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RESEARCH ARTICLE

Clinical and pathological characteristics of Chinese patients with *BRCA* related breast cancer

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Abstract Breast cancers related to *BRCA* mutations are associated with particular biological features. Here we report the clinical and pathological characteristics of breast cancer in Chinese women with and without *BRCA* mutations and of carriers of *BRCA1* mutations compared to *BRCA2* mutations. Two hundred and 26 high-risk Hong Kong Chinese women were tested for *BRCA* mutations, medical information was obtained from medical records, and risk and demographic information was obtained from personal interviews. In this cohort, 28 (12.4%) women were *BRCA* mutation carriers and among these carriers, 39.3% were *BRCA1* and 60.7% were *BRCA2* mutations. Mutation carriers were more likely to have a familial history of breast and ovarian cancer, high-grade cancers, and triple negative (TN) cancers. Prevalence of TN was 48.3% in *BRCA* carriers and 25.6% in non-carriers and was 67.7% in *BRCA1* and 35.3% in *BRCA2* carriers. Estrogen receptor (ER) negative cancer was significantly associated with

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BRCA1 mutations, especially in those under 40 years of age. *BRCA*-related breast cancer in this Chinese population is associated with family history and adverse pathological/prognostic features, with *BRCA2* mutations being more prevalent but *BRCA1* carriers having more aggressive and TN cancers. Compared to Caucasian populations, prevalence of *BRCA2* mutations and TN cancer in BRCA2 mutation carriers in Chinese population are elevated.

Keywords Breast cancer · *BRCA* mutation · Pathology · Clinical features · Chinese

Abbreviations

DCIS	Ductal carcinoma in situ
TN	Triple negative cancer
LVI	Lymphovascular invasive
ER	Estrogen receptor
PR	Progesterone receptor

Introduction

BRCA mutations are known to be related to breast cancers with distinct clinical and pathological features compared to sporadic breast cancers (Basu et al. 2008; Atchley et al. 2008). There are also known clinical and pathologic differences between tumors arising from inheritance of mutations of *BRCA*1 and *BRCA*2 genes (Chappuis et al. 2000). In addition, studies in Western literature report potential epidemiological, clinical, and biological differences in breast cancer between Asian and Caucasian populations (John et al. 2007, Fackenthal and Olopade 2007). These data highlight the need to determine clinical and pathological characteristics in *BRCA* carriers in different populations, since these differences may affect future risk assessment, treatment planning, and outcomes.

To address these issues we report information from a multicenter study of Chinese high-risk patients residing in the Hong Kong Special Administrative Region of the People's Republic of China (HKSAR) in Southern China. This study identifies clinical and tumor pathologic features of breast cancer related to *BRCA* mutation inheritance, compared to those without mutations, and compares cancers from *BRCA1* and *BRCA2* mutation carriers.

Materials and method

Patients

A total of 226 clinically high-risk breast and/or ovarian cancer patients (probands), referred to the Hong Kong Hereditary and High Risk Breast Cancer Programme (www.HRBCP.org) from March 2007 to November 2008, were recruited prospectively. Based on the lower incidence of breast cancer in Asia cohorts, clinically high risk female patients who were included in this study; were defined as those who: (1) had at least one-first- or second- degree relative with breast and/or ovarian cancer, regardless of age; (2) were less than 50 years of age at diagnosis; (3) had bilateral breast cancer; (4) had triple negative (TN) or medullary type pathology; (5) had at least one relative with cancers other than breast and ovarian cancer that are known to be related to *BRCA* mutations; or (6) they were an ovarian cancer patient with a family history of breast cancer. A standard epidemiological questionnaire, including a detailed family history, was administered to patients and medical information, including pathology reports, was retrieved from the patient's medical records. Information from the epidemiological questionnaire included age at breast cancer diagnosis, other cancers diagnosed in the patient, and a family history of breast, ovarian, and other cancers in first, second, and third degree relatives. In addition, the following were categorized as having been used or not used: alcohol; tobacco; contraceptive pills, patches or injections; hormone replacement treatments; and infertility medications. Women were also asked if they had ever been pregnant and breast fed any child and if they were pre- or post-menopausal. Eligible patients were offered *BRCA* counseling and testing, and were consented for genetic testing and blood and tumor collection. Patients who tested positive for a *BRCA* mutation were asked to help recruit their first-degree relatives, who were also offered testing. This project was approved by the Ethical Committees of all the participating hospitals and centers in Hong Kong.

BRCA mutation detection by conventional DNA sequencing and MLPA

BRCA1 and BRCA2 mutation detection was performed on genomic DNA extracted from peripheral blood samples or paraffin embedded tissues, as described previously (Kwong et al. 2008). Mutation analysis was performed by direct DNA sequencing of all coding exons of BRCA1 and BRCA2 and multiplex ligation-dependent probe amplification (MLPA) (Sellner and Taylor 2004; Hogervorst et al. 2003; Schouten et al. 2002, Bunyan et al. 2004).

