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

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jmedgenet-2015-103132>).

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Received 16 March 2015

Revised 1 July 2015

Accepted 2 July 2015

Published Online First

17 July 2015

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.

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this review, we summarise the current spectrum of deleterious *BRCA1* and *BRCA2* mutations including novel, previously unpublished mutations among Asian countries, and where available, those Asians residing in Western countries.

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.^{3–4} 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.^{6–7} Although there are increasing reports from Asia, the majority of studies to date have

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.

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To cite: Kwong A, Shin VY, Ho JCW, et al. *J Med Genet* 2016;**53**:15–23.

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

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 ²⁴	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	
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	38 39

Continued

Table 1 Continued

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
Thailand†	Yes	Yes				At least three relatives with breast cancer or one with ovarian cancer	33 40
Turkey†	<40–50 years	Yes	Bilateral	Yes		At least two first-degree relatives with breast cancer and/or ovarian cancer Family history of breast and/or ovarian cancer† Patients with prostate cancer with family history of breast cancer, ovarian cancer, or prostate cancer	41–45
Vietnam	Unselected					Unselected for family history	9
USA/Canada	<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 Ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish)	

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

†Criteria varied among different research groups in the country.

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%.^{13 75 76} 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.^{26 69} 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

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

Country†	BRCA1 mutations			References	BRCA2 mutations			
	Total distinct mutations	Total no. of cases	Frequently occurring mutations‡ (no. of entries)		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	48	c.981_982delAT (4), c.1465G>T (3), c.5470_5477del8 (4)	11 13 46	41	51	c.1832C>A (3), c.6591_6592delTG (3)	11 13
Hong Kong	44	63	c.470_471delCT (10), c.4372C>T (4), c.5406+1_5406+3delGTA (3)	14 47	39	68	c.2808_2811delACAA (3), c.3109C>T (15), c.7878G>A (5)	14
Japan	34	46	c.188T>A (10)	48 49	26	35	c.5576_5579delTTAA (4), c.6952C>T (4),	49
Korea	51	172	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_5506del11insA (20)	26 50–52	69	278	c.1399A>T (26), c.3744_3747delTGAG (24), c.5576_5579delTTAA (15), c.6724_6725delGA (8), c.7480C>T (51), c.9076C>T (10)	26 52
Mongolia	1	1	c.3333delA (1)	53	—	—	—	
Taiwan	3	3	c.5030_5033delCTAA (1), c.5335delC (1), c.5536C>T (1)	39	3	3	c.2442delC (1), c.2845delT (1), c.6468_6469delTC (1)	38
South-eastern Asia (no data was available for Cambodia, Lao and other south-eastern Asia countries)								
Indonesia	1	1	Deletion of exon 13 to exon 15 (1)	19	3	5	c.2471_2476delTAAATG (2), c.6547G>T (2)	19
Malaysia	39	55	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	3	p.Gln1538* (1), c.5335delC (1), p.Arg1835* (1)	34	7	12	c.4631delA (4)	34
Singapore	20	32	c.68_69delAG (2), c.2726dupA (9), c.3858_3861delTGAG (2)	36 54	16	17	c.4151delT (2)	36
Thailand	4	6	c.3181delA (2), c.3748G>T (2)	33 40	5	11	c.5299_5307del9 (5)	33 40
Vietnam	1	1	c.66dupA (1)	9	1	1	c.4478_4481delAAAG (1)	9
South-central Asia (no data was available for Afghanistan, Kazakhstan and other south-central Asia countries)								
Bangladesh	3	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_5628delTAAGGAA (1)	
India	16	32	c.68_69delAG (15), c.5260G>T (3)	16–18 55	9	9		
Iran	7	11	c.969_970insC (3), c.1016delA (3)	21 22	2	2	c.3751dupA (1), c.6033_6034insGT (1)	22
Pakistan	34	56	c.66dupA (4), c.1961dupA (3), c.4065_4068delTCAA (4), c.4485–1G>A (3), c.4508C>A (6)	31 32	20	21	c.3109C>T (2),	31–33
Sri Lanka	4	4	c.737T>G (1), c.2967delT (1), c.5075–2A>T (1), c.5289delG (1)	56	3	6	c.2175_2176insA (4)	57
Western Asia (no data was available for Georgia, Jordan, Kuwait and other western Asia countries)								
Iraq	1	1	c.68_69delAG (1)	23	—	—	—	
Israel§	8	30	c.2934T>G (23)	25 58	7	8	c.1763_1766delATAA (2)	25
Lebanon	3	5	c.131G>T (2), c.5444G>A (2)	27	2	2	c.5576_5579delTTAA (1), c.9257–1G>A (1)	27
Oman	2	4	Deletion (2)/ duplication (2) of exon 1–2	30	—	—		
Saudi Arabia	—	—	—		1	1	c.2254_2257delGACT (1)	59
Syria	1	1	c.68_69delAG (1)	23	—	—	—	
Turkey	18	42	Deletion of exon 1–2 (17), Deletion of exon 18 (3), c.5266dupC (6)	42 45	6	7	c.9100_9101insC (2)	41 42 44 60
Yemen	1	2	c.68_69delAG (2)	23	1	3		
Beyond Asia (cases of Asian descent)								
Canada	2	2	c.1016delA (1), c.3288_3289delAA (1)		3	3	c.905_906insA (1), c.8954–5A>G (1), c.9117G>A (1)	
USA	37	49	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)	

