Will Chinese ovarian cancer patients benefit from knowing the BRCA2 mutation status?

Guo-Yan Liu¹² and Wei Zhang¹

Abstract

In Western countries, the mutation status of the BRCA1 and BRCA2 genes is commonly determined for genetic counseling among members of families with a history of breast or ovarian cancer, especially for women of the Ashkenazi Jewish ethnicity. Recent studies in the Cancer Genome Atlas project have demonstrated that BRCA2 mutation carriers are more responsive to platinum-based chemotherapy among high-grade serous ovarian cancer patients. Thus, in Western countries, the mutation status of BRCA1 and BRCA2 is recognized to have an important value with which to assess cancer risk and therapeutic response. However, very limited studies of BRCA1 and BRCA2 mutations and their implications for counseling and therapeutic prediction have been conducted in China. Therefore, a potentially important genetic test that is technically simple has not benefited Chinese women with an increased risk of breast or ovarian cancer. This article summarizes the current progress in the study of BRCA1/2 mutation in China and recommends an increased effort in applying advances in genetic testing to the clinical management of Chinese patients with ovarian cancer.

Key words Ovarian cancer, BRCA mutation, drug response, survival

Ovarian cancer is the second most common gynecological malignancy and the leading cause of death from a gynecological cancer in Western countries. The 5-year survival rate for patients with advanced ovarian cancer is approximately 30%–40%. Family history of ovarian cancer is one of the strongest risk factors for the development of this cancer. About 5%–10% of ovarian epithelial cancer is inherited, and over 90% of early onset cancers in families with both breast and ovarian cancers are associated with mutations of BRCA1 or BRCA2¹⁵. There is no comprehensive epidemiologic information for ovarian cancer in China. The estimated incidence of ovarian cancer among the Chinese female population was 4.65 per 100,000 people in 2004². In China, similar to countries in the West, 2.7%–5.4% women diagnosed with epithelial ovarian cancer have been reported to have hereditary breast-ovarian cancer (HBOC) syndrome³⁴⁶⁷⁸.

Limited Information on BRCA1 and BRCA2 Mutations among Chinese Patients with Ovarian Cancer

Hundreds of unique mutations have been identified in both BRCA1 and BRCA2. The type of mutations appears to differ in ethnic groups and geographic locations. A number of founder effects have been observed in certain populations. For example, mutation “hot spots” for the Ashkenazi Jewish population are present at 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2. In populations with a high prevalence of BRCA founder mutations, such as the Ashkenazi Jewish population and families from the Netherlands, Iceland, Poland, and Sweden, the likelihood of germline BRCA mutation are estimated around 10%.

The first commercialized BRCA1/2 gene mutation test became available in the United States, and now many companies and health providers (e.g. Myriad
Genetics, Mayo Clinic, etc.) provide clinical BRCA gene testing services in the United States. Patients or hospitals can send blood or oral samples to Clinical Laboratory Improvement Amendment (CLIA)–certified service providers to isolate DNA for polymerase chain reaction (PCR) amplification. The amplified products are directly sequenced in the forward and reverse directions using fluorescent dye-labeled sequencing primers. Chromatographic tracings of each amplicon are analyzed by performing a computer-based review, followed by visual inspection and confirmation. Recombination-specific PCR and multiplexed quantitative PCR assays are used to detect specific rearrangements and large full gene rearrangements. While screening is not recommended for the general population, BRCA testing should be considered for women whose close relatives have been diagnosed with breast and/or ovarian cancer(s).