Clinical and pathological assessment

Clinical and pathological features included in the analysis were abstracted from medical records. These factors, related to extent of cancer at diagnosis and to treatment and prognosis, include: (a) type of breast cancer (in situ or

invasive); (b) grade (1–3, with lower numbers indicating more normal looking and slower growing cancers); stage (measure of extent of disease using the TNM system); (c) tumor size (T0, no tumor or in situ, sometimes classified as Tis, T1 = < 2 cm, T2 = 2–5 cm, T3 = > 5 cm); (d) lymph nodes (N) (N0 = no spread to nodes, N1 = 1–3 nodes, N2 = 4–9 nodes, N3 = > 9 nodes plus other criteria); (e) metastasis to distant organs (M0 = no spread, M1 = spread to other organs); (f) lymphatic invasion (LVI), which is usually detected from tumor on prepared slides; (g) Ki67, an index (%) measuring a cancer antigen found in dividing cells; and (h) three receptors related to tumor cells accepting or rejecting estrogen (ER), progesterone (PR), or HER2/*neu*, all of which tend to fuel growth of breast cancer and are determinants of treatment and prognosis. The final measure is "triple negative" cancer, which are tumors that are ER-, PR-, and HER2-. The ER/PR scoring is performed by the Allred scoring system in which comprised of proportion score and intensity score. The proportional score (i.e. % of positive cells) is: 0, completely negative; 1, <1/100; 2, 1/100–1/10; 3, 1/10–1/3; 4; 1/3–2/3 and 5, >2/3. The intensity score is: 0, negative; 1, weak; 2, intermediate and 3, strong. The total score is the sum of both and a score of >2 is considered positive. The HER2 criterion is based on ASCO/CAP guideline 2007. HER2 positive is defined as IHC3+ and if 2+ will reflex to FISH and categorized as HER2+ for a ratio of >2.2 (HER2 to chromosome 17 ratio) on dual colour system. A HER2 negative result is defined as IHC 0 or 1+ (Allred et al. 1998).

Statistical analysis

Chi Square (X^2) test was used to determine differences in characteristics among mutation carriers and non-carriers and between *BRCA1* and *BRCA2* carriers, with *P*-value of 0.05 or less being statistically significant, when data were categorical (Fisher's Exact test was used where counts were less than five). Linear by linear associations were used when data were ordinal. A case–control analytic approach was used to estimate the odds ratios of demographic, behavioral, clinical, and pathological variables being associated with carrier status and, if a carrier, being a BRCA1 or a BRCA2 carrier. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models (SPSS 16.0, SPSS Inc, Chicago, USA). Univariate (unadjusted) models were used since multivariate analyses were limited by small sample sizes. However, where multivariate models were possible the OR's were similar to the univariate models.

Results

Risk factors

A total of 226 female patients who met the criteria for being at high risk for breast cancer were tested for *BRCA* mutations and 28 (12.4%) were mutation carriers, of which 11 (39.3%) were *BRCA1* and 17 (60.7%) were *BRCA2* mutations. Fifty (22.1%) of these women had bilateral breast cancer; 32.1% among BRCA carriers and 20.7% among non-carriers. The median age at diagnosis of breast cancer was 42 years (range 21–82). Seven patients also had ovarian cancer and their median age at ovarian cancer diagnosis was 49 years (range 23–65). All patients were Chinese of which 84% originated from Guangdong province of Southern China. The majority (69.3%) was born in Hong Kong but over 70% of their parents were born in Mainland China.

When all patients was categorized into those less than age 40 and 40 or above, 55.6% of *BRCA* mutation carriers had breast cancer diagnosed before 40 years of age, compared to 36.0% of non-carriers, which is statistically significant at $P = 0.05$ and has an OR of 0.45; CI, 0.20–1.02 (Table 1). Our data also shows that *BRCA* carriers were 10 times more likely to have also been diagnosed with ovarian cancer (4/28; 14.3%) than non-carriers (3/198; 1.5%) (OR, 10.83; CI, 2.29, 51.34; $P = 0.005$). Only one ovarian cancer was seen in patients less than 40 years of age and she was in a mutation carrier. *BRCA* carriers and non-carriers did not differ for any of the other risk factors shown in Table 1 (use of alcohol, tobacco, contraceptive pills, infertility drugs, and hormone replacement therapy, having breast fed; and being menopausal); Although there is no statistically significance, mutation carriers were twice as likely to those who never have been pregnant as non-carriers (OR, 0.50; CI, 0.23–1.12.; $P = 0.09$).

Family history and age

BRCA mutation carriers were three times more likely to report family history of *any* cancer than non-carriers (OR, 3.05; CI 0.88–10.51) but this did not reach a significant difference (Table 2). *BRCA* carriers were statistically more likely to have relatives with breast cancer (OR, 2.99; CI, 1.29–6.93; $P = 0.01$) and ovarian cancer in family members (OR, 5.13; CI, 1.70–15.47; $P = 0.002$), compared to non-carriers. Furthermore, there was also statistically significant in linear relationship between the number of family members with breast cancer for *BRCA* carriers and non carriers, when looking at any family member (1st, 2nd, and 3rd degree relatives) with breast cancer ($OR^{+}_{(1\ vs.\ 3)}$, 25.6;

Table 1 Association of breast cancer risk factors between BRCA mutation carriers and non-carriers ($N = 226$)

