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Comprehensive spectrum of *BRCA1* and *BRCA2* deleterious mutations in breast cancer in Asian countries

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Abstract

Approximately 5%–10% of breast cancers are due to genetic predisposition caused by germline mutations; the most commonly tested genes are *BRCA1* and *BRCA2* mutations. Some mutations are unique to one family and others are recurrent; the spectrum of *BRCA1/BRCA2* mutations varies depending on the geographical origins, populations or ethnic groups. In this review, we compiled data from 11 participating Asian countries (Bangladesh, Mainland China, Hong Kong SAR, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Thailand and Vietnam), and from ethnic Asians residing in Canada and the USA. We have additionally conducted a literature review to include other Asian countries mainly in Central and Western Asia. We present the current pathogenic mutation spectrum of *BRCA1/BRCA2* genes in patients with breast cancer in various Asian populations. Understanding *BRCA1/BRCA2* mutations in Asians will help provide better risk assessment and clinical management of breast cancer.

INTRODUCTION

Breast cancer is the most frequent malignancy and the most leading cause of cancer deaths in women worldwide. In 2012, there were estimated to be 522 000 breast cancer deaths, which accounted for 14.7% of all cancer deaths among women (GLOBOCAN 2012, http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). According to the American Cancer Society, the 5-year survival rate for patients with breast cancer ranged from 22% to 100% according to the cancer stages, but this varies for different geographical origins.¹ Familial breast cancer accounts for 5%–10% of all breast cancers and is known to be caused by germline mutations in certain genes.² Deleterious mutations in breast cancer-associated genes (*BRCA1* and *BRCA2*) account for 20%–40% of the familial breast cancer.³⁴ Women with *BRCA1/BRCA2* mutations have very high lifetime risks of developing breast and ovarian cancer.⁵ Meta-analyses indicated that *BRCA1* mutation carriers have a 57%–65% lifetime probability of developing breast cancer while *BRCA2* carriers have a 45%–49% lifetime probability.⁶⁷ Although there are increasing reports from Asia, the majority of studies to date have focused on the prevalence and spectrum of *BRCA1* and *BRCA2* mutations in white populations from Europe and North America, African and African-American populations. Asians comprise 60% of the 7 billion people in the world and this population is rapidly increasing. The two most populated countries alone, China and India, constitute 37% of the world population. According to the US Census Bureau, 4.8% of the

American populations are Asians. Hence, there is a need for better understanding of the mutation spectrum of these high-penetrance genes and cancer risk prediction in Asians, so that appropriate genetic testing and management/surveillance programmes can be implemented. Globally, there are important differences in age-specific incidence rates of breast cancer between countries and between ethnic groups.⁸ In this review, we summarise the current spectrum of deleterious *BRCA1* and *BRCA2* mutations including novel, previously unpublished mutations among Asian countries, and where available, those Asians residing in Western countries.

STUDY POPULATION

Our cohort represents a study population from 47 Asian countries under the geographical definition from GLOBOCAN, together with regions including Hong Kong and Taiwan, and the Asian populations residing in North America. Mutational information of *BRCA1* and *BRCA2* genes (GenBank accession no.: U14680.1 and U43746.1 respectively) were collected from the Hong Kong Hereditary Breast Cancer Family Registry (<http://www.asiabreastregistry.com>), Korean Hereditary Breast Cancer study, study groups of the Asian Hereditary Breast Cancer Consortium (ABRCA) and collaborating centres in North America (Canada and USA). We also consolidated data from the Breast Cancer Information Core (BIC), Human Genome Variation Society, unpublished data and published literatures of *BRCA1/BRCA2* mutations in Asia (including India, Pakistan, Turkey, Iran, Iraq, Syria, Yemen and other Asian countries). Only pathogenic mutations in *BRCA1/BRCA2* genes, which cause deleterious effects to the protein functions, were included in this report. Other genetic variants of uncertain clinical significance (namely VUS) are out of the scope of this study and will be published as a separate study by the ABRCA Consortium group.

This study was approved by the Institutional Review Board (IRB) of the University of Hong Kong and IRBs of the collaborating centres. Mutational information of *BRCA1* and *BRCA2* were generated, specifically (1) mutation type; (2) date/year of test result; (3) patient ethnicity; (4) country where the mutation was identified; (5) frequency of entries in BIC; and (6) whether the mutation has been reported to be recurrent or founder mutation. Literature search also included mutation frequencies in specific groups including patients with breast cancer at young age, triple-negative breast cancer (TNBC) and bilateral breast cancer. The distribution of *BRCA1* and *BRCA2* mutations in each country was also recorded.

