Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
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Review:

BRCA1/2 associated hereditary breast cancer*

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Received Dec. 8, 2007; revision accepted Dec. 13, 2007; published online Jan. 6, 2008

Abstract: Breast cancer is one of the leading causes of death in women today. Some of the patients are hereditary, with a large proportion characterized by mutation in *BRCA1* and/or *BRCA2* genes. In this review, we provide an overview of these two genes, focusing on their relationship with hereditary breast cancers. *BRCA1/2* associated hereditary breast cancers have unique features that differ from the general breast cancers, including alterations in cellular molecules, pathological bases, biological behavior, and a different prevention strategy. But the outcome of *BRCA1/2* associated hereditary breast cancers still remains controversial; further studies are needed to elucidate the nature of *BRCA1/2* associated hereditary breast cancers.

Key words: *BRCA1*, *BRCA2*, Hereditary breast cancer
doi:10.1631/jzus.B0710617 **Document code:** A **CLC number:** R737.9

INTRODUCTION

Although the advancement of diagnostic techniques and treatment in the last decade has greatly contributed to the survival of cancer patients, breast cancer is still one of the leading causes of death in women today. It is estimated that there are approximately 180510 new occurrences of breast cancer and 40910 breast cancer deaths (40460 women, 450 men) in the year of 2007 in the US (American Cancer Society, 2007). Among breast cancer patients, up to 5%~10% are considered directly relating to the inheritance of mutation in *BRCA1* or *BRCA2* (Claus *et al*., 1996), which accounts for most of the hereditary breast cancers. Moreover, women carrying these mutations have a lifetime breast cancer risk of 60%~80% (Easton *et al*., 1993; Struewing *et al*., 1996); therefore, detection of mutation in these two genes can serve as a molecular predictor for women with a family history of breast cancer.

As a consequence of current trends in multidisciplinary therapy for breast cancers, *BRCA1* and *BRCA2*, like other genes, have not only served as molecular markers for hereditary breast cancer risk screening, but also become important indicators for breast cancer prevention, treatment and prognosis. In this review, we provide an overview of these two well-known breast cancer susceptibility genes, focusing on their relationship with hereditary breast cancers.

FUNCTIONS AND MUTATIONS

BRCA1 was first located to chromosome 17 via a genetic linkage analysis in 23 early-onset breast cancer families (Hall *et al*., 1990), and was cloned and isolated in 1994 (Miki *et al*., 1994). Further research had localized it to 17q21 with a length of 100 kb. *BRCA1* has 24 exons, including 2 non-translating exons, encoding a protein of 1863 amino acids, which is characterized by a zinc-binding RING-finger domain at the amino terminus and BRCA1 carboxyl-terminal (BRCT) domain at the carboxyl terminus.

BRCA1 is classified as a tumor suppressor gene

* Project supported by the National Natural Science Foundation of China (No. 30772510) and the Joint Program of Ministry of Health and Zhejiang Provincal Government of China (No. WKJ2006-2-008)

and plays an important role in surveillance of cell cycle and repair of DNA damage. Evidence shows that BRCA1 is phosphorylated by the checkpoint kinase ataxia telangiectasia mutated (ATM) protein after ionizing radiation (Cortez *et al*., 1999). Mediator of DNA damage checkpoint protein 1 (MDC1) can regulate BRCA1 to the sites of DNA lesions and phosphorylate it through ATM dependent pathways (Lou *et al*., 2003). After activation, BRCA1 can bind to p53, RAD50-MRE11-NBS1 (R-M-N) complex and RAD51, conducting homologous recombination or non-homologous end-joining (NHEJ) which is of great importance in DNA damage repair. The zinc-binding RING-finger domain of BRCA1 can interact with BRCA1 associated RING domain 1 (BARD1) forming a heterodimeric complex that has ubiquitin ligase activity (Hashizume *et al*., 2001), and the complex itself may be involved in DNA damage repair.