	BRCA Mutations							
	Carriers ($N = 28$)*		Non-carriers ($N = 198$)*				Unadjusted	
	n	Col %	*n*	Col %	χ^2	*P*-value	OR†	95% CI
Age first diagnosed with breast cancer[a]								
Age group:								
<40	15	55.6	71	36.0			*1.00***	
≥40	12	44.4	126	64.0	3.82	**0.05**	**0.45**	**(0.20, 1.02)**
Had ovarian cancer								
No	24	85.7	195	98.5			1.00	
Yes	4	14.3	3	1.5	13.33	**0.005**	**10.83**	**(2.29, 51.34)**
Alcohol:								
No	27	96.4	182	91.9			*1.00***	
Yes	1	3.6	16	8.1	0.72	0.40	0.42	(0.05, 3.31)
Smoking:								
No	26	92.9	184	92.9			*1.00***	
Yes	2	7.1	14	7.1	<0.001	0.99	1.01	(0.22, 4.70)
Taking contraceptive pills/injection/patch:								
No	17	63.0	107	56.9			*1.00***	
Yes	10	37.0	81	43.1	0.35	0.55	0.78	(0.34, 1.79)
Taking hormonal replacement treatment:								
No	16	84.2	108	90.0			*1.00***	
Yes	3	15.8	12	10.0	0.57	0.45	1.69	(0.43, 6.64)
Taking infertility drug:								
No	25	100.0	175	96.2				
Yes	0	0.0	7	3.8	0.99	1.00	–	–
Whether had breast feed a child:								
No	14	77.8	90	66.7			*1.00***	
Yes	4	22.2	45	33.3	0.90	0.34	0.57	(0.18, 1.84)
Menopause:								
No	14	50.0	103	52.0			*1.00***	
Yes	14	50.0	95	48.0	0.04	0.84	1.08	(0.49, 2.39)
Ever been pregnant:								
No	13	46.4	60	30.3			*1.00***	
Yes	15	53.6	138	69.7	2.92	0.09	0.50	(0.23, 1.12)

Bold figure: Significant at <0.05

[a] There were two patients with ovarian cancer only, so there were 224 patients with breast cancer

* Values may not sum to 100% because of missing data

** Referent

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

CI, 4.88–134.37) or only considering 1st degree relatives ($OR^{+}_{(1\ vs.\ 2)}$, 25.00; CI, 2.87–218.18). No statistical difference was seen for 2nd degree relatives. Twenty-two of the women with breast cancer were from families with both breast and ovarian cancer; 32% of *BRCA* carriers and 7% of non-carriers (data not shown). Of those with a family history of other malignancies, the most common were lung, colon, liver, nasopharyngeal, gastric, esophageal, and pancreatic cancers (data not shown), but there were no statistical difference between carriers and non-carriers. Mutation carriers were more likely to have family members with breast cancer when stratified by age (Table 3). This association was seen in both age groups, but was only statistically different when the age group was over 40 (OR, 3.75; CI, 1.01–14.51; $P = 0.04$). The opposite was true for a family history of ovarian cancer where carriers age 40 or

Table 2 Association of BRCA mutation carriers and non-carriers and family history of breast and ovarian cancers

	BRCA Mutations							
	Carriers ($N = 28$)*		Non-carriers ($N = 198$)*				Unadjusted	
	n	Col %	*n*	Col %	χ^2	*P*-value	OR†	95% CI
Family history								
Whether family members had any cancer:								
No	3	10.7	53	26.8			*1.00***	
Yes	25	89.3	145	73.2	3.39	0.07	3.05	(0.88, 10.51)
Type of cancer for family members								
Breast cancer:								
No	9	32.1	116	58.6			*1.00***	
Yes	19	67.9	82	41.4	6.94	**0.01**	**2.99**	**(1.29, 6.93)**
Ovarian cancer:								
No	22	78.6	188	94.9			*1.00***	
Yes	6	21.4	10	5.1	10.00	**0.002**	**5.13**	**(1.70, 15.47)**
Breast cancer (among families with breast cancer, $n = 101$)								
No. of family member had breast cancer:								
1	5	26.3	64	78.0			*1.00***	
2	8	42.1	15	18.3		**0.003**	**6.83**	**(1.95, 23.85)**
≥3	6	31.6	3	3.7	22.47	**<0.001**	**25.60**	**(4.88, 134.4)**
No. of 1st degree relative had breast cancer:								
0	1	5.3	25	30.5			*1.00***	
1	7	36.8	46	56.1		0.22	3.80	(0.44, 32.70)
≥2	11	57.9	11	14.4	19.25	**0.004**	**25.00**	**(2.87, 218.2)**
No. of 2nd degree relative had breast cancer:								
0	12	63.2	58	70.7			*1.00***	
1	5	26.3	20	24.4		0.75	1.21	(0.38, 3.86)
2	2	10.5	4	4.9	0.76	0.34	2.42	(0.40, 14.73)

Bold figure: significant at <0.05

* Values may not sum to 100% because of missing data

** Referent

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

younger were nine times more likely to have relatives with ovarian cancer (OR, 8.63; CI, 1.30–57.17; $P = 0.04$), compared to non-carriers (Table 3). Although younger age increases mutation carrier rate (OR, 0.45 $_{(<40 \text{ vs. } \geq 40);}$ CI, 0.20–1.02; $P = 0.05$). The presence of family history increases the chance of BRCA mutation by 2–10 times. Without family history, women age 41 and above have a low risk of mutation (0–8.3%) in this cohort (Table 6).