Selection criteria

The inclusion criteria for *BRCA1/BRCA2* genetic testing varied among research groups in our study and in the published literatures, and are summarised in table 1. In general, the study samples consisted of high-risk individuals of familial breast and/or ovarian cancer who satisfied any one of the following criteria:

1. having a strong family history of breast cancer and/or ovarian cancer;
2. having early-onset breast cancer, diagnosed at age less than 50 years;
3. having bilateral breast cancer;
4. having TNBC;

5. having male breast cancer;
6. having medullary type pathology;
7. having a family history of cancer, other than breast or ovary, which are known to be related to *BRCA1/BRCA2* mutations, such as stomach and prostate;
8. having ovarian cancer and a family history of breast cancer.

***BRCA1/BRCA2* pathogenic mutations in Asians**

In this review, all the novel or unpublished *BRCA1/BRCA2* mutation information were collected through the ABRCA including research groups from Bangladesh, Mainland China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Thailand and Vietnam, together with the collaborating centres in North America. Published mutation data were obtained through literature search. To the best of our knowledge, this is the most up-to-date overview of the *BRCA1/BRCA2* pathogenic mutation spectrum in Asian population available. Table 2 illustrates the total numbers of *BRCA1/BRCA2* distinct mutations and mutation-positive cases, and a selection of the most frequent mutations identified in each Asian country and in North America. The full spectra of germline *BRCA1/BRCA2* deleterious mutations are listed in the online supplementary tables S1 and S2. To date, 510 distinct types of deleterious *BRCA1/BRCA2* mutations (268 *BRCA1* and 242 *BRCA2*) have been identified in Asian patients with breast cancer, most of which are frameshift or nonsense mutations.

The most common *BRCA1* mutation reported in our data set was 185delAG (c.68_69delAG; no. of cases: 29), which is a well-known Ashkenazi Jewish mutation, and this mutation was detected in the Indian and Arabic populations, but not in Eastern Asia. The second most reported *BRCA1* mutation was c.390C>A (no. of cases: 28), which was solely found in the Japanese and Korean patients. Other common *BRCA1* mutations include c.470_471delCT (no. of cases: 16; BIC entries: 10) and c.981_982delAT (no. of cases: 9; BIC entries: 9). *BRCA1* c.470_471delCT mutation was identified in Chinese patients that were populated in Hong Kong, Malaysia and the USA, and was also identified in Japanese and Pakistani patients. *BRCA1* c.981_982delAT was seen in Chinese and Korean patients in Hong Kong, Korea, Malaysia and Shanghai. Both of these mutations were identified as recurrent mutation in Chinese population, which contributed to 20.6% of all *BRCA1* mutations in the Chinese cohort in Hong Kong, Southern China.¹⁴

The most common *BRCA2* mutations were *BRCA2* c.7480C>T (no. of cases: 53; BIC entries: 11), c.1399A>T (no. of cases: 29; BIC entries: 2) and c.3744_3747delTGAG (no. of cases: 26; BIC entries: 8). They were frequently observed in Korean and Chinese patients.

To date, there are 28 distinct mutations in *BRCA1* gene and 41 mutations in *BRCA2* gene that have neither been previously reported nor been listed in the BIC database (see online supplementary tables S1 and S2); thus they are considered to be novel mutations identified in Asian populations. Among these novel mutations, four *BRCA1* and eight *BRCA2* distinct mutations had been identified in more than one individual. In this study, 40 *BRCA1* and 25 *BRCA2* mutations, comprising 12.7% (65 of 510) of all distinct mutations, were listed in the

BIC database with records of Asian ethnicities only, suggesting that these could be the Asian-specific pathogenic mutations.