†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
	139	6 (4.3)	—	—	<35 years; 4 (2.8)	8 (5.8)	25 (18)	—	10
China	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
	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

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.

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Correction notice This article has been corrected since it published Online First. The acknowledgements section has been updated.

Acknowledgements The authors would like to thank members of the Asian Hereditary Breast Cancer Consortium (ABRCA) for their contributions and support in this study, especially Drs Yuntao Xie, Zhi-Ming Shao, Guo-Jun Zhang, Ute Hamann, Samuel Haryono, Sue K. Park, Min Hyuk Lee, Jong Won Lee, Muhammad Usman Rashid, Rodney Dofitas, Peter Ang, Philip lau, and Pimpicha Patmasiriwat. City of Hope Clinical Cancer Genetics Community Research Network and the Hereditary Cancer Research Registry, supported in part by Award Number RC4CA153828 (PI: J. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Contributors AK, EK, SN, SHT, ASGL, J-HS, OMG, JNW, SAN, JMF and S-WK conceived and designed the study. AK, JCWH, EK, SN, S-HT, ASGL, J-HS, OMG, AWK, JNW, M-TS, FBFL, T-LC, ESKM and SWK contributed to data acquisition. VYS and JCWH interpreted data and drafted the manuscript. AK, VYS, JCWH, SN, SHT, OMG, AWK, T-LC, SAN, JMF, ESKM and S-WK reviewed the manuscript. All authors approved the final manuscript.

Funding This study was partly supported by the Dr Ellen Li Charitable Foundation, the Kerry Group Kuok Foundation Limited, the National Institutes of Health (1R03CA130065), the National R&D Program for Cancer Control, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (#1020350), the Canadian Breast Cancer Research Alliance and the Canadian Cancer Society Research Institute.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board of the University of Hong Kong.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Howlander N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst* 2010;102:1584–98.
- Ripperger T, Gadzicki D, Meindl A, Schlegelberger B. Breast cancer susceptibility: current knowledge and implications for genetic counselling. *Eur J Hum Genet* 2009;17:722–31.
- Fackenthal JD, Olopade OI. Breast cancer risk associated with *BRCA1* and *BRCA2* in diverse populations. *Nat Rev Cancer* 2007;7:937–48.
- Couch FJ, Nathanson KL, Offit K. Two decades after *BRCA*: setting paradigms in personalized cancer care and prevention. *Science* 2014;343:1466–70.
- Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struwing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1998;62:676–89.
- Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117–30.
- Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol* 2007;25:1329–33.
- Deapen D, Liu L, Perkins C, Bernstein L, Ross RK. Rapidly rising breast cancer incidence rates among Asian-American women. *Int J Cancer* 2002;99:747–50.
- Ginsburg OM, Dinh NV, To TV, Quang LH, Linh ND, Duong BT, Royer R, Llacuachqui M, Tulman A, Vichodez G, Li S, Love RR, Narod SA. Family history, *BRCA* mutations and breast cancer in Vietnamese women. *Clin Genet* 2011;80:89–92.
- Chen WQ, Pan KF, Ouyang T, Li JF, Wang TF, Fan ZQ, Fan T, Lin BY, Lu YY, You WC, Xie YT. *BRCA1* germline mutations and tumor characteristics in Chinese women with familial or early-onset breast cancer. *Breast Cancer Res Treat* 2009;117:55–60.
- Zhang J, Pei RG, Pang ZY, Ouyang T, Li JF, Wang TF, Fan ZQ, Fan T, Lin BY, Xie YT. Prevalence and characterization of *BRCA1* and *BRCA2* germline mutations in Chinese women with familial breast cancer. *Breast Cancer Res Treat* 2012;132:421–8.

