis performed to analyze the entire coding region of *BRCA1* and *BRCA2* include the next generation sequencing and full sequencing of all exons and intron-exon junctions. From the diagnosis of triple negative breast cancer (TNBC) patients, TNBC is associated with the lack of tailored therapies and the treatment option available for TNBC patients is mainly chemotherapy. The poor prognosis of TNBC leads to determine the predictive biomarkers in order to develop treatment efficacy. This review will address the current clinical therapies available to treat TNBC patients.

Keywords: *BRCA1, BRCA2,* chemotherapy, founder mutation, polymorphism, TNBC.

Introduction

Among women, breast cancer is a common malignancy. Despite the similarity in histological grade of breast cancer tumours, not limited to that involving *BRCA1* and *BRCA2,* each may exhibit distinct responses to systemic therapy and different outcomes (Badve *et al.*, 2011). Triple negative breast cancer (TNBC) is defined as a breast cancer with a triplet of negative hormones of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Oakman *et al*., 2010). With the lifetime risk of more than 10%, it is considered one among the most lethal cancers (Lehmann *et al*., 2011). Indeed, the mutation of the susceptibility genes, *BRCA1* and *BRCA2* are the common contributors to the malignancy where 5-10% cases are likely to be hereditary (Cancer Genome Atlas Network, 2012). The diagnosed TNBC patients are frequently related to *BRCA1* and *BRCA2* mutation carriers (Mavaddat *et al*., 2012). From the previous studies, these two susceptibility genes account for approximately 15% of inherited cases of breast and ovarian cancers (Couch *et al*., 2014; Kanchi *et al*., 2014).

TNBC tumours are likely to arise in *BRCA* mutation carriers and have a similar profile of gene expression with the *BRCA*-deficient tumours (Haffty *et al*., 2006). The purpose of this article is to review the polymorphisms of *BRCA1* and *BRCA2* variants in TNBC patients and to discuss the clinical outcomes among TNBC patients.

Polymorphisms of BRCA1 and BRCA2

Polymorphisms exhibited in human genome can lead to the susceptibility of genetics to cancer. This genetic variation confers increased risk of cancers associated with genes involved mainly in carcinogen metabolism, cell cycle control, repair of DNA, epigenetic regulation and apoptosis (Tan *et al*., 2010). The predisposing genes such as *BRCA1* and *BRCA2* have been associated with 5% to 10% of breast cancer (Liebens *et al*., 2007). *BRCA1* and *BRCA2* have been proven to function as tumour suppressor genes when tested on mice models. The knockout mice models exhibited enhancement of tumorigenesis after the loss of *BRCA1* and *BRCA2* genes as shown in Fig. 1(A) (Jonkers *et al*., 2001). This indicated that *BRCA1* and *BRCA2* act as tumour suppressor genes. These genes demonstrate an elevated sensitivity towards DNA damaging chemical agents and to PARP (poly adenosine diphosphate-ribose polymerase1) inhibitors (Levanat and Cvok, 2010). The *BRCA1* and *BRCA2* mutations were mostly found in forms of deletions, insertions or point mutation. The exon 11 which is the largest exon of the gene was the disease-causing region mostly found (Sana and Irshad, 2012). The genetic variation of *BRCA1* and *BRCA2* differs from each population. For example, the founder mutations of Ashkenazi Jewish (*BRCA1* c.185delAG, c.5382insC, *BRCA2* c.1029delA, c.5645c>A) are not found in every population as different population exhibits different *BRCA1* and *BRCA2* mutations (Kim and Choi, 2013). Compared with Western countries, there is lack of information on deleterious mutations in Asian countries. It has been noted that many rare variants were discovered in these *BRCA1* and *BRCA2* genes.

Japanese population

BRCA1 and *BRCA2* encode large proteins. One study in Japan has performed the next generation sequencing (NGS) to analyse the entire coding regions of *BRCA1* and *BRCA2* in 135 patients diagnosed with breast or ovarian cancer (Hirotsu *et al*., 2015). The patients recruited were chosen regardless of family history. The study detected deleterious mutations in 10 patients (7.4%). From these 10 mutations; 5 were nonsense, 4 were frameshift and one was a missense mutation. Among these mutations, the Japanese founder mutations were also identified which were actually nonsense mutations as previously discovered (Sekine *et al*., 2001; Nakamura *et al*., 2015). The founder mutations in several populations are shown in Table 1. The two variants are *BRCA1* p.L63X (c.188T>A) and p.Q934X (c.2800C>T). The NGS analysis also showed 23 missense variants which include 10 *BRCA1* variants and 13 *BRCA2* variants. In these 23 missense variants, 4 *BRCA1* and 5 *BRCA2* variants are common polymorphisms according to 1000 Genome Project Data. From the collected data, NGS proved to be effective in detecting causative mutations distributed in the *BRCA1* and *BRCA2* genes. Hence, molecular diagnosis of *BRCA1* and *BRCA2* genetic alterations is suitable with the utility of NGS as stated by Costa *et al*. (2013).