There were 41 distinct *BRCA1* mutations and 35 *BRCA2* mutations reported in multiple locations across Asia, and some were also found in the Asian populations of North America (see online supplementary tables S1 and S2). These recurrent mutations accounted for 37.5% (233 of 622) of all *BRCA1* mutation-positive cases and 36.9% (215 of 583) of all *BRCA2* mutation-positive cases in this report (table 2). In total, the frequency of *BRCA1* mutations outnumber that of *BRCA2* mutations (622 vs 583). However, this was not the case in all Asian countries; in China, Hong Kong, Korea and Philippines, *BRCA2* mutations outnumber that of *BRCA1* mutations (table 2). In most non-Asian countries the total frequency of *BRCA2* mutations observed in Asian populations is more than that for *BRCA1* mutations. However, the reverse situation was usually observed in Caucasian or other non-Asian populations.^{61–63} A number of common mutations specific to non-European populations have been reported in Hispanic, African–American, Middle Eastern and Asian populations.^{64,65}

In Asia, the prevalence of *BRCA1/BRCA2* mutations from unselected patients with breast cancer had been reported to range from 0.8% to 4.4% (all age groups).^{34,66,67} This is comparable to data from Western countries (1.8% to 3.6%).⁶⁸ Nonetheless, the reported prevalence varies from country to country; a recent report indicated that the prevalence of *BRCA1/BRCA2* mutations in Korea from patients with non-familial high-risk breast cancer was 9.8%.⁶⁹

There are mutations which have been recurrently seen across different countries. To the best of our knowledge, there is no report showing that families sharing the same mutation among the countries were related. All the haplotyping was done in their own countries as it is rather difficult to obtain the samples for analysis. This would be an important piece of missing information that needs to be answered; therefore a consortium has been established to clarify this issue.

BRCA1/BRCA2 mutations, in particular, *BRCA1* mutations are associated with young age of onset of cancer and with TNBC. Table 3 summarises the relationship of *BRCA1/BRCA2* mutations and these phenotypic characteristics which have been reported in Asia. The definition of young age for the purposes of testing varied between studies, and cut-offs ranged from 30 to 45 years. In Singapore, young age was defined as <30 years, whereas in Hong Kong young age was defined as <45 years, the suggested age of testing criteria under the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for ‘Genetic/Familial High-Risk Assessment: Breast and Ovarian’. Based on positive family history, studies from Korea, Hong Kong and Malaysia contained probands with the highest proportions of patients (ranged from 50% to 61%) who had family history of breast and/or ovarian cancer. However, this proportion varied greatly among different Asian countries, due to their relatively small study cohort sizes, and further study is needed in order to provide more accurate estimation in different countries.

TNBC is featured by the absence or lack of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 phenotype, and it accounts for 10%–20% of all breast cancers. TNBC has been reported to be associated with *BRCA1/BRCA2* mutation, where 50% of high-risk patients with TNBC and a positive family history were tested positive for *BRCA1/BRCA2* mutation.⁸⁰ *BRCA1/BRCA2* mutation was detected in approximately 40% of unselected Ashkenazi Jewish women with TNBC, and the majority of these were *BRCA1* mutation.⁸¹ In the USA, there was a higher proportion of *BRCA1* mutation (20%) than *BRCA2* mutation (4%) in patients with TNBC.⁸² Likewise, in the Asian populations, more TNBC cases were found to be associated with *BRCA1* mutation than *BRCA2* mutations. Several Chinese cohort studies showed that the prevalence of *BRCA1* mutations among selected patients with TNBC ranged from 18.6% to 36.8%, while *BRCA2* mutation only ranged from 7.3% to 10.5%.¹³⁷⁵⁷⁶ A similar discrepancy in *BRCA1/BRCA2* mutation prevalence (24.5% vs 3.6%) has also been reported in a Malaysian study of patients with TNBC with Malay, Chinese and Indian ancestries.⁷⁷ Taken together, these observations suggested that *BRCA1* mutation dominance in patients with TNBC was present in both Asian and the West.

Published data had shown that the prevalence of *BRCA1/BRCA2* mutation was identified in approximately 20% of Korean patients with bilateral breast cancers.²⁶⁶⁹ A similar mutation analysis revealed that 20% of patients with bilateral breast cancer were *BRCA1* mutation carriers and 12% were *BRCA2* mutation carriers; 8% of the patients had a family history of breast and ovarian cancer in a first-degree or second-degree relative.⁸³ Similarly, a higher frequency of *BRCA1* mutation was also seen in women with bilateral breast cancer in Canada.⁸⁴

In addition to the widely studied *BRCA1* and *BRCA2*, genetic testing for mutations in other familial breast cancer-associated genes, for instance, *PTEN*, *TP53*, *ATM*, *CHEK2* and *PALB2*, using multiple-gene sequencing panels had shown its important clinical values with the advances in next-generation sequencing technology. In a recent study, 141 women tested negative for *BRCA1/BRCA2* mutations had been identified for 16 pathogenic variants in other cancer susceptibility genes, giving a prevalence of 11.4% using multiple-gene sequencing.⁸⁵ However, the interpretation of results from such multiple-gene panels and their applications in routine diagnostic utility remain to be optimised. Moreover, the mutation data on cancer susceptibility genes other than *BRCA1/BRCA2* in Asian populations is also largely unknown.

