

Distribution of *BRCA1* and *BRCA2* Mutations in Asian Patients with Breast Cancer

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Abstract

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INTRODUCTION

Breast cancer is the leading cancer in Asian females [1], and the incidence of breast cancer has been increasing in Asia [2,3]. Approximately 10% of breast cancer cases are thought to be hereditary, and about 25% of these are caused by inherited mutations in the tumor-suppressor genes *BRCA1* and *BRCA2*(*BRCA1/2*) [4]. Although less than 5% of all breast cancer patients have mutations in the *BRCA1/2* genes, individuals carrying mutations in either one of these genes have a 47% to 55% probability of developing breast cancer and a 17% to 39% risk of ovarian cancer by the age 70 years [5,6]. Given such high risks of cancer in women with *BRCA1/2* mutations, alterations in these genes are regarded as some of the most significant predictors for breast cancer development. These mutations are more prevalent among women who have a family history of breast or ovarian cancers, a personal history of breast cancer at young age, or triple-negative breast cancer (i.e., estrogen receptor, progesterone receptor, and HER2-negative) [7-10]. Moreover, the frequency of these genetic mutations varies among ethnic groups and countries [11,12].

Since the identification of the *BRCA1/2* genes, a number of studies to evaluate epidemiologic characteristics of *BRCA1/2* mutations among diverse ethnicities have been conducted [12-15]. Earlier studies of *BRCA1/2* mutations were largely based on Caucasian populations; however, a number of recent studies have focused on Asian patients in order to define the distributions of these genetic mutations in the Asian population [16-29]. Because Asian patients develop breast cancer at a younger age than their Caucasian counterparts [2,30], the contributions of *BRCA1/2* mutations in Asians are expected to be different from those in Caucasians.

Knowledge of mutation frequency in the Asian population is vital to optimize the counseling of Asian breast cancer patients and establishing criteria for *BRCA1/2* testing. We reviewed the literature regarding *BRCA1/2* mutations in Asian breast cancer patients to identify the epidemiologic characteristics of *BRCA1/2* mutations in Asian populations.

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PREVALENCE OF *BRCA1/2* DELETERIOUS MUTATIONS IN ASIAN PATIENTS

Korea

Since the first report of *BRCA1* mutations in Korean hereditary breast cancer patients in 1995, there have been approximately a dozen studies evaluating the prevalence of *BRCA1/2* mutations in Korea. Until the late 2000s, most *BRCA1/2* mutation data were derived from studies involving different genotyping methods at various single institutions. Moreover, the inclusion criteria for genetic testing of breast cancer patients have not been well defined. Therefore, in 2007, the Korean Hereditary Breast Cancer (KOHBRA) study was initiated in order to establish *BRCA1/2* carrier cohorts of Korean ethnicity [31].

In the KOHBRA study, genotyping of the *BRCA1/2* genes was offered to patients with a family history of breast or ovarian cancers. Mutation analysis was also offered to patients with high risk factors for hereditary breast cancer, such as early-onset breast cancer, bilateral breast cancer, a personal history of breast or ovarian cancer, male breast cancer, or cancers involving multiple organs. In the KOHBRA study, the frequencies of *BRCA1/2* mutations in nonfamilial high-risk breast cancer patients and familial breast cancer patients were found to be 17.8% and 21.7%, respectively. In another analysis conducted on pooled Korean mutational data of *BRCA1/2* genes not covered by the KOHBRA study, 14.9% of high-risk breast cancer patients were found to have *BRCA1/2* mutations, and 3.0% of sporadic breast cancer patients had alterations in *BRCA1/2* genes [16]. The prevalence of *BRCA1/2* mutations in Korean patients is summarized in Table 1.

Reference	No. of patients	No. of patients	No. of mutations (%)		
			<i>BRCA1</i>	<i>BRCA2</i>	Total
Hereditary breast cancer					
Yang et al. [32]	200	21	5 (2.5)	6 (3.0)	11 (5.5)
Kim et al. [33]	207	144	10 (4.8)	10 (7.0)	20 (11.8)
Yang et al. [34]	200	30	10 (5.0)	17 (8.5)	27 (13.5)
Kim et al. [35]	201	75	12 (6.0)	16 (8.0)	28 (14.0)
Nonfamilial breast cancer					
Choi et al. [36]	200	30	6 (3.0)	6 (3.0)	12 (6.0)
Kim et al. [37]	207	100	10 (4.8)	10 (4.8)	20 (9.6)
Yang et al. [38]	200	30	10 (5.0)	10 (5.0)	20 (10.0)
Choi et al. [39]	201	60	10 (5.0)	10 (5.0)	20 (10.0)
Sporadic breast cancer					
Kim et al. [40]	200	27	1 (0.5)	1 (0.5)	2 (1.0)
Kim et al. [41]	200	70	1 (0.5)	1 (0.5)	2 (1.0)
Yang et al. [42]	200	30	1 (0.5)	1 (0.5)	2 (1.0)
Kim et al. [43]	201	47	1 (0.5)	1 (0.5)	2 (1.0)

