| **Title** | Clinical and pathological characteristics of Chinese patients with BRCA related breast cancer |
|-----------|------------------------------------------------------------------------------------------|
| **Author(s)** | Kwong, A; Wong, LP; Wong, HN; Law, FBF; Ng, EKO; Tang, YH; Chan, WK; Suen, DTK; Choi, C; Ho, LS; Kwan, KH; Poon, M; Wong, TT; Chan, K; Chan, SWW; Ying, MWL; Chan, WC; Ma, ESK; Ford, JM; West, DW |
| **Citation** | Hugo Journal, 2009, v. 3 n. 1, p. 63-76 |
| **Issued Date** | 2009 |
| **URL** | http://hdl.handle.net/10722/144981 |
| **Rights** | The Author(s); This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. |
Clinical and pathological characteristics of Chinese patients with BRCA related breast cancer

Ava Kwong · L. P. Wong · H. N. Wong · F. B. F. Law · E. K. O. Ng · Y. H. Tang · W. K. Chan · D. T. K. Suen · C. Choi · L. S. Ho · K. H. Kwan · M. Poon · T. T. Wong · K. Chan · S. W. W. Chan · M. W. L. Ying · W. C. Chan · E. S. K. Ma · J. M. Ford · D. W. West

Received: 7 September 2009 / Revised: 8 March 2010 / Accepted: 11 March 2010 / Published online: 10 April 2010
© The Author(s) 2010. This article is published with open access at Springerlink.com

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 preliminary results presented in part at San Antonio Breast Cancer Symposium 10–14 December 2008 and ASCO meeting 29 May—2 June 2009.

A. Kwong · H. N. Wong · E. K. O. Ng · Y. H. Tang · D. T. K. Suen · C. Choi Division of Breast Surgery, Queen Mary and Tung Wah Hospital, The University of Hong Kong, Pokfulam, Hong Kong
L. P. Wong · F. B. F. Law · E. S. K. Ma Department of Molecular Pathology, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong
W. K. Chan Department of Pathology, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong
T. T. Wong Department of Surgery, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong
L. S. Ho Princess Margaret Hospital, Kowloon, Hong Kong
K. H. Kwan Tuen Mun Hospital, Tuen Mun, Hong Kong
M. Poon Queen Elizabeth Hospital, King’s Park, Hong Kong
K. Chan Pamela Youde Nethersole Hospital, Mid-levels, Hong Kong

S. W. W. Chan
United Christian Hospital, Kwun Tong, Hong Kong
M. W. L. Ying
Kwong Wah Hospital, Kowloon, Hong Kong
W. C. Chan
North District Hospital, Chinese University of Hong Kong, Ma Liu Shui, Hong Kong
A. Kwong · J. M. Ford · D. W. West
Stanford University School of Medicine, Stanford, CA, USA
D. W. West
North California Cancer Center, San Diego, CA, USA
A. Kwong
The Hong Kong Hereditary and High Risk Breast Cancer Programme, Happy Valley, Hong Kong
A. Kwong · L. P. Wong · D. T. K. Suen · L. S. Ho · T. T. Wong · E. S. K. Ma
The Hong Kong Hereditary Breast Cancer Family Registry, Happy Valley, Hong Kong
e-mail: akwong@asiabreastregistry.com
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 BRCA1 and BRCA2 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/ner, 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 (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 when 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;
CI, 4.88–134.37) or only considering 1st degree relatives (OR\(^1\) vs. 2\(^1\), 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 1 Association of breast cancer risk factors between BRCA mutation carriers and non-carriers (\(N = 226\))

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

### 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 (\(N = 198\))^* | \(\chi^2\) | \(P\)-value | OR† | 95% CI |
|----------------|--------------------------|-------------------------------|--------|-----------|------|------|
| \(n\) | \(Col\%\) | \(n\) | \(Col\%\) | | | |
| 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) |
| \(\geq 3\) | 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) |
| \(\geq 2\) | 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)