Little is known about the penetrance of BRCA founder mutations in Chinese populations. Studies on breast cancer in Hong Kong[6,8], Singapore[8], and Taiwan[9] suggested that BRCA1 mutations 589delCT, IVS7-24delACTGTTCTTT, V91I, and 1081delG and BRCA2 mutation 3109C>T are recurrent. Among them, BRCA1 mutation 1081delG and BRCA2 mutation 3109C>T were determined to have founder effects, but only in the regions of Guangdong and Hong Kong. The mutation status in populations from southern China and in Cantonese-speaking Chinese appears to be different from that of the population in northern China[7]. Very few studies have sequenced the full length of BRCA1/2 genes in Chinese populations. A few analyses on BRCA1/2 sequences focused on hereditary or early onset breast cancer showed that BRCA1 1100delAT and BRCA1 5589del8 may have founder effects[11]. For the mutation rate of BRCA in ovarian cancer in China, one report showed that among 39 high-risk familial cases, the BRCA mutation rate was as high as 41.0% compared with 12.5% in 32 sporadic cases[12].

In Western countries, inherited mutations in the BRCA1 or BRCA2 genes confer a lifetime risk of 75% for breast cancer development and 20%–60% for ovarian cancer. Because of the significantly elevated risk in developing cancer, individuals with BRCA1 and BRCA2 deleterious mutations and their family members frequently use this genetic information for enhanced cancer surveillance, counseling, and decision making on risk-reducing prophylactic mastectomy and oophorectomy, or chemopreventive measures, such as tamoxifen or raloxifene treatment for breast cancer and oral contraceptive pills for ovarian cancer. Women who carry BRCA1/2 mutations often opt for more intensive screening at an early age for ovarian cancer, including pelvic examination, transvaginal ultrasound, and serial monitoring of tumor marker CA125. In the United States and Europe, genetic testing is widely used and can identify BRCA1/2 mutations in high-risk women, who more often select prophylactic surgery rather than surveillance.

Although there have been research-based studies on the prevalence of BRCA1/2 mutations in Asian countries for the last decade, clinical testing for BRCA1/2 mutations, genetic counseling, and prevention intervention of these high-risk individuals have not been widely implemented. Data on cancer family history, genetic testing, and preventive intervention in China are even more scarce. A recent study suggested that Chinese BRCA1/2 mutation carriers opt for cancer surveillance more often than prophylactic surgery and have a lack of interest in the use of chemoprevention drugs[13].

BRCA2 but not BRCA1 Mutations Are Associated with Improved Survival and Response to Therapy

Ovarian cancer in which mutant BRCA1/2 is inherited has long been accepted to exhibit the well known “BRCA syndrome,” characterized by a constellation of clinicopathologic features including younger age at onset, serous high grade type (under-representation of mucinous tumors, poor differentiation), advanced stage at presentation, high probability of durable remission with platinum, and a better prognosis. And a BRCA1/2-deficient phenotype (BRCAness) has been extended to part of sporadic ovarian cancer (homologous recombination defect)[14]. In contrast, there are few reports on the clinicopathologic features of BRCA-related ovarian cancer in China. In 2005, Li et al. [15] analyzed 91 cases of HBOC and concluded that ovarian cancer patients with HBOC had a younger age at diagnosis than patients with sporadic ovarian cancer, and most of the former had advanced disease with poor differentiation. However, no survival difference between these two groups was found. A report in 2010 showed that high-risk familial ovarian cancer patients were predisposed to higher grade disease, higher serum CA125 level at onset, longer recurrence period, and longer overall survival compared with patients with sporadic ovarian cancer[16].

Although there are many studies on the association of BRCA1/2 mutations with survival of ovarian cancer patients internationally, few studies report and analyze BRCA1 and BRCA2 separately, which may result in important clinical differences in tumors being overlooked. According to data from The Cancer Genome Atlas (TCGA), our group recently studied the clinical outcomes of 316 patients with high-grade serous ovarian cancer, all of whom underwent surgery followed by platinum-
based chemotherapy\cite{10}. Patients were stratified according to the presence of BRCA1 mutations (37 cases), BRCA2 mutations (27 cases), BRCA1 promoter methylation (33 cases), and wild-type BRCA (219 cases). We observed that patients with BRCA1 mutations were younger at diagnosis (mean age, 55.9 years), followed by those with wild-type BRCA (mean age, 61.8 years; \( P = 0.006 \)) or BRCA2 mutations (mean age, 60.9 years; \( P = 0.03 \)).