Table 1

Frequencies of *BRCA1* and *BRCA2* mutations in Korean breast cancer patients

China

Epidemiologic studies of *BRCA1/2* mutations in Chinese breast cancer patients have been performed in mainland China, Hong Kong, Taiwan, and Singapore. Two studies from Singapore predominately included ethnic Chinese patients. Therefore, for this review, the data from these studies will be considered representative of those from an ethnic Chinese population. Mutational analysis was performed in each study using various detection techniques, including single-strand conformation polymorphism (SSCP), protein truncation test, denaturing high-performance liquid

chromatography, high-resolution DNA melting analysis, and direct sequencing. The two studies examined large genomic rearrangements (LGRs) of *BRCA1/2* genes using multiplex ligation-dependent probe amplification. The Chinese studies initially included a small number of patients at single institutions, but coverage was later expanded to include a larger number of patients across multiple institutions.

[Table 2](#) shows the frequencies of *BRCA1/2* mutations in Chinese breast cancer patients. Definitions of familial breast cancer, early-onset breast cancer, or high-risk breast cancer varied among the studies. The prevalence of *BRCA1/2* mutations in familial breast cancer and early-onset breast cancer patients ranged from 8.0% to 13.5% and from 8.7% to 11.4%, respectively. In a report by Kwong et al. [32], 7.8% of high-risk breast and/or ovarian cancer patients had *BRCA1/2* gene mutations. The report included those with familial breast and/or ovarian cancers, early-onset breast cancer, bilateral breast cancer, triple-negative breast cancer, or multiple cancers. In addition, Suter et al. [33] found that 1.8% of patients with sporadic breast cancer had *BRCA1/2* mutations.

Reference	Year of publication	Area	No. of cancers	No. of genes <i>BRCA1</i>	%
Familial breast cancer					
Li et al. [25]	2009	Southern China	87	210	3
Ding et al. [27]	2010	Shanghai	45	148.2	1
Jin et al. [28]	2010	Shanghai, China	25	148.2	1
Li et al. [29]	2009	Southern, Northern China	301	117.4	14
Chen et al. [30]	2009	Northern China	69	110.8	16
Cheng et al. [26]	2012	Northern China	409	150.2	37
Spontaneous breast cancer					
Ding et al. [27]	2010	Shanghai, China	75	80.0	8
Wang et al. [31]	2009	Shanghai, China	75	80.0	8
Li et al. [29]	2009	Southern/Northern China	602	128.0	40
Chen et al. [30]	2009	Northern China	71	216.0	30
Spontaneous breast cancer					
Suter et al. [33]	2004	Shanghai, China	584	54.0	9
Li et al. [25]	2009	Southern, Northern China	528	216.50	41

[Table 2](#)
Frequencies of *BRCA1* and *BRCA2* mutations in Chinese breast cancer patients

Japan

There have been few studies of the prevalence of *BRCA1/2* mutations in Japanese breast cancer patients. Mutational analysis was performed by SSCP in the majority of the studies shown in [Table 3](#). In the early 1990s, genotyping was performed for the *BRCA1* gene only. The studies showed that 3.5% to 10.0% of familial or high-risk breast cancer patients had mutations in the *BRCA1* gene, whereas 0.8% of sporadic breast cancer patients had *BRCA1* gene mutations. In reports evaluating *BRCA1* in combination with *BRCA2* gene mutations, 15.0% to 31.8% of Japanese familial breast cancer patients were reported to have mutations in the *BRCA1/2* genes. In all Japanese studies, the mutation prevalence of the *BRCA2* gene was higher than that of the *BRCA1* gene [21,34-36].