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 (grade 1–2 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,
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) \( \leq 0.41 \); 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; \( P = 0.20 \)), 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 BRCA1 and 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, 1.03–26.60; \( P = 0.04 \)) 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, 1.03–26.60; \( P = 0.04 \)), 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 | \( \chi^2 \) | P-value | OR‡ | 95% CI |
|-----------------|--------------------|--------------------------|------------|-----------|---------|------|--------|
| LVI (Lymphatic invasion): | | | | | | | |
| Absent/suspicious* | 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 | 1.00** | | |
| 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 | 1.00** | | |
| 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 | 1.00** | | |
| 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) |

* 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)
| BRCA Mutations‡ | BRCA1 (n = 15) | BRCA2 (n = 22) | Unadjusted |
|-----------------|---------------|---------------|------------|
|                 | n  | Col % | n  | Col % | χ² | P-value | OR† | 95% CI |
| LVI (Lymphatic invasion): | | | | | | | | |
| Absent/suspicious* | 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 | – | – |

* 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 % | χ² | 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 | 1.00** |
| >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 | 1.00** |
| No FH and TN | 16 | 88.9 | 2 | 11.1 | 1.00** |
| FH and non TN | 96 | 86.5 | 15 | 13.5 | 13.66 | 0.003 | – – |
The 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 BRCA1 and BRCA2 groups in our cohort. This may be attributed to the higher BRCA2 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

---

**Table 6 continued**

| BRCA mutations | Non-carriers \((n = 198)^*\) | Carriers \((n = 28)^\dagger\) | Unadjusted OR\(\dagger\) | 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

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

\(\dagger\) Univariate Odd Ratios comparing "Carriers" versus "Non-carriers" (reference group)
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 BRCA1 (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 BRCA2 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 BRCA2 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 is 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 immunohistopathological profiles showing that these cancers are more related to the triple negative phenotype.

Acknowledgments We would like to thank Dr. Ellen Li Charitable Foundation, The Kerry Kuok Foundation Ltd, The Hong Kong Cancer Fund and National Institute of Health in collaboration with The North California Cancer Center for their support of the Hong Kong Hereditary and high risk breast cancer program (www.HRBCP.org) and The Hong Kong Hereditary Breast Cancer Family Registry (www.asiabreastrogistry.com). We would also like to thank laboratory staff who contributed to the study including To Man Yan and Cheung Man Ting.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

Albano WA, Recabaren JA, Lynch HT, Campbell AS, Mailliard JA, Organ CH, Lynch JF, Kimberling WJ (1982) Natural history of hereditary cancer of the breast and colon. Cancer 50:360–363

Allred DC, Harvey JM, Berardo M, Clark GM (1998) Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 11:155–168

Anderson DE, Badzioch MD (1985) Bilaterality in familial breast cancer patients. Cancer 56:2092–2098

Ansquer Y, Gautier C, Fourquet A, Asselain B, Stoppa-Lyonnet D (1998) Survival in early-onset BRCA1 breast-cancer patients. Institute curie breast cancer group. Lancet 352:541

Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK (2008) Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 26:4282–4288

Basu SK, Schwartz C, Fisher SG, Hudson MM, Tarbell N, Muhs A, Marcus KJ, Mendenhall N, Mauch P, Kun LE, Constine LS (2008) Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin’s disease. Int J Radiat Oncol Biol Phys 72:34–40

Bernstein JL, Thompson WD, Risch N, Holford TR (1992) The genetic epidemiology of second primary breast cancer. Am J Epidemiol 136:937–948

Breast Cancer Information Core (BIC) Database. http://research.nhgri.nih.gov/bic/

Brose MS, Rebeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL (2002) Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 94:1365–1372