This review encapsulates the up-to-date *BRCA1/BRCA2* mutation spectrum in Asia and Asians residing in Western countries and provides new insights into the distribution and characteristics of *BRCA1* and *BRCA2* mutations in Asia. The identification of common mutations in some ethnic groups or geographical locations raises the possibility of defining more efficient strategies for genetic testing. In particular, the high frequency of these mutations may provide information for genetic test panels that facilitate the ease of genetic testing for these individuals in Asian countries and those Asians who reside in the West, and may have value in optimising efficient strategies for genetic testing for *BRCA1* and *BRCA2* mutations associated with breast and ovarian cancer susceptibility which would be particularly useful. The discrepancies of the frequencies of mutations vary across countries

or even within the same country, maybe due to different selection criteria, genetic testing methods, different availability and cost of testing. In Japan, a 'Myriad Genetics'-based laboratory is used, while the other Asian countries did the testing in their own laboratories, most of which were supported by research grants and donations or were even self-financed. Hence, the limitations to access to these tests would be the cost and affordability of the test. The National Comprehensive Cancer Network Guidelines for 'Genetic/Familial High-Risk Assessment: Breast and Ovarian' provide a good backbone but it may need to be adjusted to improve applicability due to the lower incidence in breast cancer in Asia, lack of family history and likely different mutation spectrum and penetrance in this ethnic group.

Future directions

Despite our understanding of the *BRCA1/BRCA2* mutations, there remain many unanswered questions. A large number of VUS still need to be classified as pathogenic or not, and due to their low frequencies of occurrence, some variants will probably never be classified. There are also increased reports of *BRCA1/BRCA2* missense mutations, particularly in the less tested ethnicities, some of which have already been classified as pathogenic. Such reports are likely to increase when more genetic tests are being performed in different ethnic groups. Characterising VUS in familial breast cancers will be the future direction of the ABRCA Consortium group and will be included in the separated study.

Functional studies of *BRCA1* and *BRCA2* can provide valuable information on their roles in cancer development. Regardless of entering the era of next-generation high-throughput sequencing, many mutations in *BRCA1* and *BRCA2* to date still remain unclassified in terms of their pathogenicity, and much work would need to be done to better understand the mutations of these genes, particularly in different ethnic populations. The establishment of an Asian registry of *BRCA1/BRCA2* mutation carriers would allow more organised research work to be done on this population.

CONCLUSION

BRCA1/BRCA2 mutations have been identified to be the main contributor of hereditary breast cancer, which increases the lifetime risk of breast cancer in women. The overall prevalence of *BRCA1/BRCA2* mutations in Asians is comparable to that in other ethnic groups. In most Asian countries, the frequency of mutations in *BRCA1* is similar or slightly higher than that in *BRCA2*, except in Korea and Philippines. With the knowledge of the mutation spectrum *BRCA1/BRCA2* mutation carriers, improved genetic counselling and cancer management are likely to benefit Asian patients with breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Inclusion criteria for *BRCA1/BRCA2* genetic testing by research groups in different countries (any one of the risk factors)