- 12 Song CG, Hu Z, Wu J, Luo JM, Shen ZZ, Huang W, Shao ZM. The prevalence of BRCA1 and BRCA2 mutations in eastern Chinese women with breast cancer. *J Cancer Res Clin Oncol* 2006;132:617–26.
- 13 Li WF, Hu Z, Rao NY, Song CG, Zhang B, Cao MZ, Su FX, Wang YS, He PQ, Di GH, Shen KW, Wu J, Lu JS, Luo JM, Liu XY, Zhou J, Wang L, Zhao L, Liu YB, Yuan WT, Yang L, Shen ZZ, Huang W, Shao ZM. The prevalence of BRCA1 and BRCA2 germline mutations in high-risk breast cancer patients of Chinese Han nationality: two recurrent mutations were identified. *Breast Cancer Res Treat* 2008;110:99–109.
- 14 Kwong A, Ng EKO, Wong CLP, Law FBF, Au T, Wong HN, Kurian AW, West DW, Ford JM, Ma ESK. Identification of BRCA1/2 founder mutations in Southern Chinese breast cancer patients using gene sequencing and high resolution DNA melting analysis. *PLoS ONE* 2012;7:e43994.
- 15 Rajkumar T, Soumitra N, Nancy NK, Swaminathan R, Sridevi V, Shanta V. BRCA1, BRCA2 and CHEK2 (1100 del C) germline mutations in hereditary breast and ovarian cancer families in South India. *Asian Pac J Cancer Prev* 2003;4:203–8.
- 16 Valarmathi MT, Sawhney M, Deo SS, Shukla NK, Das SN. Novel germline mutations in the BRCA1 and BRCA2 genes in Indian breast and breast-ovarian cancer families. *Hum Mutat* 2004;23:205.
- 17 Saxena S, Chakraborty A, Kaushal M, Kotwal S, Bhatnager D, Mohil RS, Chintamani C, Aggarwal AK, Sharma VK, Sharma PC, Lenoir G, Goldgar DE, Szabo CI. Contribution of germline BRCA1 and BRCA2 sequence alterations to breast cancer in Northern India. *BMC Med Genet* 2006;7:75.
- 18 Vaidyanathan K, Lakhotia S, Ravishankar HM, Tabassum U, Mukherjee G, Somasundaram K. BRCA1 and BRCA2 germline mutation analysis among Indian women from south India: identification of four novel mutations and high-frequency occurrence of 185delAG mutation. *J Biosci* 2009;34:415–22.
- 19 Purnomosari D, Pals G, Wahyono A, Aryandono T, Manuaba TW, Haryono SJ, van Diest PJ. BRCA1 and BRCA2 germline mutation analysis in the Indonesian population. *Breast Cancer Res Treat* 2007;106:297–304.
- 20 Saleh-Gohari N, Mohammadi-Anaie M, Kalantari-Khandani B. BRCA1 gene mutations in breast cancer patients from Kerman Province, Iran. *Iran J Cancer Prev* 2012;5:210–15.
- 21 Keshavarzi F, Javadi GR, Zeinali S. BRCA1 and BRCA2 germline mutations in 85 Iranian breast cancer patients. *Fam Cancer* 2012;11:57–67.
- 22 Yassaee VR, Zeinali S, Hariri I, Jarvandi S, Mohagheghi MA, Hornby DP, Dalton A. Novel mutations in the BRCA1 and BRCA2 genes in Iranian women with early-onset breast cancer. *Breast Cancer Res* 2002;4.