Korean population

In Korea, the prevalence of *BRCA1* and *BRCA2* mutations was discovered to be higher among the patients who had family history of breast or ovarian cancer (Kim *et al*., 2012). For Koreans, the patients develop cancer at younger age compared with the counterparts from the Western countries. The median age was in the late 40s which exceeded 10 years younger than patients from Europe or North America (Jung *et al*., 2011). There is a strong association between age of onset and genetic susceptibility for cancer development. Due to Korean patients having early onset breast cancer, genetic testing at young age could be proposed regardless of family history. This mutation screening can be helpful for guiding treatment. Genetic testing for *BRCA1* and *BRCA2* is relatively expensive and has been offered only in the clinical genetic settings. This is especially to patients who have early-onset breast cancer or to women with significant family history of breast or ovarian cancer (Phuah *et al*., 2012).

From the studies, 150 *BRCA1* and *BRCA2* mutations have been discovered in 420 Korean patients. From this, 73 variants were of *BRCA1* mutations in 211 patients,

and 77 variants were of *BRCA2* mutations in 209 patients. Among these mutations, a total of 84 mutations were suggested as Korean-specific origin as they were not found in other ethnic groups. The Korean founder mutation *BRCA2* c.7480C>T summed up to 19.6% accounted for 41 out of 209 patients which were recorded as the highest variant encountered in the study. This is consistent with the haplotype analysis conducted by Seong *et al*. (2009). However, the *BRCA1* and *BRCA2* mutation prevalence is inconsistent among the studies set up in Korea due to different patient selection criteria which lead to the planning of a large cohort study for high-risk Korean women. The distinct criteria comprised dissimilar number of patients, variable inclusion criteria and diverse methods for ascertainment. In addition, the Korean founder mutation is not prevalent in other population. The polymorphism can be seen to differ in different ethnicity as mentioned previously by Kim and Choi (2013).

Table 1 *BRCA1* and *BRCA2* founder mutations

Population	***BRCA1* mutation**	***BRCA2* mutation**	Reference
Ashkenazi Jewish	c.185delAG c.5382insC	c.1029delA c.5645c>A	Comen *et al.* (2011)
Japanese	Q934X L63X	5802delAATT	Ikeda *et al*. (2001); Sekine *et al*. (2001)
Korean		c.7480C>T	Seong *et al*. (2009)
Filipinos		4265delCT 4859delA	De Leon Matsuda *et al*. (2002)
Malaysian	2846insA		Lee *et al*. (2003)
Chinese	1081delG		Khoo *et al*. (2002)

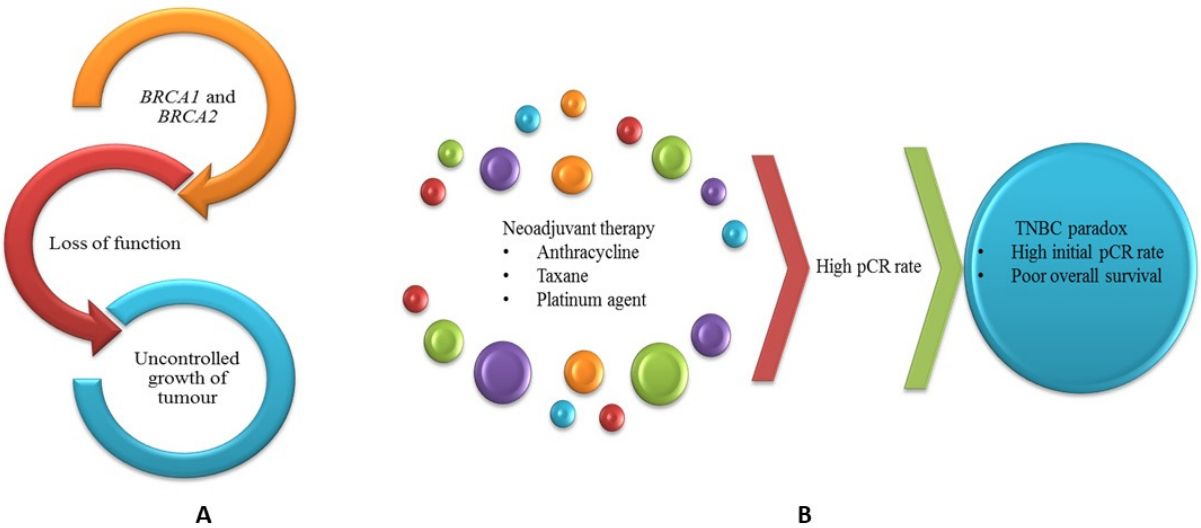

Fig. 1 (A) Loss of function of *BRCA1* and *BRCA2* results in tumour. (B) Triple negative breast cancer paradox (pCR: pathologic complete response).