Location*	Early onset of breast cancer (age)	Ovarian cancer	Bilateral breast cancer	Male breast cancer	Triple-negative breast cancer	Family history and other risk factors	References
Bangladesh	<40 years					Unselected for family history	9
China, Beijing	<35 years		Bilateral, age <50 years			At least one first-degree or second-degree relative with breast and/or ovarian cancer, regardless of age	10-11
China, Shanghai	<35 years					At least one first-degree or second-degree relative with breast and/or ovarian cancer, regardless of age At least one first-degree relative with malignant tumour beyond breast and ovarian cancer	12-13
Hong Kong	<45 years	Yes	Bilateral	Yes	Yes	At least one first-degree or second-degree relative with breast and/or ovarian cancer, regardless of age	14
India [†]	<35–40 years	Yes		Yes		Family history of breast and/or ovarian cancer [‡]	15–18
Indonesia	<40 years		Bilateral			Diagnosed age <50 years, with at least one first-degree or second-degree relative with breast or ovarian cancer, regardless of age At least two first-degree or second-degree relatives with breast cancer	19
Iran [‡]	<35–45 years	Yes	Two breast primaries	Yes		Family history of breast and/or ovarian cancer [‡] With multiple organ cancers including breast	20–22
Iraq, Syria, and Yemen	<40 years	<45 years				At least two first-degree or second-degree relatives with breast or ovarian cancer At least one relative with breast and ovarian cancer	23
Israel		Yes				Asymptomatic women from high-risk breast/ovarian cancer families ^{§,4}	24-25
Japan	<45 years	Yes	Bilateral, age <50 years	Yes		Diagnosed age <50 years, with at least one close relative with breast cancer <50 years, or one close relative with ovarian cancer, regardless of age At least two close relatives with breast cancer and/or ovarian cancer, regardless of age	

Location *	Early onset of breast cancer (age)	Ovarian cancer	Bilateral breast cancer	Male breast cancer	Triple-negative breast cancer	Family history and other risk factors	References
Korea	<40 years	Yes	Bilateral	Yes		With family history of breast or ovarian cancer With multiple organ cancers including breast	26
Lebanon		Yes		Yes		At least one relative with breast cancer under age of 50 years At least two first-degree or second-degree relatives with breast cancer and/or ovarian cancer	27
Malaysia	<35 years	Yes	Bilateral	Yes		At least one relative with breast cancer under age of 35 years, male breast cancer, or multiple cancers At least two relatives with breast or ovarian cancer, and at least one diagnosed at age <50 years At least three relatives with breast or ovarian cancer	28-29
Oman	<40 years		Bilateral		Yes		30
Pakistan †	<30 years	Yes, age<45 years		Yes		At least two first-degree or second-degree (through a male) female relatives with breast cancer, and at least one diagnosed at age <50 years At least three relatives with breast cancer, and at least one diagnosed at age <50 years At least one relative with breast and ovarian cancer	31-33
Philippines	<50 years	Yes	Bilateral	Yes		At least two relatives with breast or ovarian cancer At least one relative with two primaries, both breast and ovarian cancer, or multiple cancers	34
Singapore †	<40 years	Yes	Two breast primaries			At least one close relative with breast and/or ovarian cancer <i>priori</i> risk of 10% (BRCA ^{PRO} model) †	35-37
Taiwan	<35 years		Bilateral			Diagnosed age <50 years, with at least one close relative with breast cancer or ovarian cancer At least three relatives with breast cancer or one with ovarian cancer	38-39
Thailand †	Yes	Yes				At least two first-degree relatives with breast cancer and/or ovarian cancer	33-40
Turkey †	<40-50 years	Yes	Bilateral	Yes		Family history of breast and/or ovarian cancer †	41-45

Location *	Early onset of breast cancer (age)	Ovarian cancer	Bilateral breast cancer	Male breast cancer	Triple-negative breast cancer	Family history and other risk factors	References
Vietnam USA/Canada	Unselected <45 years	Yes	Bilateral, age <50 years	Yes		Patients with prostate cancer with family history of breast cancer Patients with prostate cancer with family history of breast cancer Patients with prostate cancer with family history of breast cancer Unselected for family history Diagnosed age <50 years, with at least one close relative with breast cancer <50 years, or one close relative with ovarian cancer, regardless of age At least two close relatives with breast cancer and/or ovarian cancer, regardless of age Ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish)	9

Keywords: breast cancer, ovarian cancer, al.

* No information of *BRCA1/BRCA2* mutation was found in Afghanistan, Kazakhstan and other Asian countries.

† Criteria varied among different research groups in the country.