Bunyan DJ, Eccles DM, Sillibourne J, Wilkins E, Thomas NS, Shea-Simonds J, Duncan PJ, Curtis CE, Robinson DO, Harvey JF, Cross NC (2004) Dosage analysis of cancer predisposition genes by multiplex ligation-dependent probe amplification. Br J Cancer 91:1155–1159

Chappuis PO, Nethercott V, Foulkes WD (2000) Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. Semin Surg Oncol 18:287–295

Chen W, Pan K, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Lu Y, You W, Xie Y (2008) BRCA1 germline mutations and tumor characteristics in Chinese women with familial or early-onset breast cancer. Breast Cancer Res Treat

Claus EB, Petruzella S, Matloff E, Carter D (2005) Prevalence of BRCA1 and BRCA2 mutations in women diagnosed with ductal carcinoma in situ. JAMA 293:964–969

Eisinger F, Stoppa-Lyonnet D, Longy M, Kerangueven F, Noguchi T, Bailly C, Vincent-Salomon A, Jacquemin J, Birnbaum D, Sobol H (1996) Germ line mutation at BRCA1 affects the histoprog-nostic grade in hereditary breast cancer. Cancer Res 56:471–474

Fackenthal JD, Olopade OI (2007) Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 7:937–948

Fatouros M, Baltiyanni G, Roukos DH (2008) The predominant role of surgery in the prevention and new trends in the surgical treatment of women with BRCA1/2 mutations. Ann Surg Oncol 15:21–33

Fine RE, Whitworth PW, Kim JA, Harness JK, Boyd BA, Burak WE Jr (2003) Low-risk palpable breast masses removed using a vacuum-assisted hand-held device. Am J Surg 186:362–367

Foulkes WD, Chappuis PO, Wong N, Brunet JS, Vespriini D, Rozen F, Yuan ZQ, Pollak MN, Kuperstein G, Narod SA, Begin LR (2000) Primary node negative breast cancer in BRCA1 mutation carriers has a poor outcome. Ann Oncol 11:307–313
Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gunpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC (2002) Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 20:1480–1490

Gayther SA, Russell P, Harrington P, Antoniou AC, Easton DF, Ponder BA (1999) The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes. Am J Hum Genet 65:1021–1029

Gogas J, Markopoulous C, Skandalakis P, Gogas H (1993) Bilateral breast cancer. Am Surg 59:733–735

Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, Harris L, Halt W, Toppmeyer D (2006) Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 24:5652–5657

Hartman M, Czene K, Reilly M, Bergh J, Lajou I, Trichopoulos D, Adami HO, Hall P (2005) Genetic implications of bilateral breast cancer: a population based cohort study. Lancet Oncol 6:377–382

Hogervorst FB, Nederlof PM, Gille JJ, McElgunn CJ, Grippeling M, Pruntel R, Regnerus R, van Welsm T, van Spaendonk R, Menko FH, Kluijt I, Dommering C, Verhoef S, Schouten JP, van’t Veer LJ, Pals G (2003) Large genomic deletions and duplications in the BRCA1 gene identified by a novel quantitative method. Cancer Res 63:1449–1453

Hwang ES, McLennan JL, Moore DH, Crawford BB, Esserman LJ, Hogervorst FB, Nederlof PM, Gille JJ, McElgunn CJ, Grippeling M, Hartman M, Czene K, Reilly M, Bergh J, Lagiou P, Trichopoulos D, Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, Harris L, Halt W, Toppmeyer D, Adami HO, Hall P, Ponder BA, Ford D, Peto J, Stoppa-Lyonnet D, Bignon YJ, Neuhausen S, Daly PA, Ormiston W, McManus R, Scherneck S, Isser A, Smyth E, Steel CM, Carter DC (1994) Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation in the general population. Eur J Cancer 30:642–647

Imyanitov EN, Hansson KP (2003) Molecular pathogenesis of bilateral breast cancer. Cancer Lett 191:1–7