Malaysian population

In Malaysia, one study was conducted from January 2003 to February 2012 in which 1,454 patients were recruited into the MyBrCa study to determine the predictor of germline *BRCA1* mutation in TNBC (Phuah *et al*., 2012). The germline DNA samples were screened using the Sanger sequencing and multiple ligation-dependent probe amplification (MLPA) for *BRCA1* and *BRCA2* mutations in which the mutations could be detected in 431 women with 110 women diagnosed with TNBC indicating that TNBC patients were more likely to have *BRCA1* than *BRCA2* mutations. 24.5% women had germline mutation in *BRCA1* (23 out of 110) and *BRCA2* (4 out of 110). This data is consistent with other studies conducted in cohorts of TNBC patients, where 11% to 39% had germline mutations in *BRCA1* and *BRCA2* (Young *et al*., 2009; Comen *et al*., 2011), and other cohorts of estrogen negative breast cancer patients where 24% to 29% had germline mutations in *BRCA1* and *BRCA2* (Chang *et al*., 2001; Foulkes *et al*., 2003).

Another different study provides the prevalence of mutations of *BRCA1* and *BRCA2* in the multi-ethnic population in Malaysia (Thirthagiri *et al*., 2008). The patients recruited had an early-onset breast cancer ranging from 40 to 44 years. According to the data collected from the study, the prevalence of *BRCA2* mutations in Malay patients was higher than *BRCA1* mutations. The contradiction of prevalence from other studies is not known. The probable factor stated includes genetic drift, cohort selection or the prevalence of a modifying genetic or environmental factor which disrupts the penetrance of *BRCA1* or *BRCA2* among Malays. It was postulated that *BRCA2* may play an important role in genetic susceptibility among Malay cohorts as in Filipinos and Japanese (Ikeda *et al*., 2001; De Leon Matsuda *et al*., 2002). Thus, it was suggested to study further by recruiting a large cohort of Malay individuals to evaluate the possibilities. Mutation testing has been suggested by cost-effectiveness analyses for TNBC patients younger than 50 years old. Since 10% to 25% of those patients have *BRCA1* and *BRCA2* mutations, the testing may be a cost-effective approach (Kwon *et al*., 2010).

A study was conducted in University Malaya Medical Centre to compare the clinicopathological features of *BRCA* mutations (Yip *et al*., 2009). They started the patient recruitment in 2003. The recruitment criteria included early onset breast cancer (≤40 years) and 1 or more cases of breast cancer in first or second-degree relatives. From the collected data, the Malays exhibited high *BRCA2* carriers compared to *BRCA1* carriers (5 *BRCA2* carriers, 2 *BRCA1* carriers). This shows that *BRCA2* mutations may be more prevalent in Asian population in contrast with studies in Caucasian population where *BRCA1* mutations are more prevalent than *BRCA2* mutations (Foulkes *et al.,* 2004).

Clinical therapies

The issues related to TNBC are the lack of tailored therapies for TNBC patients and the overlapping of basal-like cancer profiles. Due to the lack of standard molecular targets, patients diagnosed with TNBC are improbable to benefit from the current viable targeted therapies which include the endocrine therapy and anti HER2 agents (Hudis and Gianni, 2011). Hence, the only available option for treatment in these patients is mainly chemotherapy with standard cytotoxic agents. These agents can be anthracycline, taxanes, ixabepilone and platinum agents. From the past trials conducted, TNBC has exhibited a high response rate (RR) towards neoadjuvant chemotherapy where it includes taxanes and anthracyclines. However, as in Fig. 1(B), they exhibited poorer overall survival despite their initial responsiveness where this behaviour is referred to as “TNBC paradox” (Carey *et al*., 2007; Fornier and Fumoleau, 2012). It is particularly responsive to cytotoxic chemotherapy; however, it showed a low bearing on the patient survival.

Since *BRCA* is associated with DNA repair mechanisms, TNBC has been postulated to be sensitive with the DNA damaging drugs such as platinum derivatives (De Laurentiis *et al*., 2010). This

is due to the ability of *BRCA1* to repair defective homologous recombination which confers sensitivity towards certain systemic agents. This associated breast cancer has shown sensitivity to agents that cause interstrand cross-links which include the platinum drugs, mitomycin and bifunctional alkylating agent. However, there is limited data to support this as trials are under way or planned (Sirohi *et al*., 2008).