Cancer types

Fifty of the 226 women had bilateral breast cancer; 32.1% (9/28) of *BRCA* mutation carriers and 20.7% (41/198) of non-carriers. There were 22 synchronous and 28 metachronous cancers and although *BRCA* mutation carriers had a higher percentage of metachronous cancers (88.9%, 8/9 vs. 48.8%, 20/41), the difference was not statistically significant ($P = 0.06$). Both carriers and non-carriers who were younger than age 40 were significantly more likely to have metachronous cancer than the older group (87.5%, 14/16 vs. 41.2%, 14/34; $P = 0.002$). The opposite was true for those with age above 40 were synchronous cancer is more likely (12.5%, 2/16 vs. 58.8%, 20/34; $P = 0.002$) (data not shown). Without family history chance of a women with bilateral breast cancer to carry a BRCA mutation is 10% but this doubles in the presence of family history (Table 6).

The distribution of all 276 cancers found in the 226 patients (50 had bilateral cancer) according to pathological characteristics is shown in Table 4. *BRCA* carriers had higher grade cancers (Grade 3) than non-carriers ($OR_{(\text{grade } 1–2 \text{ vs. } 3),}$ 2.56; CI, 1.06–6.19; $P = 0.03$), but less lymphatic invasion (LVI) of cancer cells (OR, 0.18; CI, 0.04–0.80; $P = 0.01$). *BRCA* carriers were less likely to have invasive cancer when compared to in situ cancer,

Table 3 Association between BRCA mutation carriers and non-carriers for personal and family history of breast and ovarian cancer by age

		BRCA mutations				χ^2	*P*-value	Unadjusted	
		Carriers ($N = 28$)*		Non-Carriers ($N = 198$)*					
		n	Col %	*n*	Col %			OR†	95% CI
Family history									
Whether family members had breast cancer:									
<40	No	6	40.0	46	64.8			*1.00***	
	Yes	9	60.0	25	35.2	3.18	0.07	2.76	(0.88, 8.65)
≥40	No	3	25.0	70	55.6			*1.00***	
	Yes	9	75.0	56	44.4	4.11	**0.04**	**3.75**	**(1.01, 14.51)**
Whether family members had ovarian cancer:									
<40	No	12	80.0	69	97.2			*1.00***	
	Yes	3	20.0	2	2.8	6.68	**0.04**	**8.63**	**(1.30, 57.17)**
≥40	No	10	83.3	118	93.7			*1.00***	
	Yes	2	16.7	8	6.3	1.74	0.21	2.95	(0.55, 15.81)

Bold figure: significant at <0.05

* Values may not sum to 100% because of missing data

** Referent

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

but this was not statistically significant (OR, 0.58; CI, 0.24–1.40; $P = 0.22$). Within invasive cancer comparison, *BRCA* carriers were significantly more likely to have smaller cancers ($OR_{(T1\ vs.\ T2–4)}$,0.41; CI, 0.17–0.98; $P = 0.05$). No differences were seen between carriers and non-carriers for stage cancers ($OR_{(stage\ 1\ vs.\ stages\ 2–4)}$, 0.63; CI, 0.26–1.52; $P = 0.3$), cancers with less lymph node involvement ($OR_{(N1\ vs.\ N1-3)}$, 0.57; CI, 0.23–1.39; $P = 0.21$). metastatic spread. *BRCA* mutation carriers were also more likely to have cancers being negative for ER (OR, 2.78; CI, 1.28–5.88), PR (OR, 2.44; CI, 1.10–5.56), and HER2 (OR, 2.13; CI, 0.93, 5.00), and two times more likely to have TN cancer (OR, 2.11, CI, 1.22–5.88) than non-carriers (Table 4). Even without family history, 11.1% of those with TN cancers are BRCA mutation carriers although presence of family history doubles this risk (29.3%). In the presence of family history, TN patients are still more likely to be a mutation carrier (OR 2.65; CI 1.12–6.29; $P = 0.024$).There was no difference in Ki-67 expression between the two groups.

Comparison of BRCA1and BRCA2 Cancers

As shown in Table 5, breast cancers patients with *BRCA1* mutations were compared to patients with *BRCA2* mutations. Of the 37 cancers found in the 28 *BRCA* carriers (9 had bilateral cancer), 15 (41%) were *BRCA1* carriers and 22 (59%) were *BRCA2* carriers. *BRCA1* carriers were younger at diagnosis than *BRCA2* carriers; 80.0% vs. 41.2% were less than 40 years of age (data not shown). *BRCA1* carriers had more invasive cancers (92.3% vs. 66.7%), but this is not statistically different (OR, 6.00; CI, 0.65–50.00). In excluding Stage 0 cancers to compare only invasive cancers, *BRCA1* carriers were more likely to have large tumors ($OR_{(T1\ vs.\ 2)}$, 7.69; CI, 1.16–5.00; $P = 0.04$) although cancers in *BRCA1* carriers were no different when compared to *BRCA2* carriers by stage ($OR_{(stage\ 1\ vs.\ 2+)}$, 1.17, CI, 0.22–6.08; $P = 0.12$).. There were too few cases with nodal involvement to calculate an OR using N1 as the referent.

