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Effect of BRCA2 Mutation on Familial Breast Cancer Survival: A Systematic Review and Meta-analysis

Jun SHAO (邵 军)[1†], Jie YANG (杨 洁)[2†], Jun-nai WANG (王俊耐)[2], Long QIAO (乔 龙)[2], Wei FAN (范 威)[1], Qing-lei GAO (高庆蕾)[2#], Yao-jun FENG (冯尧军)[1#]
[1]*Department of Breast Cancer, Hubei Cancer Hospital, Wuhan 430079, China*
[2]*Cancer Biology Research Centre, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

Summary: Reports of BRCA2 genetic mutations on the prognosis of familial breast cancer (BC) patients have been contradictory. True difference in survival, if it exists, would have important implications for genetic counseling and in treatment of hereditary BC. The purpose of this study was to compare overall survival rate (OSR) among BRCA2 mutation carriers, non-carriers and sporadic BC patients. We searched the PUBMED and EMBASE databases and retrieved 4529 articles using keywords that included breast cancer, BRCA, prognosis and survival. Nine articles were selected for systematic review and among them 6 were included in our meta-analysis. We used the fixed and random effect models to calculate the summary odds ratio (OR) and corresponding 95% confidence interval (CI). BRCA2 mutation carriers had significantly higher long-term OSR than non-carriers (OR=0.69 [95% CI=0.5–0.95]), while both short-term and long-term OSR of BRCA2 mutation carriers did not differ from those of patients with sporadic disease (OR=1.11 [95% CI=0.74–1.65]; 0.85 [95% CI=0.38–1.94], respectively). For BC-specific survival rate (BCSSR), BRCA2 mutation carriers had a similar BCSSR to the non-carriers (OR=0.61 [95% CI=0.28–1.34]). There was no significant difference in disease-free survival (DFS) between BRCA2 mutation carriers and patients with sporadic disease. Our results suggest that BRCA2 mutation increases long-term OSR in hereditary BC, which reminds us a new prospect of management of the disease.
Key words: BRCA2 gene mutation; overall survival rate; familiar breast cancer

BRCA2 is the second major breast cancer (BC) susceptibility gene which was found localized to the chromosome 13q in 1994[1] and was cloned in 1995 to 1996[2, 3]. Germ line mutations of the BRCA2 gene are associated with a hereditary history of male and female BC[4]. Many studies reported the typical tumor characteristics of BRCA1-associated BC, such as the basil-like phenotype and the high histological grade. According to the clinical research, most reports described a similar or worse survival in BRCA1-associated BC as compared to sporadic BC[5, 6].

Although less data are available on BRCA2-associated BC, the phenotype appears to be partly similar to that of BRCA1, with respect to the young age and the high clinical stage at diagnosis and the increased risk of bilateral BC[5, 7, 8]. Reports about prognostic impact of BRCA2 mutation in patients with breast/ovarian cancers have controversial results. One has reported a significantly better prognosis[9], and a borderline improvement in the overall survival (OR) of BRCA2 mutation carriers has been reported by Phillips *et al*[10], and several studies have shown no difference in OR between the mutated and non-mutated groups[11–13], whereas other studies have reported a trend toward a worse prognosis[14]. However, all these reports can be criticized either for too small sample size or for problems in selecting control group.

The aim of this study was to assess the role of BRCA2 mutations in prognosis in familial BC by carrying out a systematic review of the literature followed by a meta-analysis, and to estimate to what extent the BRCA2 mutation influences patients' prognosis.

1 MATERIALS AND METHODS

1.1 Identification of Studies

We searched published articles, letters, abstracts, and review articles in the ''PUBMED'' and ''EMBASE'' database. Since the first BRCA2 article was published in 1994, we searched literatures published from January 1994 to August 2014. We used keywords such as breast neoplasm, breast tumor, breast carcinoma, breast malignance or BC and BRCA* and prognosis*, survival*, outcome or marker. The inclusion criteria for our systematic review were as follows: addressing familial BC or hereditary BC cancer, analyzing patients' prognosis according to BRCA2 status, and outcome was survival related, such as OR and disease-free survival (DFS). We only chose articles written in English and conducted among human subjects (fig. 1).

1.2 Operational Definitions

DFS was defined as local recurrence free and/or

Jun SHAO, E-mail: tjjyang@126.com; Jie YANG, E-mail: yangjie@tjh.tjmu.edu.cn
†The authors contributed equally to this work.
#Corresponding authors, Yao-jun FENG, E-mail: 37865915@qq.com; Qing-lei GAO, E-mail: qlgao@tjh.tjmu.edu.cn

metastasis-free survival. Short-term was defined as near 5 years (range: 4–5) and long-term was defined as probably 10 years (range: 7–10).

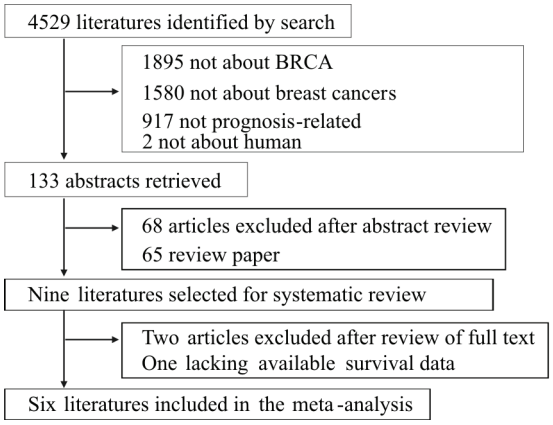

Fig. 1 Flow chart of publication selection

1.3 Statistical Methods

We used the adjusted odd ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) reported in the article. We separated short-term DFS and OS to long-term DFS and OS for BRCA2 mutation.