In a platinum-based chemotherapy study conducted by Sirohi *et al.* (2008), the patients who completed these treatments with a clinical and radiological complete response (CR) did not undergo any surgery. In fact, these patients received radical radiotherapy only. Moreover, the combination regimens in neoadjuvant and adjuvant settings also include the anthracycline. This caused a difficulty in knowing whether the response was due to the platinum salt or anthracycline or both. From the study, the patients diagnosed with TNBC were younger compared to non-TNBC with a median of 47 versus 53 years. The development of metastases for these TNBC patients was shorter (28 versus 36 months) with a shorter disease-free survival (DFS) on anthracyclines. The patients also showed similar disease-free interval on taxanes. The metastatic cohort patients also were administered with platinum along with mitomycin C. It was postulated that this might have contributed to the better outcome. The disadvantage of this platinum agent is that it has poor clinical outcome even if it has higher response rate. Moreover, it requires close scrutiny. Thus, assessing its effectiveness can be challenging as focused trial has not been executed and performed. However, clinically, randomized data regarding TNBC sensitivity towards platinum agent are limited and require more convincing and evidence in terms of safety and efficacy. In contrast, there are several clinical data available to support the efficacy of taxanes in TNBC (Rouzier *et al*., 2005; Carey *et al*., 2007; Liedtke *et al*., 2008).

TNBC patients treated with neoadjuvant anthracycline-based (doxorubicin and cyclophosphamide) chemotherapy showed markedly higher clinical response compared to non-TNBC patients (Carey *et al*., 2007). This showed that the TNBC patients were more sensitive to anthracycline based chemotherapy than luminal breast cancer patients. A study conducted by Liedtke *et al*. (2008) collected a clinical database at M.D. Anderson Cancer Center in Houston where stage I-III breast cancer patients were tested for neoadjuvant chemotherapy. The clinical outcomes collected were the rate of pathologic complete response (pCR), progression free survival (PFS), site-specific distribution of recurrence, post recurrence survival (PRS), and overall survival (OS). For this study, the pCR rate was higher in TNBC patients compared with the non-TNBC patients and showed excellent survival regardless of the receptor status. Nevertheless, after the neoadjuvant chemotherapy, TNBC and residual disease patients exhibited significantly shorter overall and post recurrence survival compared to non-TNBC patients.

In another clinical study conducted by Tan *et al*. (2008), TNBC patients were recruited for adjuvant anthracycline-based chemotherapy following primary surgery with regard to metastasis free (MFS), local relapse free (LRFS) and breast cancer specific survival (BCSS). The TNBC phenotype associated significantly with shorter MFS and BCSS after treatment with adjuvant anthracycline-based chemotherapy. Besides, the relapse and death risk showed dramatically higher rate for TNBC. This happened during the first 3 years of follow-up session, whereas, the non-TNBC patients showed higher risk of relapse and death in year 4 to 6 of follow-up. This can be supported by the study conducted by Dent *et al*. (2007) who described the TNBC to have a shorter median time from relapse to death.

Thus, from these clinical studies, it can be concluded that TNBC patients have an excellent response rate towards neoadjuvant chemotherapy despite showing poor results in MFS and BCSS in patients treated with adjuvant anthracycline-based chemotherapy after primary surgery. The relevance of *BRCA1* and *BRCA2* mutations can help in

developing a standardized targeted therapy to perform an effective treatment towards TNBC patients. Due to low and insignificant data on *BRCA1* and *BRCA2,* the current therapies are not well formulated to encounter the *BRCA1* and *BRCA2* tumours where patients are only given chemotherapy with standard cytotoxic agents. Screening tools for *BRCA1* and *BRCA2* also need to be developed to help in cancer prevention in relatives carrying the same mutation.

Conclusions

The elevated risk of breast cancer is associated with the genetic variation in *BRCA1* and *BRCA2* mutation function mainly in DNA repair and cell cycle control. Mutational analysis by total genome sequencing is crucial in identifying the genetic variation in *BRCA1* and *BRCA2* to further analyse the sequence of the variants. The prevalence of *BRCA1* and *BRCA2* can lead to an efficient prognosis and survival of breast cancer. The prevalence of *BRCA1* and *BRCA2* is important in identifying the suitable targeted therapy for neoadjuvant therapy in TNBC patients. It is evident that the Asian population is associated with an early age of onset for breast cancer (≤50 years). The *BRCA1* and *BRCA2* prevalence differ in distinct ethnicity and the genetic variation differs in each population. It is vital for a large cohort of population to be recruited to increase the accuracy in analysing the genetic variations in *BRCA1* and *BRCA2* mutations. A large scale of clinical study is crucial to further verify the occurrence of *BRCA1* and *BRCA2* mutations in Asian population.

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