Examining biomarkers, *BRCA1* mutation related cancers are significantly more likely to be ER negative, 75.0% vs. 36.8% (OR, 5.14; CI, 1.03–25.60; $P = 0.04$), but there were no statistical differences in either PR or HER2 tumors between the two groups. The prevalence of TN cancers in *BRCA1* carriers was 67.7% vs. 35.3% in *BRCA2* carriers, although this was not statistically significant (OR, 3.67; CI 0.77–17.43) (Table 5). Furthermore, *BRCA2* and *BRCA1* carriers did not have significant differences in the number of family members with breast cancer or ovarian cancer in these families (data not shown).

Outcome

Though not shown in any of the tables, there was no significant difference in the type of surgery (breast conservation and mastectomy) received between *BRCA* mutation carriers and non-carriers ($P = 0.31$). The median follow-

Table 4 Association between BRCA mutation carriers and breast cancer pathology

	BRCA mutations‡							
	Carriers ($N = 28$) *		Non-Carriers ($N = 239$) *				Unadjusted	
	n	Col %	*n*	Col %	χ^2	*P*-value	OR†	95% CI
LVI (Lymphatic invasion):								
Absent/suspicious[a]	20	90.9	107	64.5			*1.00***	
Present	2	9.9	59	35.5	6.20	**0.01**	**0.18**	**(0.04, 0.80)**
Grade:								
1 and 2	9	37.5	103	60.6			*1.00***	
3	15	62.5	67	39.4	4.59	**0.03**	**2.56**	**(1.06, 6.19)**
Type:								
DCIS (Ductal carcinoma In Situ)	8	23.5	33	15.2			*1.00***	
Invasive	26	76.5	84	84.8	1.49	0.22	0.58	(0.24, 1.40)
Stage:								
Stage 0	8	25.8	32	15.7				
Stage 1	10	32.3	56	27.5			*1.00***	
Stage 2, 3, and 4	13	41.9	116	56.9	1.80	0.30	0.63	(0.26, 1.52)
T stage (Tumor size):								
T0	8	24.2	30	14.6				
T1	16	48.5	74	36.1			*1.00***	
T2, 3 and 4	9	27.3	84	41.0	6.50	**0.05**	**0.41**	**(0.17, 0.98)**
N stage (Lymph node involvement):								
N0	22	75.9	130	64.0			*1.00***	
N1, 2, and 3	7	24.1	73	36.0	1.57	0.21	0.57	(0.23, 1.39)
M stage (Metastatic):								
M0	32	100.0	201	95.7				
M1	0	0	9	4.3	1.42	0.23	–	–
ER (Estrogen receptor):								
Positive	15	48.4	141	72.3			*1.00***	
Negative	16	51.6	54	27.7	7.16	**0.007**	**2.78**	**(1.28, 5.88)**
PR (Progesterone receptor):								
Positive	11	36.7	112	58.6			*1.00***	
Negative	19	63.3	79	41.4	5.07	**0.02**	**2.44**	**(1.10, 5.56)**
Cerb 2 (Protein of HER2 Oncogene):								
Positive	9	31.0	87	49.2			*1.00***	
Negative	20	69.0	90	50.8	3.29	0.07	2.13	(0.93,5.00)
Triple negative ($ER^-/PR^-/Cerb2^-$):								
No	15	51.7	131	74.4			*1.00***	
Yes	14	48.3	45	25.6	6.26	**0.01**	**2.11**	**(1.22, 5.88)**
Ki67 index (% of growing cells):								
<12%	6	60.0	28	50.9			*1.00***	
>12%	4	40.0	27	49.1	0.28	0.60	0.69	(0.18,2.70)

[a] There were two BRCA non-carriers and two BRCA carriers with LVI suspicious

Bold figure: Significant at <0.05

* Values may not sum to 100% because of missing data

** Referent

‡ Includes 41 bilateral cancers in non-mutation carriers (14%) and 9 bilateral cancers in mutation carriers (24%)

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

Table 5 Association between BRCA1 and BRCA2 mutation carriers and breast cancer pathology

	BRCA Mutations‡							
	BRCA1 ($n = 15$)		BRCA2 ($n = 22$)				Unadjusted	
	n	Col %	*n*	Col %	χ^2	*P*-value	OR†	95% CI
LVI (Lymphatic invasion):								
Absent/suspicious[a]	9	90.0	11	91.7			*1.00***	
Present	1	10.0	1	8.3	0.02	0.89	1.22	(0.07, 20.00)
Grade:								
2	4	36.4	5	38.5			*1.00***	
3	7	63.6	8	61.5	0.01	0.92	1.10	(0.17,4.81)
Type:								
DCIS (Ductal carcinoma In Situ)	1	7.7	7	33.3			*1.00***	
Invasive	12	92.3	14	66.7	2.93	0.09	6.00	(0.65, 50.00)
Stage:								
Stage 0	1	8.3	7	36.8				
Stage 1	5	41.7	5	26.3			*1.00***	
Stage 2, 3	6	50.0	7	36.8	1.28	0.86	1.17	(0.22, 6.08)
T stage (Tumor size):								
T0	1	7.7	7	35.0				
T1	5	38.5	11	55.0			*1.00***	
T2	7	53.8	2	10.0	7.52	**0.04**	**7.69**	**(1.16, 5.00)**
N stage (Lymph node involvement)								
N0	11	91.7	11	64.7			*1.00***	
N1 and 2	1	8.3	6	35.3	2.89	0.12	0.17	(0.02,1.61)
ER (Estrogen receptor):								
Positive	3	25.0	12	63.2			*1.00***	
Negative	9	75.0	7	36.8	4.29	**0.04**	**5.14**	**(1.03, 25.60)**
PR (Progesterone receptor):								
Positive	3	25.0	8	44.4			*1.00***	
Negative	9	75.0	10	55.6	1.17	0.28	2.40	(0.48, 11.93)
Cerb 2 (Protein of HER2 Oncogene):								
Positive	4	33.3	5	29.4			*1.00***	
Negative	8	66.7	12	70.6	0.05	0.82	0.83	(0.17, 4.09)
Triple negative *($ER^-/PR^-/Cerb2^-$)*:								
No	4	33.3	11	64.7			*1.00***	
Yes	8	67.7	6	35.3	2.77	0.10	3.67	(0.77, 17.43)
Ki67 index (% of growing cells):								
<12%	1	100.0	5	55.6				
>12%	0	0.0	4	44.4	0.74	0.39	–	–