In 1995, a second gene termed *BRCA2* was found related to hereditary breast cancer (Wooster *et al*., 1995). It covers about 70 kb of genomic sequence in 13q12, encoding a protein of 3418 amino acids. The coding region of *BRCA2* is composed of 27 exons with a non-translating exon. However, the gene sequence of *BRCA2* bears no obvious homology to any known gene including *BRCA1*, and the protein contains no defined functional domains (Tavtigian *et al*., 1996; Wooster *et al*., 1995). BRCA2 can bind with BRCA1, participating in DNA damage response pathway associated with the activation of homologous recombination and double-strand break repair (Chen *et al*., 1999).

For their key role in maintaining genomic integrity and supervising cell cycle, mutations in *BRCA1* and *BRCA2* are found strongly related to hereditary breast cancers. However, the types of mutation differ in distribution by ethnicity and geographic location. The "hot spot" sites of mutation for Ashkenazi Jewish are present at 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2* (Abeliovich *et al*., 1997), whereas 3171ins5 is the characterized mutation from high-risk families examined in Sweden (Einbeigi *et al*., 2001). The prevalence of mutations in *BRCA1* and *BRCA2* also varies in diverse populations. For example, the *BRCA1* mutation frequency in Finnish breast cancer patients is 0.4% (Syrjakoski *et al*., 2000), whereas by contrast the number for its neighbor country, Sweden, is 7% (Zelada-Hedman *et al*., 1997). Among all the genetic alterations in *BRCA1* and *BRCA2*, 85% are frameshift or nonsense mutations, yielding a truncated protein product (Struewing *et al*., 1995). The cells, therefore, have a decreased ability to repair damaged DNA; the genomic instability is observed in animal models due to this defect (Yu *et al*., 2000). Tumor tissues from carriers of mutant *BRCA1* or *BRCA2* gene are presented with chromosomal abnormalities including losses of 5q, 4q, 4p, 2q, 12q, 13q and 6q significantly more commonly than the normal control group (Tirkkonen *et al*., 1997).

PATHOLOGY

Hereditary breast cancers arising in carriers of *BRCA1* and/or *BRCA2* genes mutations differ from sporadic breast cancers of age-matched controls and from non-*BRCA1/2* hereditary breast carcinomas in their morphological, immunophenotypic and molecular characteristics. *BRCA1* associated breast carcinomas have the "basal-like" phenotype (Perou *et al*., 2000), a subtype of high grade (usually Grade 3), high mitotic count, estrogen receptor (ER) and Her2 negative carcinomas (Breast Cancer Linkage Consortium, 1997; Lakhani *et al*., 1998), characterized by the expression of basal or myoepithelial markers such as basal keratins (Foulkes *et al*., 2003), P-cadherin, epidermal growth factor receptor, etc. (Honrado *et al*., 2005). *BRCA1* associated breast carcinomas usually have the over-expressions of the cell-cycle proteins such as cyclins A, B1 and E, and S-phase kinase-associated protein 2 (SKP2) (Honrado *et al*., 2005). *BRCA2* associated breast carcinomas are rarely that "basal-like" phenotype, but a subtype that has higher grade (usually Grade 2/3) than sporadic age-matched controls (Breast Cancer Linkage Consortium, 1997), and tend to be ER and progesterone receptor (PR) positive (Lakhani *et al*., 2002; Robson *et al*., 2004). *BRCA2* associated breast carcinomas usually have the over-expressions of cyclin D1 and p27 (Honrado *et al*., 2005). Recent studies have shown that non-*BRCA1/2* associated breast cancers tend to have lower grades and mitotic counts than *BRCA1/2* associated hereditary breast cancers (Honrado *et al*., 2005).

PREVENTION

Penetrance refers to the probability of developing disease in a carrier of a deleterious mutation and is usually detected at a given age. It appears that the risk of cancer among women who carry a *BRCA1* or *BRCA2* mutation could be modified by some specific genes or by an environmental factor and lifestyles. In the case of hereditary breast cancers, the candidate modifier genes that have been studied are related to the metabolism of sex hormones and to DNA repair. Four genes, *Androgen Receptor* (*AR*), *Nuclear Receptor Coactivator 3* (*NCOA3*), *RAD51* and *H-ras*, have been suggested as potential modifiers of risk in *BRCA1* or *BRCA2* mutation carriers, but the evidence for these is too weak to guide clinical practice (Narod, 2002). Hormonal factors (oophorectomy, pregnancy, breastfeeding, oral contraceptives, tubal ligation, tamoxifen, hormone replacement therapy, etc.) have also been tried to modify the risk of breast cancer. Some studies indicate that oophorectomy reduces risk in *BRCA1* mutation carriers and probably in *BRCA2* mutation carriers, whereas tamoxifen reduces the risk in *BRCA2* mutation carriers (King *et al*., 2001) and probably in *BRCA1* mutation carriers (Narod *et al*., 2000), although ER status is usually negative in those *BRCA1* mutation carriers.