Most importantly, we found unexpected differences in the clinical predictive value of BRCA1 versus BRCA2 lesions when comparing overall survival, progression-free survival (PFS), and chemotherapy response. BRCA2 mutations were associated with improved overall survival and PFS and an increased rate of response to primary platinum chemotherapy, whereas the outcomes of BRCA1-mutated or BRCA1-methylated cases were not statistically different from those of wild-type BRCA cases. Mechanically, BRCA2-mutated but not the BRCA1-mutated cases exhibited a “mutator phenotype,” containing significantly more mutations than wild-type BRCA cases across the whole exome. This is the first detailed analysis on the differential relationship of BRCA1 and BRCA2 mutations with genomic instability in Ovarian cancer. The results suggest that BRCA2 mutations may underlie marked genomic instability resulting in extensive gene mutations in the cancer cells, and this instability may also be responsible for increased vulnerability to DNA-damaging chemotherapies.

Thus, there are two major notable clinical differences between BRCA1- and BRCA2-related ovarian cancers: the age of presentation and chemosensitivity/survival. In most reported studies, BRCA1-mutated Ovarian cancers are diagnosed approximately 5 to 10 years earlier than the BRCA2-mutated and non-BRCA2-mutated cancers (median age, 50–55 vs. 60, respectively) \cite{16,17,18,19,20,21}. By multivariate analysis in our study, BRCA2-mutated patients showed longer PFS and overall survival than BRCA1-deficient and wild-type BRCA ovarian cancers \cite{22}.

**Implications for the Management of BRCA-related Ovarian Cancer and Recommendations**

Because BRCA2 mutation status is associated with improved survival and response to therapy, there could be several implications for ovarian cancer management. BRCA2 mutation status could be used as a genetic marker for prognosis. Clinicians could set better expectations for patients, including education on the benefit of chemotherapy and more active confrontation of the disease to improve the quality of life. Meanwhile, as BRCA2-mutant cells are more sensitive to platinum-based schedules, and BRCA2 mutations were associated with longer platinum-free duration than BRCA1 mutations and wild-type BRCA in ovarian cancer patients\cite{23}, this knowledge could influence chemotherapeutic choices in the recurrent setting as well with a new generation of drugs. This new generation of drugs includes poly(ADP-ribose)polymerase (PARP) inhibitors, which have demonstrated cytotoxic effects on BRCA1-deficient or BRCA2-deficient cells\cite{24,25}, a phenomenon called synthetic lethality. Promising results of clinical trials with PARP inhibitor in BRCA-associated carcinomas (including ovarian cancer) have been reported\cite{26,27}. Future analysis will determine whether BRCA2-mutated cases are more sensitive to PARP inhibitors.

Unfortunately, because the mutation rates of BRCA1/2 in ovarian cancers and their role in prognosis among Chinese women have not been defined, the importance of BRCA mutation status in ovarian cancer management is not well understood at present. Indeed, it is not clear whether BRCA1/2 mutations and founder mutations differ between southern and northern Chinese populations. It is not entirely impossible for such a difference to exist given that Cantonese-speaking southern Chinese have a significantly increased risk in developing nasopharyngeal cancer. Regardless, we believe it is worthwhile for Chinese researchers to carry out comprehensive analysis of BRCA1/2 mutations among Chinese breast and ovarian cancer patients to determine whether BRCA1/2 mutation status is clinically important. Because the techniques for measuring BRCA1/2 mutations are standard and relatively inexpensive, the medical care system should consider coverage of BRCA1/2 mutation screening for the high-risk families. Implications of these genetic markers will likely translate to more Chinese women benefitting from personalized treatment in the future.

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**References**

[1] Sowter HM, Ashworth A. BRCA1 and BRCA2 as ovarian cancer susceptibility genes. Carcinogenesis, 2005, 26(10): 1651–1656.