[a] There were only two BRCA2 with LVI suspicious

Bold figure: *P*-value <0.05

* Values may not sum to 100% because of missing data

** Referent

‡ Includes 4 bilateral cancers in BRCA1 mutation carriers (27%) and 5 bilateral cancers in BRCA2 mutation carriers (23%)

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

Table 6 Association between BRCA mutation carriers and breast cancer pathology

	BRCA mutations							
	Non-carriers ($n = 198$)*		Carriers ($n = 28$)*				Unadjusted	
	n	Row %	*n*	Row %	χ^2	*P*-value	OR†	95% CI
Age first diagnosed to have breast cancer								
Age group:								
≤40								
Without FH	22	91.7	2	8.3			*1.00***	
With FH	52	78.8	14	21.2	2.00	0.22	2.96	(0.62, 14.14)
Without bilateral cancer	63	85.1	11	14.9			*1.00***	
With bilateral cancer	11	68.8	5	31.2	2.42	0.15	2.60	(0.76, 8.96)
Non TN‡	46	83.6	9	16.4			*1.00***	
TN‡	17	63.0	10	37.0	4.35	**0.037**	3.01	(1.04, 8.67)
41–45								
Without FH	12	100.0	0	0.0			*1.00***	
With FH	38	92.7	3	7.3	0.93	1.00	–	–
Without bilateral cancer	42	97.7	1	2.3			*1.00***	
With bilateral cancer	8	80.0	2	20.0	4.75	**0.088 #**	10.50	(0.85, 130.07)
Non TN‡	33	97.1	1	2.9			*1.00***	
TN‡	10	83.3	2	16.7	2.74	0.16	6.60	(0.54, 80.61)
46–50								
Without FH	11	91.7	1	8.3			*1.00***	
With FH	27	87.1	4	12.9	0.18	1.00	1.63	(0.16, 16.27)
Without bilateral cancer	29	90.6	3	9.4			*1.00***	
With bilateral cancer	9	81.8	2	18.2	0.62	0.59	2.15	(0.31, 14.94)
Non TN‡	23	85.2	4	14.8			*1.00***	
TN‡	10	100.0	0	0.0	1.66	0.56	–	–
>50								
Without FH	8	100.0	0	0.0			*1.00***	
With FH	27	90.0	3	10.0	0.87	1.00	–	–
Without bilateral cancer	22	88.0	3	12.0			*1.00***	
With bilateral cancer	13	100.0	0	0.0	1.69	0.54	–	–
Non TN‡	29	96.7	1	3.3			*1.00***	
TN‡	8	80.0	2	20.0	3.00	0.15	7.25	(0.58, 90.55)
Without bilateral cancer								
Without FH	44	95.7	2	4.3			*1.00***	
With FH	113	86.9	17	13.1	2.69	0.16	3.31	(0.73, 14.92)
With bilateral cancer								
Without FH	9	90.0	1	10.0			*1.00***	
With FH	32	80.0	8	20.0	0.54	0.67	2.25	(0.25, 20.44)
Non triple negative ($ER^-/PR^-/Cerb2^-$)‡:								
Without FH	35	100.0	0	0.0			*1.00***	
With FH	96	86.5	15	13.5	5.27	**0.022**	–	–
Had triple negative ($ER^-/PR^-/Cerb2^-$)‡:								
Without FH	16	88.9	2	11.1			*1.00***	
With FH	29	70.7	12	29.3	2.28	0.19	1.26	(0.97, 1.62)
No FH and non TN	35	100.0	0	0.0				
No FH and TN	16	88.9	2	11.1				
FH and non TN	96	86.5	15	13.5				
FH and TN	29	70.7	12	29.3	13.66	**0.003**	–	–

Table 6 continued

	BRCA mutations							
	Non-carriers ($n = 198$)*		Carriers ($n = 28$)*				Unadjusted	
	n	Row %	*n*	Row %	χ^2	*P*-value	OR†	95% CI
With family history								
Non TN	96	86.5	15	13.5			*1.00***	
TN	29	70.7	12	29.3	5.09	0.024	2.65	(1.12, 6.29)

Bold figure: *P*-value <0.05; # mean marginally significant

* Values may not sum to 100% because of missing data

** Referent

‡ Includes 41 bilateral cancers in non-mutation carriers (14%) and 9 bilateral cancers in mutation carriers (24%)

† Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)

up time for the cohort was 19 months for both carriers and non-carriers. *BRCA* mutation carriers, however, may have more local relapse or second primary cancer compared to non-carriers (15.6% vs 7.5%, $P = 0.13$), but the mean time to local relapse showed no significant difference between *BRCA* mutation carriers and non-carriers. Only three *BRCA* mutation carriers had relapse at the time of analysis.