Johannsson O, Loman N, Moller T, Kristoffersson U, Borg A, Olsson H (1999) Incidence of malignant tumours in relatives of BRCA1 and BRCA2 germline mutation carriers. Eur J Cancer 35:1248–1257

Johannsson OT, Idvall I, Anderson C, Borg A, Barkardottir RB, Egilsson V, Olsson H (1997) Tumour biological features of BRCA1-induced breast and ovarian cancer. Eur J Cancer 33:362–371

John EM, Miron A, Gong G, Philip AI, Feltberg A, Li FP, West DW, Whittemore AS (2007) Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 298:2869–2876

Kirschhoff T, Satagopan JM, Kauff ND, Huang H, Kolachana P, Palmer C, Rapaport H, Nafa K, Ellis NA, Offit K (2004) Frequency of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish patients with colorectal cancer. J Natl Cancer Inst 96:68–70

Kwang A, Cheung PS, Wong AY, Hung GT, Lo G, Tsao M, Chan EW, Wong T, Ma M (2008) The acceptability and feasibility of breast cancer screening in the east. Breast 17:42–50

Lakhani SR, Jacquemier J, Sloane JP, Gusterson BA, Anderson TJ, van de Vijver MJ, Farid LM, Venter D, Antoniou A, Storfer-Isser A, Smyth E, Steel CM, Haites N, Scott RJ, Goldgar D, Neuhausen S, Daly PA, Ormiston W, McManus R, Scharneke S, Ponder BA, Ford D, Petro J, Stoppa-Lyonnet D, Bignon YJ, Struewing JP, Spurr NK, Bishop DT, Klijn JG, Devilee P, Guillaumette CJ, Lasset C, Lenoir G, Barkardottir RB, Egilsson V, Hamann U, Chang-Claude J, Sobol H, Weber B, Stratton MR, Easton DF (1998) Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90:1138–1145

Larson SM, Erdi Y, Akhurst T, Mazumdar M, Macapinlac HA, Finn RD, Casilla C, Fazzari M, Srivastava N, Yeung HW, Humm JL, Guilm J, Downey R, Karpeh M, Cohen AE, Ginsberg R (1999) Tumor treatment response based on visual and quantitative changes in global tumor glycolysis using PET-FDG imaging. The visual response score and the change in total lesion glycolysis. Clin Positron Imaging 2:159–171

Li N, Zhang X, Cai Y, Xu Z, Zhang L, Pan KF, Wu LY, Wang MR (2006) BRCA1 germline mutations in Chinese patients with hereditary breast and ovarian cancer. Int J Gynecol Cancer 16(Suppl 1):172–178

Li SS, 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 (1999) Molecular characterization of germline mutations in the BRCA1 and BRCA2 genes from breast cancer families in Taiwan. Hum Genet 104:201–204

Lucassen A, Watson E, Eccles D (2001) Evidence based case report: advice about mammography for a young woman with a family history of breast cancer. BMJ 322:1040–1042

Lynch HT, Deters CA, Snyder CL, Lynch JF, Villeneuve P, Silberstein J, Martin H, Narod SA, Brand RE (2005) BRCA1 and pancreatic cancer: pedigree findings and their causal relationships. Cancer Genet Cytopogenet 158:119–125

Moran MS, Yang Q, Harris LN, Jones B, Tuck DP, Haffty BG (2008) Long-term outcomes and clinicopathologic differences of African-American versus white patients treated with breast conservation therapy for stage-four breast cancer. Cancer 113:2565–2574

Mosleh R, Chu W, Karlan B, Fishman D, Risch H, Fields A, Smotkin D, Ben-David Y, Rosenblatt J, Russo D, Schwartz P, Tung N, Warner E, Rosen B, Friedman J, Brunet JS, Narod SA (2000) BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet 66:1259–1272

Ng R, Pond GR, Tang PA, MacIntosh PW, Siu LL, Chen EX (2008) Correlation of changes between 2-year disease-free survival and 5-year overall survival in adjuvant breast cancer trials from 1966 to 2006. Ann Oncol 19:481–486