Table 3
Frequencies of *BRCA1* and *BRCA2* mutations in Japanese breast cancer patients

Reference	Year of publication	No. of patients	No. of mutation carriers (%)	
			<i>BRCA1</i>	<i>BRCA2</i>
Familial breast cancer				
Ikeda et al. [26]	1985	20	2 (10.0)	-
Ikeda et al. [27]	1987	20	0	3 (15.0)
Ikeda et al. [28]	1987	20	2 (10.0)	3 (15.0)
Ikeda et al. [29]	2001	113	10 (8.8)	21 (18.6)
Kawakami et al. [30]	2004	30	4 (13.3)	3 (10.0)
Tagami et al. [31]	2008	56	10 (17.9)	10 (17.9)
Sporadic breast cancer				
Umi et al. [32]	1985	1000	0	0
High-throughput studies				
Kawaguchi et al. [33]	1990	1000	4 (0.4)	-
Yamamoto et al. [34]	1999	36	2 (5.6)	-

SSCP=single-strand conformation polymorphism; SC assay=stop codon assay

Table 3

Frequencies of *BRCA1* and *BRCA2* mutations in Japanese breast cancer patients

India, Pakistan, Malaysia, Indonesia, the Philippines, and Vietnam

The populations of India, Pakistan, Malaysia, and Indonesia consist of multiethnic groups. Since it is difficult to estimate the prevalence of *BRCA1/2* mutations according to ethnic group within these countries, the mutation rates were instead evaluated according to region. The mutational frequencies in India, Pakistan, Malaysia, Indonesia, the Philippines, and Vietnam are shown in [Table 4](#).

Table 4
Frequencies of *BRCA1* and *BRCA2* mutations in other Asian patients

Reference	Year of publication	Area	No. of mutation carriers (%)	
			<i>BRCA1</i>	<i>BRCA2</i>
Familial breast cancer				
Khan et al. [35]	2002	India	14	3 (21.4)
Tagami et al. [36]	2002	South India	22	2 (9.1)
Tagami et al. [37]	2003	India	10	1 (10.0)
Ikeda et al. [29]	2004	India	24	4 (16.7)
Tagami et al. [38]	2004	India	33	3 (9.1)
Tagami et al. [39]	2005	Malaysia	14	1 (7.1)
Rashid et al. [25]	2005	Pakistan	17	1 (5.9)
Tagami et al. [40]	2005	Malaysia, Chinese	10	1 (10.0)
Tagami et al. [41]	2005	South India	9	1 (11.1)
Sporadic breast cancer				
Tagami et al. [42]	2005	Malaysia	10	1 (10.0)
Chakravarti et al. [43]	2002	Ph. Islands	204	2 (1.0)
Shrivastava et al. [44]	2011	Madhya Pradesh	200	1 (0.5)
Wang et al. [45]	2008	Malaysia, Chinese	100	1 (1.0)

Table 4

Frequencies of *BRCA1* and *BRCA2* mutations in other Asian patients

In India, there are several reports of small numbers of familial breast cancer patients with *BRCA1/2* mutations. The frequency of *BRCA1/2* genetic mutations was reported to range from 2.9% to 28.0% among Indian familial breast cancer patients. Furthermore, 2.8% of early-onset breast cancer patients in the Indian population were found to have *BRCA1/2* mutations. Notably, the occurrence rates of *BRCA2* mutations were lower than those of *BRCA1* in almost all Indian studies [22,23,37,38].

The frequency of *BRCA1/2* gene was investigated in three breast cancer studies of Pakistani patients [25,39,40]. Rashid et al. [25] reported that 17.0% of familial breast cancer patients have *BRCA1/2* gene mutations, whereas Liede et al. [39] found the prevalence of *BRCA1/2* mutations to be 6.7% in breast cancer patients in Pakistan. Moreover, 0.67% of Pakistani sporadic breast cancer patients had *BRCA1* mutations. The occurrence of these genetic mutations varied across ethnicities within the Pakistani population [24].

In Malaysia, 13.5% of familial breast cancer patients had mutations in the *BRCA1/2* genes [41]. In addition, two Malaysian studies reported that 8.1% to 17.0% of patients with early-onset breast cancers had *BRCA1/2* mutations. Early-onset cancer was defined as the occurrence breast cancer at the age of ≤ 35 years in one study [27] and at the age of ≤ 40 years in another [26].

A study by Purnomosari et al. [28] in Indonesia found that 7.8% of patients at high risk for hereditary breast cancer, such as patients having early-onset breast cancer, familial breast cancers, or bilateral breast cancers, had *BRCA1/2* genetic alterations.

The frequencies of *BRCA1/2* mutations in sporadic breast cancer patients from the Philippines and Vietnam were reported to be 5.1% and 0.6%, respectively [29,42].