Discussion

Most studies of *BRCA* gene mutations have been conducted in Western populations. Limited studies have been carried out in Chinese populations but none have described the clinico-pathological characteristics in detail. Women in our study were referrals to the Hong Kong Hereditary and High Risk Breast Cancer Programme and they were selected for testing for *BRCA* mutations using similar criteria as other studies, except women with breast cancer under 50 years of age were accepted even if they did not have any family history of cancer and if they had even one other family member with breast or ovarian cancer irrespective of age. These inclusion criteria are less stringent than other studies, which would suggest that the expected *BRCA* mutation rate may be lower than measured in other studies. In contrast, the detection rate of 12.4% was slightly higher than that reported in other Chinese series (Song et al. 2005; Chen et al. 2008; Suter et al. 2004; Ng et al. 2008; Li et al. 1999; Song et al. 2006; Sng et al. 2000). This high prevalence of *BRCA* mutations may be due to a genuinely higher rate of *BRCA* mutations in our cohort or to the nature of the referrals to our clinic compared to others.

In our cohort, women with *BRCA* mutations were more likely to be diagnosed with breast cancer at less than 40 years of age compared to non-carriers and in our sub-group analysis *BRCA1* mutation carriers were younger than *BRCA2* carriers, as seen in the western literature. Although the overall mean age at diagnosis of breast cancer is younger than Caucasians in our locality, this finding may be due to the small sample size and a larger population is needed to confirm this difference although the overall mean age at diagnosis of breast cancer is younger in Hong Kong than some other populations.

Patients with *BRCA* mutations more commonly have a personal and family history of breast and/or ovarian cancer than non-carriers. Amongst mutation carriers, the number of family members with breast cancer (67.9%) and with ovarian cancer (21.4%) is high which is similar to that seen in the Western literature (Frank et al. 2002) but higher than in a previous study in mainland China, which looked at only *BRCA1* mutations where 40% had family members with breast or ovarian cancers (Li et al. 2006). It has also been reported that carriers of *BRCA1* mutations have a greater family history of ovarian cancers than *BRCA2* mutation carriers (Gayther et al. 1999, Ramus et al. 2007). However, unlike Caucasian data the distribution of family members with breast and ovarian cancer is similar for the *BRCA*1 and *BRCA*2 groups in our cohort. This may be attributed to the higher *BRCA*2 mutation carriage generally in our cohort.

Apart from the increased risk of breast and ovarian cancer, increased risk of a broad spectrum of cancers in the Western literature has been reported in mutation carriers. In particular, these included stomach (Brose et al. 2002; Johannsson et al. 1999), pancreas (Lynch et al. 2005), prostate (Moslehi et al. 2000) and colon cancer (Breast Cancer Information Core (BIC) Database). In our cohort we found a similar spectrum of cancers although these cancers did not have a significant increase in frequency, which may be due to the small number of carriers in our cohort. There is a comparatively high percentage of stomach, colon and pancreas cancers in families of patients

with *BRCA* mutations (Kirchhoff et al. 2004; Tiling et al. 2001; Niell et al. 2004; Jakubowska et al. 2002). Although it is likely that the phenotypic presentation of other cancers is related to the *BRCA* mutations, since some of these family members with other cancers have not been tested for mutations we cannot rule out the occurrence of sporadic cancers in these families. One family with a novel *BRCA2* mutation showed stomach cancer only in one generation and breast cancer in the next generation, with a *BRCA2* mutation found in both members with breast and stomach cancer, thus illustrating the relationship between *BRCA2* mutation and stomach cancer (Kwong et al. 2008).

It has been observed that the risk of secondary cancer in women who have a family history of breast cancer is increased and, therefore, likely to be genetically related (Bernstein et al. 1992; Anderson and Badzioch 1985). Unselected cases of bilateral breast cancer are also related to *BRCA* mutations although the relationship is not strong, ranging from 5% to 20% where early onset bilateral breast cancer increases such association. Contralateral breast cancer has been reported to increase in women with hereditary breast cancer (Robson et al. 1999; Lucassen et al. 2001). In our cohort only 50 patients had bilateral breast cancer and the mutation rate was 18% (9/50), comparable to 5–20% found in Western literature (Imyanitov and Hanson 2003). Women with metachronous tumors tended to be younger at diagnosis as compared with those having synchronous bilateral cancers in our cohort, which is similar to that reported (Gogas et al. 1993; Hartman et al. 2005).Family history, however, still plays an important role in this group of patients where the mutation rate doubles in the presence of family history.