Niel BL, Rennert G, Bonner JD, Almog R, Tomsho LP, Gruber SB (2004) BRCA1 and BRCA2 founder mutations and the risk of colorectal cancer. J Natl Cancer Inst 96:15–21

Noguchi S, Kasugai T, Miki Y, Fukutomi T, Ema M, Nomizu T (1999) Clinicopathologic analysis of BRCA1- or BRCA2-associated hereditary breast carcinoma in Japanese women. Cancer 85:2200–2205

Petit JY, Veronesi U, Luiini A, Orecchia R, Rey PC, Martella S, Didier F, De Lorenzi F, Rietjens M, Garusi C, Sonzogni A, Galimberti V, Leida E, Lazzari R, Giraldo A (2005) When mastectomy becomes inevitable: the nipple-sparing approach. Breast 14:527–531

Porter DE, Cohen BB, Wallace MR, Smyth E, Chetty U, Dixon JM, Steel CM, Carter DC (1994) Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation in families linked to BRCA1 on chromosome 17q12–21. Br J Surg 81:1512–1515

Ramos SJ, Harrington PA, Pye C, DiCioccio RA, Cox MJ, Garlinghouse-Jones K, Oakley-Girvan I, Jacobs J, Hardy RM, Whittemore AS, Ponder BA, Piver MS, Pharoah PD, Gayther SA (2007) Contribution of BRCA1 and BRCA2 mutations to inherited ovarian cancer. Hum Mutat 28:1207–1215

Robson M, Levin D, Federici M, Satagopan J, Bogolymny F, Heerdt A, Borgen P, McCormick B, Hudis C, Norton L, Boyd J, Offit K (1999) Breast conservation therapy for invasive breast cancer in Ashkenazi women with BRCA gene founder mutations. J Natl Cancer Inst 91:2112–2117

Schneider BP, Winer EP, Foulkes WD, Garber J, Perou CM, Richardson A, Sledge GW, Carey LA (2008) Triple-negative
Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, Shao ZM (2005) Mutational analysis of BRCA1 and BRCA2 genes in early-onset breast cancer patients in Shanghai. Zhonghua Yi Xue Za Zhi 85:3030–3034

Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, Shao ZM (2006) BRCA1 and BRCA2 gene mutations of familial breast cancer from Shanghai in China. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 23:27–31

Suter NM, Ray RM, Hu YW, Lin MG, Porter P, Gao DL, Zaucha RE, Iwasaki LM, Sabacan LP, Langlois MC, Thomas DB, Ostrander EA (2004) BRCA1 and BRCA2 mutations in women from Shanghai China. Cancer Epidemiol Biomarkers Prev 13:181–189

Tiling R, Linke R, Untch M, Richter A, Fieber S, Brinkbaumer K, Tatsch K, Hahn K (2001) 18F-FDG PET and 99mTc-sestamibi scintimammography for monitoring breast cancer response to neoadjuvant chemotherapy: a comparative study. Eur J Nucl Med 28:711–720

van der Groep P, Bouter A, van der Zanden R, Siccama I, Menko FH, Gille JJ, van Kalen C, van der Wall E, Verheijen RH, van Diest PJ (2006) Distinction between hereditary and sporadic breast cancer on the basis of clinicopathological data. J Clin Pathol 59:611–617

Verhoog LC, Brekelmans CT, Seynaeve C, Dahmen G, van Geel AN, Bartels CC, Tilanus-Linthorst MM, Wagner A, Devilee P, Halley DJ, van den Ouweland AM, Meijers-Heijboer EJ, Klijn JG (1999) Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 17:3396–3402

Silva E, Gatalica Z, Snyder C, Vranic S, Lynch JF, Lynch HT (2008) Hereditary breast cancer: part II. Management of hereditary breast cancer: implications of molecular genetics and pathology. Breast J 14:14–24