- 23 Bar-Sade RB, Bhothisuwan K, Modan B, Gak E, Hirsh-Yechezkel G, Theodor L, Novikov I, Gershoni-Baruch R, Risel S, Papa MZ, Ben-Baruch G, Friedman E. The 185delAG BRCA1 mutation originated before the dispersion of Jews in the diaspora and is not limited to Ashkenazim. *Hum Mol Genet* 1998;7:801–5.
- 24 Laitman Y, Simeonov M, Herskovitz L, Kushnir A, Shimon-Paluch S, Kaufman B, Zidan J, Friedman E. Recurrent germline mutations in BRCA1 and BRCA2 genes in high risk families in Israel. *Breast Cancer Res Treat* 2012;133:1153–7.
- 25 Laitman Y, Borstein RT, Stoppa-Lyonnet D, Dagan E, Castera L, Goisard M, Gershoni-Baruch R, Goldberg H, Kaufman B, Ben-Baruch N, Zidan J, Maray T, Soussan-Gutman L, Friedman E. Germline mutations in BRCA1 and BRCA2 genes in ethnically diverse high risk families in Israel. *Breast Cancer Res Treat* 2011;127:489–95.
- 26 Son BH, Ahn SH, Kim SW, Kang E, Park SK, Lee MH, Noh WC, Kim LS, Jung Y, Kim KS, Noh DY, Moon BI, Suh YJ, Lee JE, Choi DH, Kim SY, Jung SH, Yom CK, Lee H, Yang JH. Prevalence of BRCA1 and BRCA2 mutations in non-familial breast cancer patients with high risks in Korea: the Korean Hereditary Breast Cancer (KOHBR) Study. *Breast Cancer Res Treat* 2012;133:1143–52.
- 27 Jalkh N, Nassar-Slaba J, Chouery E, Salem N, Uhrhammer N, Golmard L, Stoppa-Lyonnet D, Bignon YJ, Megarbane A. Prevalence of BRCA1 and BRCA2 mutations in familial breast cancer patients in Lebanon. *Heredit Cancer Clin Pract* 2012;10:7.
- 28 Thirthagiri E, Lee SY, Kang P, Lee DS, Toh GT, Selamat S, Yoon SY, Taib NA, Thong MK, Yip CH, Teo SH. Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. *Breast Cancer Res Treat* 2008;10:R59.
- 29 Kang P, Mariapun S, Phuah SY, Lim LS, Liu JJ, Yoon SY, Thong MK, Taib NAM, Yip CH, Teo SH. Large BRCA1 and BRCA2 genomic rearrangements in Malaysian high risk breast-ovarian cancer families. *Breast Cancer Res Treat* 2010;124:579–84.
- 30 Al-Moundhri MS, Al-Ansari A, Al-Mawali K, Al-Bahrani B. BRCA1 gene molecular alterations in Omani breast cancer patients. *Gulf J Oncol* 2013;1:45–51.
- 31 Liede A, Malik IA, Aziz Z, de los Rios P, Kwan E, Narod SA. Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. *Am J Hum Genet* 2002;71:595–606.
- 32 Rashid MU, Zaidi A, Torres D, Sultan F, Benner A, Naqvi B, Shakoobi AR, Seidel-Renkert A, Farooq H, Narod S, Amin A, Hamann U. Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. *Int J Cancer* 2006;119:2832–9.
- 33 Ahmad J, Le Calvez-Kelm F, Daud S, Voegelé C, Vallee M, Ahmad A, Kakar N, McKay JD, Gaborieau V, Leone M, Sinilnikova O, Sangrajrang S, Tavtigian SV, Lesueur F. Detection of BRCA1/2 mutations in breast cancer patients from Thailand and Pakistan. *Clin Genet* 2012;82:594–8.
- 34 De Leon Matsuda ML, Liede A, Kwan E, Mapua CA, Cutiongco EM, Tan A, Borg A, Narod SA. BRCA1 and BRCA2 mutations among breast cancer patients from the Philippines. *Int J Cancer* 2002;98:596–603.
