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Editorial

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

Guo-Yan Liu[1,2] and Wei Zhang[1]

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 *BRCA2*[1]. 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 2004[2]. 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) syndrome[3-5].

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 6l74delT 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

Authors' Affiliations: [1]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [2]Department of Gynecology and Obstetrics, Tianjin Medical University General Hospital, Tianjin 300052, P. R. China.

Corresponding Authors:
Wei Zhang, Department of Pathology, Unit 0085, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel: +1-713-745-1103; Fax: +1-713-792-5549; Email: wzhang@mdanderson.org;
Gua-Yan Liu, Department of Gynecology and Obstetrics, Tianjin Medical University General Hospital, Tianjin 300052, P. R. China. Email: liuguoyan211@126.com.

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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[9], and Taiwan[10] suggested that *BRCA1* mutations 589delCT, IVS7-24delACTGTTCTTT, V91I, and 1081delG and *BRCA2* mutation 3109C>T are recurrent. Among them, *BRCA1* mutation 1081de1G 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 clinicopatholgic features of *BRCA*-related ovarian cancer in China. In 2005, Li *et al.*[5] 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[12].

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[15]. 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. Mechanistically, *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-*BRCA*-mutated cancers (median age, 50–55 vs. 60, respectively) [15-19]. By multivariate analysis in our study, *BRCA2*-mutated patients showed longer PFS and overall survival than *BRCA1*-deficient and wild-type *BRCA* ovarian cancers[15].

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[15], 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[20,21], a phenomenon called synthetic lethality. Promising results of clinical trials with PARP inhibitor in *BRCA*-associated carcinomas (including ovarian cancer) have been reported[22-25]. 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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