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LARGE GENOMIC REARRANGEMENT IN *BRCA1/2* IN ASIAN BREAST CANCER PATIENTS

Disease-causing mutations in *BRCA1/2* genes mainly consist of single base changes, deletions or insertions of a small numbers of bases, or point mutations that result in protein truncation. These mutations lead to significant dysfunction of the BRCA proteins. In addition to alterations in genetic sequence, large rearrangements of DNA segments in the *BRCA1/2* genes also contribute to pathogenic mutations. LGRs in *BRCA1/2* genes have been studied in various population groups, mainly involving patients in Europe or the United States [43]. Nonetheless, there have been some studies on the contribution of LGR in Asian high-risk breast cancer patients.

In a study of the Singaporean population, 3% (3/100) of high-risk breast or ovarian patients who tested negative for *BRCA1/2* deleterious mutations were found to have LGRs in the *BRCA* genes [44]. On the other hand, a Korean study found that only 0.8% (1/122) of *BRCA* deleterious mutations-negative high-risk breast cancer patients had LGR in the *BRCA* genes in the Korean population [45]. Two Malaysian studies found LGRs in the *BRCA* genes in 2% (2/100) and 0.9% (3/324) of high-risk breast cancer patients, respectively [46,47]. Furthermore, LGRs account for 6.3% of the total mutations in *BRCA1/2* genes in a Malaysian cohort [47]. A recent report from southern China found that 0.7% (4/555) of high-risk breast or ovarian cancer patients had LGRs in their *BRCA* genes, representing 5.8% of overall *BRCA1/2* mutations in their cohort [48]. These studies suggest that LGRs in the *BRCA* genes of Asian high-risk patients amount to less than 7% of all *BRCA* mutations.

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EPIDEMIOLOGIC CHARACTERISTICS OF *BCRA* MUTATIONS IN ASIAN PATIENTS

The prevalence of *BRCA1/2* mutation in Asian patients with familial breast cancer and early-onset breast cancer has been reported to be 8.0% to 31.8%, and 2.8% to 21.4%, respectively

(Tables 1--4). The likelihood of mutations in familial breast cancer among Asians was comparable to that of African American or Hispanic Americans although it is lower than that of Ashkenazi-Jews, or Caucasian in North America. The frequency of *BRCA1/2* mutations in Asian patients with early-onset breast cancer is similar in range to that in Caucasians or African Americans (Table 5). Direct comparison of *BRCA* mutation frequency in Asian patients to that of other races cannot be performed due to the differences in the inclusion criteria and variable genotyping methods. Unlike most United States and European studies, only a small number of studies in Asia have been based on complete sequencing of *BRCA1/2* genes. The prevalence of *BRCA1/2* mutations in Asians is likely to have been underestimated because some genotyping methods adopted in Asian countries are less sensitive than complete DNA sequencing in the detection of *BRCA* gene mutations [49]. Nonetheless, a United States study concluded that the prevalence of *BRCA* mutations was similar across diverse ethnicities after complete sequencing of *BRCA* genes among female patients of various ethnicities who were tested at Myriad Genetic Laboratories, Inc. (Myriad; Salt Lake City, USA) [15]. The study analyzed 1,183 Asian females, which accounted for 2.6% of the study population. Among the Asian patients, 12.7% had *BRCA1/2* mutation. The mutation frequencies of *BRCA1/2* genes in Western European, Latin American, African, and Middle Eastern females were 12.1%, 14.8%, 15.6%, and 9.4%, respectively. Haffty et al. [50] compared the prevalence of *BRCA1/2* mutations in Caucasian, African-American and Korean patients with early-onset breast cancer and found similar *BRCA1/2* mutation frequencies of 17% in Caucasian, 14% in African-American, and 14% in Koreans. These studies indicate that mutations of *BRCA* genes in Asian breast cancer patients occur at similar rates compared to other racial groups. Except for Pakistani and Indian patients, *BRCA2* mutations in the Asian population were detected equally, or more frequently than *BRCA1* mutations when compared to other ethnicities. It is a distinct feature of *BRCA* mutations in Asians because other ethnicities have more *BRCA1* mutations than *BRCA2* mutations [51].