- 35 Sng JH, Chang J, Feroze F, Rahman N, Tan W, Lim S, Lehnert M, van der Pool S, Wong J. The prevalence of BRCA1 mutations in Chinese patients with early onset breast cancer and affected relatives. *Br J Cancer* 2000;82:538–42.
- 36 Ang P, Lim IHK, Lee TC, Luo JT, Ong DCT, Tan PH, Lee ASG. BRCA1 and BRCA2 mutations in an Asian clinic-based population detected using a comprehensive strategy. *Cancer Epidemiol Biomarkers Prev* 2007;16:2276–84.
- 37 Lim YK, Lau PTC, Ali AB, Lee SC, Wong JEL, Putti TC, Sng JH. Identification of novel BRCA large genomic rearrangements in Singapore Asian breast and ovarian patients with cancer. *Clin Genet* 2007;71:331–42.
- 38 Li SSL, Tseng HM, Yang TP, Liu CH, Teng SJ, Huang HW, Chen LM, Kao HW, Chen JH, Tseng JN, Chen A, Hou MF, Huang TJ, Chang HT, Mok KT, Tsai JH. Molecular characterization of germline mutations in the BRCA1 and BRCA2 genes from breast cancer families in Taiwan. *Hum Genet* 1999;104:201–4.
- 39 Kuo WH, Lin PH, Huang AC, Chien YH, Liu TP, Lu YS, Bai LY, Sargeant AM, Lin CH, Cheng AL, Hsieh FJ, Hwu WL, Chang KJ. Multimodal assessment of BRCA1 mutations in Taiwanese (ethnic Chinese) women with early-onset, bilateral or familial breast cancer. *J Hum Genet* 2012;57:130–8.
- 40 Patmasiriwat P, Bhothisuwan K, Sinilnikova OM, Chopin S, Methakijvaroon S, Badzioch M, Padungst P, Vattanaviboon P, Vattanasapt V, Szabo C, Saunders GF, Goldgar D, Lenoir GM. Analysis of breast cancer susceptibility genes BRCA1 and BRCA2 in Thai familial and isolated early-onset breast and ovarian cancer. *Hum Mutat* 2002;20:230.
- 41 Balci A, Huusko P, Paakkonen K, Launonen V, Uner A, Ekmekci A, Winqvist R. Mutation analysis of BRCA1 and BRCA2 in Turkish cancer families: a novel mutation BRCA2 3414del4 found in male breast cancer. *Eur J Cancer* 1999;35:707–10.
- 42 Yazici H, Bitisik O, Akisik E, Cabioglu N, Saip P, Muslumanoglu M, Glendon G, Bengisu E, Ozbilen S, Dincer M, Turkmen S, Andralis IL, Dalay N, Ozelik H. BRCA1 and BRCA2 mutations in Turkish breast/ovarian families and young breast cancer patients. *Br J Cancer* 2000;83:737–42.
- 43 Manguoglu AE, Luleci G, Ozelik T, Colak T, Schayek H, Akaydin M, Friedman E. Germline mutations in the BRCA1 and BRCA2 genes in Turkish breast/ovarian cancer patients. *Hum Mutat* 2003;21:444–5.
- 44 Egeli U, Cecener G, Tunca B, Tasdelen I. Novel germline BRCA1 and BRCA2 mutations in Turkish women with breast and/or ovarian cancer and their relatives. *Cancer Invest* 2006;24:484–91.