The mutation rate of women with DCIS in our study were found to be high (19.5%, 8/41) compared to Western studies (range 0.8–12.7%) (Smith et al. 2007; Claus et al. 2005). The knowledge of the association between *BRCA* mutation and DCIS is still relatively limited but there is increasing data suggesting that this association is comparable to that of invasive cancers particularly when it is due to an early onset breast cancer (Hwang et al. 2007; Smith et al. 2007). In our study among carriers the percent with DCIS was 23.5% and among non-carriers the percent was 15.2%.

Several studies have suggested that there are biologic differences between women who carry germline *BRCA* mutations to that of non-carriers. Specifically, there have been various reports which found tumors related to such mutation to be of higher grade (Eisinger et al. 1996; Johannsson et al. 1997; Atchley et al. 2008). In our study, *BRCA* related cancers compared to those which are were 2.56 times more likely to be grade 3 compared to grades 1 and 2, whereas there is no significant difference in grades when *BRCA1* and *BRCA2* related cancers were compared, both having higher grade cancers overall.

In our cohort of patients *BRCA* carriers were more likely to have TN cancers (48.3%) compared to non-carriers (25.6%), and this TN rate in mutation carriers is similar to that found in recent studies in Caucasian populations (53%) (Haffty et al. 2006). Though not statistically significant the prevalence of TN cancers is much higher in *BRCA1* carriers (66.7%) compared to *BRCA2* carriers (35.3%), similar to that have been reported previously (Schneider et al. 2008); although amongst BRCA2 mutation carriers our cohort had a higher TN rate compared to the West (14%) and it is reversed in BRCA 1(80%) (Haffty et al. 2006). Even without family history, the BRCA mutation rate is still 11.1% suggesting that it is worthwhile to perform genetic testing even in this sporadic group. Presence of family history double of presence of a BRCA mutation. The *BRCA1* associated tumors are five times more likely to be ER negative as compared to *BRCA*2 mutation carriers ($P = 0.04$), similar to that described in Western and Asian literatures (Noguchi et al. 1999; Larson et al. 1999, Johannsson et al. 1997). These findings are consistent with more recent findings from the Western literatures suggesting that *BRCA1* associated tumors have distinct immunohistopathological profiles based on gene expression profile, that they are more likely to have basal-like tumor phenotype (Fatouros et al. 2008; Fine et al. 2003; Silva et al. 2008; Johannsson et al. 1997; van der Groep et al. 2006), and are usually that of higher grade, and have higher mitotic count (Lakhani et al. 1998) apart from its association with triple negativity. *BRCA2* related breast cancers, compared the BRCA1 cancers are less likely to behave like basal-like cancers and are more heterogeneous.

Whether *BRCA* mutation carriers are more likely to have local recurrence than non carriers is still inconclusive. Some studies suggest that local recurrence rates are comparable between the two groups (Lucassen et al. 2001) although in contrast some other studies found a higher rate of ipsilateral breast cancer recurrence (Lucassen et al. 2001; Moran et al. 2008, Seynaeve et al. 2004). In our study there is a trend for more local relapse in *BRCA* mutation carries and that the time to local relapse is shorter. However, due to the relatively short follow-up time and also a limitation in sample size, a larger study sample would be necessary for making such conclusions. The published literature suggests a superior outcome in those breast cancer which are hereditary related (Albano et al. 1982; Porter et al. 1994) although some other studies suggested worse prognosis for *BRCA* mutation carriers (Moran et al. 2008; Petit et al. 2005; Foulkes et al. 2000; Ansquer et al. 1998) or at least comparable outcomes (Verhoog et al. 1999).

This study has some limitations, the primary one being the small sample size, although it is much larger than many other reports. We are continuing to recruit women to this

study and will be able to obtain more stability in finding as the cohort grows in size. These findings are from women with breast cancer who were referred to a high risk breast cancer clinic and who were selected for this analysis based on very specific criteria related to the probability of being a *BRCA* carrier, but most studied to date have used high risk clinics to recruit women for these studies. But this work does preclude any generalization to the population prevalence of these cancers and their characteristics. We are now recruiting general cancer cases from all of the major hospitals in Hong Kong which will allow us to draw conclusions in the future from women who more generally represent the Hong Kong population. Finally, although follow-up was not a major part of this study, this cohort needs to be followed much longer to study the recurrence rates, the incidence of additional cancers, and the survival rates as they are related to these personal, genetic, clinical and molecular characteristics of these women.

In conclusion, in this study of 226 Chinese women who had 276 breast cancers that were seen at our high risk clinic we identified a very high *BRCA*2 mutation rate in our cohort. The higher prevalence of *BRCA2* mutations in our cohort, compared to Western cohorts, will allow further studies on this group of carriers. In our study, *BRCA* related breast cancer is associated with increasing number of first-degree relatives with breast and/or ovarian cancers and with higher rates of DCIS cancers. Prevalence of TN breast cancers in BRCA 2 mutation carriers was high compared to Caucasian cohorts and TN significantly increases BRCA mutation rate even in the presence of no family history. Pathologically, specific poor prognostic features are associated with *BRCA* mutation especially in the younger age group. This however, may not translate into a worse clinical outcome in this group of patients and longer follow up and further studies are necessary to understand the outcome of this group of high-risk patients. BRCA1 related cancers, though having a lower prevalence that BRCA2 cancers, were generally more aggressive cancers with immunnohistopathological profiles showing that these cancers are more related to the triple negative phenotype.

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