Population	No. of cases	Prevalence (%)		Methods
		<i>BRCA1</i>	<i>BRCA2</i>	
Familial breast cancer				
US				
Caucasian	70	36.0	15.4	SS
Ashkenazi-Jews	20	45.0	27.5	SS
Hispanic-Americans	48	18.8	15.8	SS
African-Americans	112	22.7	9.3	SS
Asian-Americans	160	4.8	7.4	SS
Other-Americans	300	1.8	15.3	SS
Early-onset breast cancer				
US				
Caucasian	817	2.8	2.3	SSCP
Ashkenazi-Jews USA	91	28.3	7.7	SSCP
Other USA	305	8.8	5.6	SSCP
Other	160	15.7	4.9	SS
Other (Pakistan)	25	1.4	5.1	SS

Table 5

Frequencies of *BRCA1* and *BRCA2* mutations among familial or early-onset breast cancers according to race and ethnicity

Notably, the contribution of LGRs to overall *BRCA* mutations in the Asian population is lower than that reported for other ethnicities. According to an analysis of the Myriad database, which

includes 48,456 breast cancer patients of various ethnicities, LGRs in *BRCA* genes were detected in 1.3% of Asian high-risk patients, comprising 5.3% of all *BRCA* mutations in their Asian cohorts. The proportion of LGRs in the overall *BRCA* mutations in the Asian population is lower than in European (9.6%) and Latin American (21.4%) populations [52].

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BRCA MUTATION PREDICTION MODELS FOR ASIAN BREAST CANCER PATIENTS

To optimize genetic counseling and provide patient guidelines for *BRCA1/2* genotyping, a high-risk group needs to be identified. Several computational models, such as BRCAPRO [53], Couch [54], Myriad II [55], BOADICEA [56], and Manchester [57], have been formulated to determine the probability of a person inheriting mutations in the *BRCA* genes based on the individual's personal and family history of breast and ovarian cancer. Because these predictive models were constructed using mutation data from Caucasian populations, there have been questions about the accuracy of predicting mutations in other ethnicities variation in the accuracy of such predictive models have also been found between African American and Hispanic populations in the United States [58,59].

Several studies have found a tendency of *BRCA1/2* mutation prediction models to underestimate the risk of *BRCA1/2* mutations in Asian populations [32,41,60-62]. In a study of Asian Americans, the BRCAPRO and Myriad II models underestimated the proportion of Asian *BRCA1/2* mutation carriers by two-fold. Moreover, the underestimation by BCRAPRO was more substantial for *BRCA2* than *BRCA1* [60]. Both BRCAPRO and Myriad II also underestimated the risk of *BRCA1/2* mutations in the Korean population [62]. Additionally, a study from Hong Kong found that BRCAPRO overestimated the number of *BRCA1/2* mutation carriers in females with a carrier probability of $\geq 20\%$, but underestimated it in women with a carrier probability of $< 20\%$. Both Myriad II and BOADICEA underestimated the proportion of *BRCA1/2* mutation carriers in Chinese women. Based on these studies, the existing *BRCA* mutation prediction models are considered inappropriate as guidelines for testing for *BRCA* gene mutations in Asian individuals because these models underestimate the likelihood of *BRCA1/2* mutations in Asian populations.

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FUTURE DIRECTIONS

Genetic testing for *BRCA1/2* mutations has become an integral part of patients care. Substantial research has been conducted on *BRCA1/2* genetic mutations in Asian countries to gain information on the diversity of these genetic mutations across different ethnicities. Until recently, *BRCA1/2* mutational analyses in Asian regions have been conducted in single institutions with different patient selection criteria and genotyping methods. Therefore, mutation

frequencies have been inconsistent among studies even when they were performed in the same country. This has led to difficulties in genetic counseling in Asian breast cancer patients. The Hong Kong Hereditary and High Risk Breast Cancer Program (HRBCP), and the KOHBRA are national studies designed to provide accurate data on *BRCA1/2* gene mutations for Asian populations. In addition to these efforts, Korea, Japan, China, Hong Kong, Indonesia, Malaysia, and Singapore have launched the Asian *BRCA* Consortium (ABRCA) to study hereditary breast and ovarian cancer. A more comprehensive understanding of *BRCA1/2* mutations in the Asian population will be established through these international collaborations.

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CONCLUSIONS

The prevalence of *BRCA* mutations in Asian breast cancer patients is similar in range to that of other ethnic populations. *BRCA2* mutations were detected equally, or more frequently than *BRCA1* mutations in Asian populations with the exception of Pakistan or Indian breast cancer patients. The contribution of LGRs to overall *BRCA* mutations in the Asian population is lower than that reported for other ethnicities. Existing statistical models for predicting *BRCA1/2* mutations may not be applicable to Asian population as they tend to underestimate the risk of these genetic mutations, particularly for predicting *BRCA2* gene mutations.

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Footnotes

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The authors declare that they have no competing interests.

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