Women with a *BRCA1* or *BRCA2* mutation who have a high risk of breast cancer could choose to undergo prophylactic bilateral total mastectomy, which reduces the incidence of breast cancer at three years of follow-up (Meijers-Heijboer *et al*., 2001). In another study, data indicate that the majority of women reported satisfaction with bilateral prophylactic mastectomy; in the meantime, they experienced psychosocial outcomes similar to those with similarly elevated breast cancer risk who did not undergo prophylactic mastectomy. Bilateral prophylactic mastectomy appears to have neither positive nor negative impact on long-term psychosocial outcomes (Geiger *et al*., 2007). According to recent research results, women who are *BRCA1/2* mutation carriers and have a history of breast cancer or ductal carcinoma in situ (DCIS), or a family history of ovarian cancer, are more likely to have undergone surgical procedures for risk reduction (Uyei *et al*., 2006). At present, it is much more difficult to develop risk-assessment tools to take into consideration all established risk factors including mutation type and position, reproductive history, exogenous hormone level, and the specific relevant modifying genes.

PROGNOSIS

Prognosis of patients carrying mutant *BRCA1* or *BRCA2* compared with general breast cancer populations still remains controversial. Several studies have proved that patients with *BRCA1* mutation have poor outcome. A research program at collaborating centers in Norway and the UK found that the five-year survival in *BRCA1*-mutated patients is 73% compared to 92% in mutation-negative patients ($P<0.001$) (Moller *et al*., 2007). One study from 496 Jewish women with breast cancer showed a similar result that the rate of breast cancer specific survival after a median follow-up period of 116 months is worse for *BRCA1* mutants than for non-carriers (62% vs 86%, $P<0.0001$) (Robson *et al*., 2004). On the contrary, some studies reported no significant differences of survival data existing between women with *BRCA1* mutations and those without. One study on Israeli women concluded that breast cancer specific rates of death are similar between carriers of a *BRCA1/2* founder mutation and non-carriers, with the hazard ratio among *BRCA1* carriers to be 0.76 and 95% confidence interval (CI) 0.45~1.30, $P=0.31$; and the hazard ratio among *BRCA2* carriers to be 1.3 and 95% CI 0.80~2.15, $P=0.28$ (Rennert *et al*., 2007). Another two studies conducted in New York and Rotterdam presented the same negative results that breast cancer specific survival is similar between the mutation carriers and non-carriers in breast cancer patients and patients at high risk for breast cancer, respectively (El-Tamer *et al*., 2004; Brekelmans *et al*., 2006).

Because of the controversial results, whether there is a real difference in survival data remains unclear. More attention is needed to examine the variable factors, such as ER status, lymph node involvement, and cancer staging.

SUMMARY

About one decade has passed since the discovery of the *BRCA1/2* genes, and we have come to realize

the constructions and major functions of BRCA1/2 proteins and also the close relationship between *BRCA1/2* mutations and hereditary breast cancers. *BRCA1/2* genes are tumor suppressor genes, the mutations of which could result in hereditary breast cancers. Several measures have been tried to reduce the risk of hereditary breast cancers. The initial results after prophylactic oophorectomy/bilateral prophylactic mastectomy and oral administration of tamoxifen show their effects on risk reduction. *BRCA1/2* associated breast cancers have their own pathologic characteristics. However, prognosis of patients carrying mutant *BRCA1/2* compared with general breast cancer populations still remains controversial. The further elucidation on the relationship between *BRCA1/2* mutations and hereditary breast cancer remains a task in the future.

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