- 45 Aktas D, Gultekin M, Kabacam S, Alikasifoglu M, Turan AT, Tulunay G, Kose MF, Ortac F, Yuce K, Tuncbilek E, Ayhan A. Identification of point mutations and large rearrangements in the BRCA1 gene in 667 Turkish unselected ovarian cancer patients. *Gynecol Oncol* 2010;119:131–5.
- 46 Zhi X, Szabo C, Chopin S, Suter N, Wang QS, Ostrander EA, Sinilnikova OM, Lenoir GM, Goldgar D, Shi YR. BRCA1 and BRCA2 sequence variants in Chinese breast cancer families. *Hum Mutat* 2002;20:474.
- 47 Khoo US, Chan KY, Cheung AN, Xue WC, Shen DH, Fung KY, Ngan HY, Choy KW, Pang CP, Poon CS, Poon AY, Ozelik H. Recurrent BRCA1 and BRCA2 germline mutations in ovarian cancer: a founder mutation of BRCA1 identified in the Chinese population. *Hum Mutat* 2002;19:307–8.
- 48 Sekine M, Nagata H, Tsuji S, Hirai Y, Fujimoto S, Hatae M, Kobayashi I, Fujii T, Nagata I, Ushijima K, Obata K, Suzuki M, Yoshinaga M, Umesaki N, Satoh S, Enomoto T, Motoyama S, Tanaka K, Japanese Familial Ovarian Cancer Study Group. Mutational analysis of BRCA1 and BRCA2 and clinicopathologic analysis of ovarian cancer in 82 ovarian cancer families: two common founder mutations of BRCA1 in Japanese population. *Clin Cancer Res* 2001;7:3144–50.
- 49 Sugano K, Nakamura S, Ando J, Takayama S, Kamata H, Sekiguchi I, Ubukata M, Kodama T, Arai M, Kasumi F, Hirai Y, Ikeda T, Jinno H, Kitajima M, Aoki D, Hirasawa A, Takeda Y, Yazaki K, Fukutomi T, Kinoshita T, Tsunematsu R, Yoshida T, Izumi M, Umezawa S, Yagata H, Komatsu H, Arimori N, Matoba N, Gondo N, Yokoyama S, Miki Y. Cross-sectional analysis of germline BRCA1 and BRCA2 mutations in Japanese patients suspected to have hereditary breast/ovarian cancer. *Cancer Sci* 2008;99:1967–76.
- 50 Seong MW, Cho SI, Noh DY, Han W, Kim SW, Park CM, Park HW, Kim SY, Kim JY, Park SS. Comprehensive mutational analysis of BRCA1/BRCA2 for Korean breast cancer patients: evidence of a founder mutation. *Clin Genet* 2009;76:152–60.
- 51 Kang E, Park SK, Yang JJ, Park B, Lee MH, Lee JW, Suh YJ, Lee JE, Kim HA, Oh SJ, Kim SW, Korean Breast Canc Soc. Accuracy of BRCA1/2 mutation prediction models in Korean breast cancer patients. *Breast Cancer Res Treat* 2012;134:1189–97.
- 52 Kim H, Cho DY, Choi DH, Choi SY, Shin I, Park W, Huh SJ, Han SH, Lee MH, Ahn SH, Son BH, Kim SW, Haffty BG. Characteristics and spectrum of BRCA1 and BRCA2 mutations in 3,922 Korean patients with breast and ovarian cancer. *Breast Cancer Res Treat* 2012;134:1315–26.
- 53 Elit L, Jack E, Kwan E, Baigal G, Narod S. A unique BRCA1 mutation identified in Mongolia. *Int J Gynecol Cancer* 2001;11:241–3.
- 54 Sng JH, Ali AB, Lee SC, Zahar D, Wong JEL, Blake V, Sharif A, Cross G, Lau PTC. BRCA1 c.2845insA is a recurring mutation with a founder effect in Singapore Malay women with early onset breast/ovarian cancer. *J Med Genet* 2003;40.