[2] National Office for Cancer Prevention and Control. National Center for Cancer Registry, Disease Prevention and Control Bureau, MOH. Chinese cancer registry annual report (2004). Beijing: Peking Union Medical College Press, 2008: 10.

[3] Shen K, Lang JH, Huang LR, et al. Diagnosis and management strategies of hereditary ovarian cancer syndrome. Chin J Obstet Gynecol, 1996, 31(12): 732–735. [in Chinese]

[4] Shi YR, Niu RF, Wei XY, et al. Investigation and analyses of family history of 144 patients with ovarian cancer. Chin J Obstet Gynecol, 2004, 39(4): 269–270. [in Chinese]
[5] Li N, Wu LY, Zhang R, et al. Clinical analysis of 91 cases of hereditary breast and ovarian cancer. Chin J Oncol, 2005, 27(4):245–247. [In Chinese]

[6] Tang NLS, Pang CP, Yeo W, et al. Prevalence of mutations in the BRCA1 gene among Chinese patients with breast cancer. J Nat Cancer Inst, 1999, 91(10):862–865.

[7] Khoo US, Chan KY, Cheung AN, et al. Recurrent BRCA1 and BRCA2 germline mutations in ovarian cancer: a founder mutation of BRCA1 identified in the Chinese population. Hum Mutat, 2002, 19(3):307–308.

[8] Kwong A, Wong LP, Wong HH, et al. A BRCA2 founder mutation and seven novel deleterious BRCA2 mutations in southern Chinese women with breast and ovarian cancer. Breast Cancer Res Treat, 2009, 117(3):683–693.

[9] Sng JH, Chang J, Feroze F, et al. The prevalence of BRCA1 mutations in Chinese patients with early onset breast cancer and affected relatives. Br J Cancer, 2000, 82(3):538–542.

[10] Li SS, Tseng HM, Yang TP, et al. Molecular characterization of germline mutations in the BRCA1 and BRCA2 genes from breast cancer families in Taiwan. Hum Genet, 1999, 104(3):201–204.

[11] Rao NY, Zhou J, Zhao L, et al. BRCA1 and BRCA2 deleterious mutation in 219 Han Chinese hereditary breast cancer patients. Chin Oncol, 2008, 5(3):370–375. [In Chinese]

[12] Tao T. Research on BRCA1/2 and its clinical importance in ovarian cancer patients from families at risk of hereditary ovarian cancer and patients with sporadic ovarian cancer. PhD thesis, 2010. [In Chinese]

[13] Kwong A, Wong CH, Shea C, et al. Choice of management of southern Chinese BRCA mutation carriers. World J Surg, 2010, 34(7):1416–1426.

[14] Turner N, Tutt A, Ashworth A, et al. Hallmarks of “BRCAness” in sporadic cancers. Nat Rev Cancer, 2004, 4(10):814–819.

[15] Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA, 2011, 306(14):1557–1565.

[16] Pharaoh PD, Easton DF, Stockton DL, et al. Survival in familial, BRCA1-associated, and BRCA2-associated epithelial ovarian cancer. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. Cancer Res, 1999, 59(4):866–871.

[17] Boyd J, Sonoda Y, Federici MG, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA, 2000, 283(17):2260–2265.

[18] Ramus SJ, Fishman A, Pharaoh PD, et al. Ovarian cancer survival in Ashkenazi Jewish patients with BRCA1 and BRCA2 mutations. Eur J Surg Oncol, 2001, 27(3):278–281.

[19] Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer, 2003, 97(9):2187–2195.

[20] Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature, 2005, 434(7035):917–921.

[21] Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumors with inhibitors of poly (ADP-ribose) polymerase. Nature, 2005, 434(7035):346.

[22] Fong PC, Ross DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med, 2009, 361(2):123–134.

[23] Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet, 2010, 376(9737):245–251.

[24] Fong PC, Yap TA, Ross DS, et al. Poly (ADP-ribose) polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol, 2010, 28(15):2512–2519.

[25] Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol, 2011,12(9):852–861.