Sng KW, Ng EH, Ng FC, Tan PH, Low SC, Chiang G, Ho GH, Ng LT, Wilde C, Tan KP (2000) Spectrum of abnormal mammographic findings and their predictive value for malignancy in Singaporean women from a population screening trial. Ann Acad Med Singapore 29:457–462

Smith KL, Adank M, Kauff N, Lafaro K, Boyd J, Lee JB, Hudis C, Offit K, Robson M (2007) BRCA mutations in women with ductal carcinoma in situ. Clin Cancer Res 13:4306–4310

Seynaeve C, Verhoog LC, van de Bosch LM, van Geel AN, Menke-Pluymers M, Meijers-Heijboer EJ, van den Ouweland AM, Wagner A, Creutzberg CL, Niermeijer MF, Klijn JG, Brekelmans CT (2004) Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy. Eur J Cancer 40:1150–1158

Sellner LN, Taylor GR (2004) MLPA and MAPH: new techniques for detection of gene deletions. Hum Mutat 23:413–419

Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G (2002) Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res 30:e57

van der Groep P, Bouter A, van der Zanden R, Siccama I, Menko FH, Gille JJ, van Kalen C, van der Wall E, Verheijen RH, van Diest PJ (2006) Distinction between hereditary and sporadic breast cancer on the basis of clinicopathological data. J Clin Pathol 59:611–617

Tiling R, Linke R, Untch M, Richter A, Fieber S, Brinkbaumer K, Tatsch K, Hahn K (2001) 18F-FDG PET and 99mTc-sestamibi scintimammography for monitoring breast cancer response to neoadjuvant chemotherapy: a comparative study. Eur J Nucl Med 28:711–720

Suter NM, Ray RM, Hu YW, Lin MG, Porter P, Gao DL, Zaucha RE, Iwasaki LM, Sabacan LP, Langlois MC, Thomas DB, Ostrander EA (2004) BRCA1 and BRCA2 mutations in women from Shanghai China. Cancer Epidemiol Biomarkers Prev 13:181–189

Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, Shao ZM (2005) Mutational analysis of BRCA1 and BRCA2 genes in early-onset breast cancer patients in Shanghai. Zhonghua Yi Xue Za Zhi 85:3030–3034

Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, Shao ZM (2006) BRCA1 and BRCA2 gene mutations of familial breast cancer from Shanghai in China. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 23:27–31

Suter NM, Ray RM, Hu YW, Lin MG, Porter P, Gao DL, Zaucha RE, Iwasaki LM, Sabacan LP, Langlois MC, Thomas DB, Ostrander EA (2004) BRCA1 and BRCA2 mutations in women from Shanghai China. Cancer Epidemiol Biomarkers Prev 13:181–189

Tiling R, Linke R, Untch M, Richter A, Fieber S, Brinkbaumer K, Tatsch K, Hahn K (2001) 18F-FDG PET and 99mTc-sestamibi scintimammography for monitoring breast cancer response to neoadjuvant chemotherapy: a comparative study. Eur J Nucl Med 28:711–720

van der Groep P, Bouter A, van der Zanden R, Siccama I, Menko FH, Gille JJ, van Kalen C, van der Wall E, Verheijen RH, van Diest PJ (2006) Distinction between hereditary and sporadic breast cancer on the basis of clinicopathological data. J Clin Pathol 59:611–617

Verhoog LC, Brekelmans CT, Seynaeve C, Dahmen G, van Geel AN, Bartels CC, Tilanus-Linthorst MM, Wagner A, Devilee P, Halley DJ, van den Ouweland AM, Meijers-Heijboer EJ, Klijn JG (1999) Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 17:3396–3402

Berrih-Naioussi J, Semaili L (2005) Mutations in BRCA genes causing breast cancer in the Maghreb. Cancer Epidemiol Biomarkers Prev 14:8010–8018

Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G (2002) Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res 30:e57