Table 2
Overview of Asian *BRCA1/BRCA2* pathogenic mutations included in this review

Country [†]	<i>BRCA1</i> mutations			<i>BRCA2</i> mutations			
	Total no. of cases	Frequently occurring mutations [‡] (no. of entries)	References	Total distinct mutations	Total no. of cases	Frequently occurring mutations [‡] (no. of entries)	References
Eastern Asia (no data was available for North Korea.)							
China	37	c.981_982delAT (4), c.1465G>T (3), c.5470_5477del8 (4)	111346	41	51	c.1832C>A (3), c.6591_6592delTG (3)	1113
Hong Kong	44	c.470_471delCT (10), c.4372C>T (4), c.5406+1_5406+3delGTA (3)	1447	39	68	c.2808_2811delACAA (3), c.3109C>T (15), c.7878G>A (5)	14
Japan	34	c.188T>A (10)	4849	26	35	c.5576_5579delTTAA (4), c.6952C>T (4),	49
Korea	51	c.390C>A (27), c.922_923delAG (7), c.1961delA (7), c.5030_5033delCTAA (6), c.5080G>T (6), c.5444G>A (10), c.5467 +1G>A (6), c.5470_5477del8 (7), c.5496_5506del11msA (20)	2650-52	69	278	c.1399A>T (26), c.3744_3747delTCAG (24), c.5576_5579delTTAA (15), c.6724_6725delGA (8), c.7480C>T (51), c.9076C>T (10)	2652
Mongolia	1	c.3333delA (1)	53	-	-	-	-
Taiwan	3	c.5030_5033delCTAA (1), c.5335delC (1), c.5536C>T (1)	39	3	3	c.2442delC (1), c.2845delT (1), c.6468_6469delTTC (1)	38
South-eastern Asia (no data was available for Cambodia, Lao and other south-eastern Asia countries)							
Indonesia	1	Deletion of exon 13 to exon 15 (1)	19	3	5	c.2471_2476delTAAATG (2), c.6547G>T (2)	19
Malaysia	39	c.68_69delAG (3), c.135-1G>C (3), c.470_471delCT (3), c.4148C>G (3)	28	32	40	c.262_263delCT (5), c.2808_2811delACAA (3)	28
Philippines	3	p.Gln1538* (1), c.5335delC (1), p.Arg1835* (1)	34	7	12	c.4631delA (4)	34
Singapore	20	c.68_69delAG (2), c.2726dupA (9), c.3858_3861delTGAG (2)	3654	16	17	c.4151delT (2)	36
Thailand	4	c.3181delA (2), c.3748G>T (2)	3340	5	11	c.5299_5307del9 (5)	3340
Vietnam	1	c.66dupA (1)	9	1	1	c.4478_4481delAAAAG (1)	9
South-central Asia (no data was available for Afghanistan, Kazakhstan and other south-central Asia countries)							
Bangladesh	3	c.2269delG (1), Duplication of exon 20-24 (1), Deletion of exon 24 (1)		3	3	c.4078delG (1), c.4570_4573delTTTC (1), c.5622_5628delTAAAGAA (1)	

Country [†]	BRCA1 mutations			BRCA2 mutations			References	Total no. of cases	Frequently occurring mutations [‡] (no. of entries)	Total no. of cases	Frequently occurring mutations [‡] (no. of entries)	References
	Total no. of cases	Total distinct mutations	Frequently occurring mutations [‡] (no. of entries)	Total distinct mutations	Total distinct mutations	Frequently occurring mutations [‡] (no. of entries)						
India	16		c.68_69delAG (15), c.5260G>T (3)	16-1855	9			9				
Iran	7		c.969_970insC (3), c.1016delA (3)	2122	2			2	c.3751dupA (1), c.6033_6034insGT (1)	2		22
Pakistan	34		c.66dupA (4), c.1961dupA (3), c.4065_4068delTCAA (4), c.4485-1G>A (3), c.4508C>A (6)	3132	20			21	c.3109C>T (2),	21		31-33
Sri Lanka	4		c.737T>G (1), c.2967delT (1), c.5075-2A>T (1), c.5289delG (1)	56	3			6	c.2175_2176insA (4)	6		57
Western Asia (no data was available for Georgia, Jordan, Kuwait and other western Asia countries)												
Iraq	1		c.68_69delAG (1)	23	-			-				
Israel [§]	8		c.2934T>G (23)	2558	7			8	c.1763_1766delATAA (2)	8		25
Lebanon	3		c.131G>T (2), c.5444G>A (2)	27	2			2	c.5576_5579delTTAA (1), c.9257-1G>A (1)	2		27
Oman	2		Deletion (2)/duplication (2) of exon 1-2	30	-			-				
Saudi Arabia	-		-		1			1	c.2254_2257delGACT (1)	1		59
Syria	1		c.68_69delAG (1)	23	-			-				
Turkey	18		Deletion of exon 1-2 (17), Deletion of exon 18 (3), c.5266dupC (6)	4245	6			7	c.9100_9101insC (2)	7		41424460
Yemen	1		c.68_69delAG (2)	23	1			3				
Beyond Asia (cases of Asian descent)												
Canada	2		c.1016delA (1), c.3288_3289delAA (1)		3			3	c.905_906insA (1), c.8954-5A>G (1), c.9117G>A (1)	3		
USA	37		p.Tyr130* (2), p.Gln563* (2), c.3442delG (3), c.5059delG (3), p.Arg1751* (6)		50			69	c.1399A>T (2), c.1583delA (2), c.3109C>T (7), p.Tyr1894* (3), Duplication of exon 15 to 18 (5)	69		