- 55 Valarmathi MT, A A, Deo SS, Shukla NK, Das SN. BRCA1 germline mutations in Indian familial breast cancer. *Hum Mutat* 2003;21:98–9.
- 56 De Silva W, Karunanayake EH, Tennakoon KH, Allen M, Amarasinghe I, Angunawala P, Ziard MH. Novel sequence variants and a high frequency of recurrent polymorphisms in BRCA1 gene in Sri Lankan breast cancer patients and at risk individuals. *BMC Cancer* 2008;8:214.
- 57 De Silva S, Tennakoon KH, Karunanayake EH, De Silva W, Amarasinghe I, Angunawala P. Novel sequence variants and common recurrent polymorphisms of BRCA2 in Sri Lankan breast cancer patients and a family with BRCA1 mutations. *Exp Ther Med* 2011;2:1163–70.
- 58 Kadouri L, Bercovich D, Elimelech A, Lerer I, Sagi M, Glusman G, Shochat C, Korem S, Hamburger T, Nissan A, Abu-Halaf N, Badriyah M, Abeliovich D, Peretz T. A novel BRCA-1 mutation in Arab kindred from east Jerusalem with breast and ovarian cancer. *BMC Cancer* 2007;7:14.
- 59 El-Harith EHA, Abdel-Hadi MS, Steinmann D, Dork T. BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia. *Saudi Med J* 2002;23:700–4.
- 60 Ozdag H, Tez M, Sayek I, Muslumanoglu M, Tarcan O, Icli F, Ozturk M, Ozcelik T. Germ line BRCA1 and BRCA2 gene mutations in Turkish breast cancer patients. *Eur J Cancer* 2000;36:2076–82.
- 61 Weitzel JN, Lagos V, Blazer KR, Nelson R, Ricker C, Herzog J, McGuire C, Neuhausen S. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev* 2005;14:1666–71.
- 62 Nanda R, Schumm LP, Cummings S, Fackenthal JD, Sveen L, Ademuyiwa F, Cobleigh M, Esserman L, Lindor NM, Neuhausen SL, Olopade OI. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA* 2005;294:1925–33.
- 63 Kwong A, Wong LP, Wong HN, Law FB, Ng EK, Tang YH, Chan WK, Suen DT, Choi C, Ho LS, Kwan KH, Poon M, Wong TT, Chan K, Chan SW, Ying MW, Chan WC, Ma ES, Ford JM, West DW. Clinical and pathological characteristics of Chinese patients with BRCA related breast cancer. *Hugo J* 2009;3:63–76.
- 64 Ferla R, Calo V, Cascio S, Rinaldi G, Badalamenti G, Carreca I, Surmacz E, Colucci G, Bazan V, Russo A. Founder mutations in BRCA1 and BRCA2 genes. *Ann Oncol* 2007;18(Suppl 6):vi93–8.
- 65 Kurian AW. BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications. *Curr Opin Obstet Gynecol* 2010;22:72–8.
- 66 Ahn SH, Hwang UK, Kwak BS, Yoon HS, Ku BK, Kang HJ, Kim JS, Ko BK, Ko CD, Yoon KS, Cho DY, Son BH. Prevalence of BRCA1 and BRCA2 mutations in Korean breast cancer patients. *J Korean Med Sci* 2004;19:269–74.
- 67 Hedau S, Jain N, Husain SA, Mandal AK, Ray G, Shahid M, Kant R, Gupta V, Shukla NK, Deo SS, Das BC. Novel germline mutations in breast cancer susceptibility genes BRCA1, BRCA2 and p53 gene in breast cancer patients from India. *Breast Cancer Res Treat* 2004;88:177–86.
- 68 Liede A, Narod SA. Hereditary breast and ovarian cancer in Asia: genetic epidemiology of BRCA1 and BRCA2. *Hum Mutat* 2002;20:413–24.
- 69 Han SA, Park SK, Ahn SH, Lee MH, Noh DY, Kim LS, Noh WC, Jung Y, Kim SW, Korean Breast Cancer Study Group. The Korean Hereditary Breast Cancer (KOHBCA) study: protocols and interim report. *Clin Oncol (R Coll Radiol)* 2011;23:434–41.
- 70 de Bruin MA, Kwong A, Goldstein BA, Lipson JA, Ikeda DM, McPherson L, Sharma B, Kardashian A, Schackmann E, Kingham KE, Mills MA, West DW, Ford JM, Kurian AW. Breast cancer risk factors differ between Asian and white women with BRCA1/2 mutations. *Fam Cancer* 2012;11:429–39.
- 71 Tang NL, Choy KW, Pang CP, Yeo W, Johnson PJ. Prevalence of breast cancer predisposition gene mutations in Chinese women and guidelines for genetic testing. *Clin Chim Acta* 2001;313:179–85.
- 72 Ahn SH, Son BH, Yoon KS, Noh DY, Han W, Kim SW, Lee ES, Park HL, Hong YJ, Choi JJ, Moon SY, Kim MJ, Kim KH, Kwak BS, Cho DY. BRCA1 and BRCA2 germline mutations in Korean breast cancer patients at high risk of carrying mutations. *Cancer Lett* 2007;245:90–5.
- 73 Choi DH, Lee MH, Bale AE, Carter D, Haffty BG. Incidence of BRCA1 and BRCA2 mutations in young Korean breast cancer patients. *J Clin Oncol* 2004;22:1638–45.
- 74 Suter NM, Ray RM, Hu YW, Lin MG, Porter P, Gao DL, Zaucha RE, Iwasaki LM, Sabacan LP, Langlois MC, Thomas DB, Ostrander EA. BRCA1 and BRCA2 mutations in women from Shanghai China. *Cancer Epidemiol Biomarkers Prev* 2004;13:181–9.
- 75 Xu J, Wang B, Zhang Y, Li R, Wang Y, Zhang S. Clinical implications for BRCA gene mutation in breast cancer. *Mol Biol Rep* 2012;39:3097–102.
- 76 Li YT, Ni D, Yang L, Zhao Q, Ou JH. The prevalence of BRCA1/2 mutations of triple-negative breast cancer patients in Xinjiang multiple ethnic region of China. *Eur J Med Res* 2014;19:35.
- 77 Phuay SY, Looi LM, Hassan N, Rhodes A, Dean S, Taib NA, Yip CH, Teo SH. Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. *Breast Cancer Res* 2012;14:R142.
- 78 Ho GH, Phang BH, Ng IS, Law HY, Soo KC, Ng EH. Novel germline BRCA1 mutations detected in women in Singapore who developed breast carcinoma before the age of 36 years. *Cancer* 2000;89:811–16.
- 79 Lee AS, Ho GH, Oh PC, Balram C, Ooi LL, Lim DT, Wong CY, Hong GS. Founder mutation in the BRCA1 gene in Malay breast cancer patients from Singapore. *Hum Mutat* 2003;22:178.
- 80 Bayraktar S, Gutierrez-Barrera AM, Liu D, Tasbas T, Akar U, Litton JK, Lin E, Albarracin CT, Meric-Bernstam F, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK. Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. *Breast Cancer Res Treat* 2011;130:145–53.
- 81 Comen E, Davids M, Kirchoff T, Hudis C, Offit K, Robson M. Relative contributions of BRCA1 and BRCA2 mutations to “triple-negative” breast cancer in Ashkenazi Women. *Breast Cancer Res Treat* 2011;129:185–90.
- 82 Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, Potter J, Lanchbury JS, Sternke-Hale K, Hennessy BT, Arun BK, Hortobagyi GN, Do KA, Mills GB, Meric-Bernstam F. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. *Clin Cancer Res* 2011;17:1082–9.
- 83 Ready KJ, Vogel KJ, Atchley DP, Broglio KR, Solomon KK, Amos C, Lu KH, Hortobagyi GN, Arun B. Accuracy of the BRCAPRO model among women with bilateral breast cancer. *Cancer* 2009;115:725–30.
- 84 Weitzel JN, Robson M, Pasini B, Manoukian S, Stoppa-Lyonnet D, Lynch HT, McLennan J, Foulkes WD, Wagner T, Tung N, Ghadirian P, Olopade O, Isaacs C, Kim-Sing C, Moller P, Neuhausen SL, Metcalfe K, Sun P, Narod SA. A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev* 2005;14:1534–8.
- 85 Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, McGuire V, Ladabaum U, Kobayashi Y, Lincoln SE, Cargill M, Ford JM. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014;32:2001–9.