[†] Countries were grouped based on the geographical definition from GLOBOCAN.

[‡] Only the most common BRCA1/BRCA2 mutations identified in each country are presented. The full BRCA1/BRCA2 mutation spectra are listed in the online supplementary tables S1 and S2.

[§] Only Jews of Asian origin were included in this study.

Table 3
Comparison of *BRCA1* and *BRCA2* studies among breast cancer cases for family history in Asian countries

Countries	No. of patients, n	<i>BRCA1</i> mutation, n (%)	<i>BRCA2</i> mutation, n (%)	<i>BRCA1/BRCA2</i> mutations, n (%)	Age of early onset, n (%)	Family history of breast cancer and/or ovarian cancer, n (%)	Triple negative, n (%)	Bilateral breast cancer, n (%)	References
Hong Kong	50	21 (42)	29	—	<35 years, 50	25	—	13 (26)	70
	130	5 (3.8)	—	—	<45 years, 56 (43)	—	—	—	71
	451	29 (6.4)	40 (8.9)	—	<40 years, 155 (34.4)	193/318 (60.7)	68/377 (18.0)	72 (16.0)	14
Korea	2139	127 (5.9)	137 (6.4)	—	—	—	—	—	52
	841	74 (8.8)	89 (10.6)	3 (0.4)	—	—	—	—	69
	354	17 (4.8)	8 (2.3)	—	<35 years; 152 (42.9)	—	—	39 (11.0)	72
	60	—	—	5 (8.3)	<35 years; 35 (58)	8 (13)	—	—	73
	173	15 (8.7)	7 (4)	—	<35 years; 74 (42.8)	86 (49.7)	—	—	66
	758	25 (3.3)	40 (5.3)	—	<40 years; 550 (72.6)	—	—	67 (8.8)	26
China	139	6 (4.3)	—	—	<35 years; 4 (2.8)	8 (5.8)	25 (18)	—	10
	448	20 (4.5)	21 (4.7)	—	<35 years; 22/253 (8.7)	31/241 (12.9)	78 (17.4)	—	13
	70	6 (8.6)	2 (2.9)	—	<35 years; 42 (60)	5 (7.1)	—	—	12
	645	54 (8.4)	73 (11.3)	123 (19.1)	<45 years; 256 (39.7)	28 (4.3)	—	—	74
	360	52 (14.4)	28 (7.8)	—	—	—	76 (21.1)	—	75
	96	18 (18.6)	7 (7.3)	—	<35 years; 26 (27.1)	28 (29.1)	96 (100)	—	76
	409	16 (3.9)	27 (6.6)	—	<40 years; 78 (19.1)	375 (91.7)	96 (23.5)	34 (8.3)	11
Vietnam	292	—	—	24 (0.8)	<40 years; 46 (15.8)	7 (2.4)	—	—	9
Malaysia	44	1 (2.3)	5 (11.4)	—	<40 years; 24 (54.5)	20 (45.5)	—	—	28
	431	37 (8.6)	28 (6.5)	—	<35 years; 131 (30.4)	236 (54.7)	110 (25.5)	39 (9.0)	77
Singapore	70	6 (8.6)	—	—	<35 years; 22 (31.4)	16 (22.9)	—	—	35
	43	7 (16.3)	—	—	<30 years; 7 (16.3)	7 (16.3)	—	—	78
Singapore-Malay	50	9 (18)	—	—	<35 years; 11 (22)	8 (16)	—	—	54
	49	6 (12.2)	—	—	<40 years, 19 (38.8)	—	—	—	79