By convention, an observed OR<1 implied better survival for the group with BRCA2 dysfunction status. This impact of BRCA2 status on survival was considered to be statistically significant if the 95% CI for the OR did not include 1. Horizontal lines indicate the 95% CI, and each box represents the OR point estimate; the box size is proportional to the number of patients included in the study. Fixed and random effect models were used to obtain the summary ORs and 95% CIs. Heterogeneity was assessed by the Cochran Q statistics, and the funnel plot was used to investigate any possible publication bias when the number of incorporated research is enough. For all analyses, a two-sided P value of <0.05 was considered to be statistically significant. All analyses were performed using Revman (version 5.3).

2 RESULTS

A total of 9 articles were included in the systematic review that is summarized in table 1 (6 articles included in meta-analysis[15–20]) and table 2. In this review, one study indicated that BRCA2-associated BC had worse survival and prognosis, two studies indicated that BRCA2-associated BC had better survival and prognosis while other studies presented BRCA mutation carriers had similar survival and prognosis compared to non-carriers or patients with sporadic disease.

The characteristics of BRCA2 mutation carriers and control groups (non-mutation and sporadic disease) in each article are summarized in table 2. The mean age was younger in BRCA2 mutation group. The proportion of patients with negative node was lower in BRCA2 mutation group, except one article[19] (and one article not stated[16]). The proportion of patients with lower histological grade was lower in BRCA2 mutation group (two articles not stated[16, 18]) too. There were less estrogen receptor (ER)(–) patients in BRCA2-mutated group than in control groups[16, 18].

2.1 Short-term and Long-term OS Rate

In the analysis of short-term (near 5 years) OS of BRCA2, 3 studies were included. BRCA2 mutation carriers had similar OS to non-carriers [summary OR=0.82 (95% CI, 0.53–1.26)]. There was no significant heterogeneity across the studies (P=0.25) (fig. 2). There were 3 studies included in the meta-analysis for long-term (7 years or greater) OS of BRCA2. Long-term OS was better in BRCA2 mutation carriers than in non-carriers [summary OR=0.66 (95% CI, 0.46–0.95)]. The heterogeneity was not significant (P=0.33) (fig. 3).

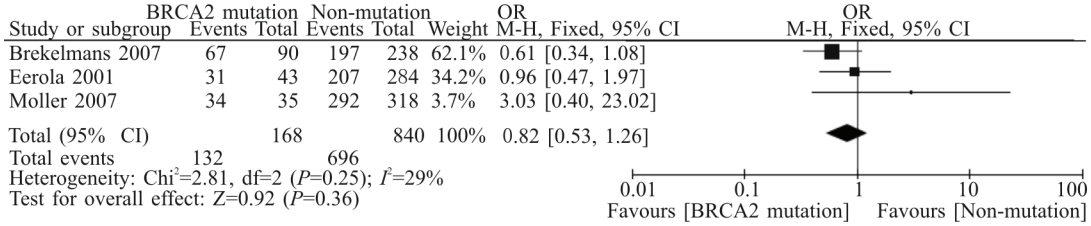

Fig. 2 Short-term OS between BRCA2 mutation carriers and non-carriers

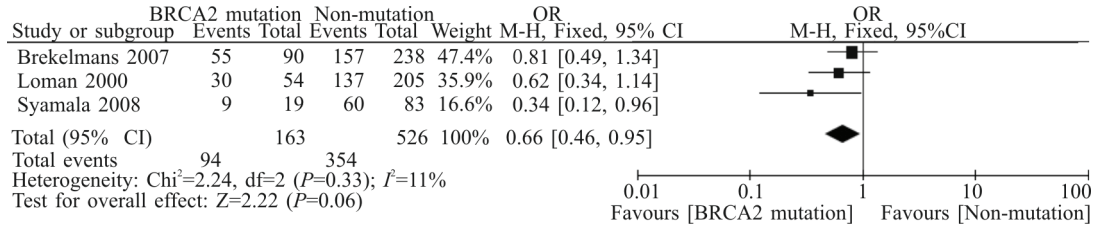

Fig. 3 Long-term OS between BRCA2 mutation carriers and non-carriers

There were 2 studies that assessed short-term OS of BRCA2 mutation carriers compared to patients with sporadic disease, and 2 studies on long-term OS of BRCA2. In the analysis of OS of BRCA2, the summary OR was 1.11 (95% CI, 0.74–1.65) for short-term OS and 0.85 (95% CI, 0.38–1.94) for long-term OS of BRCA2 mutation carriers, respectively. There was significant heterogeneity across the long-term studies (P=0.02) (fig. 4 and 5), and the random effect model was used in this meta-analysis.

Table 1 Studies included in the meta-analyses on the association of BRCA mutation and survival among breast cancer patients

Author/Year/Country	Study population	BRCA2 testing method	Outcomes	BRCA mutation	Number of total subjects	Survival (%)	RR/HR (95% CI)
Loman/2000/Sweden	Female breast cancer patients from 20 families identified in Lund and 2 families identified in Gothenburg, from the late 1995 until August 1999	PTT, SSCP analysis, or direct sequencing	8.1–8.9-year follow-up				
			OS	Non-BRCA2	214	67	RR: 1.6 (0.98-2.7)
				BRCA2 (+)	54	56	
			BCSS	Non-BRCA2	214	77	RR: 2.0 (1.2-3.4)
				BRCA2 (+)	54	57	
Eerola/2001/Finland	359 familial breast cancer patients compared with those of all other breast cancer patients diagnosed in Finland from 1953 to 1995	PTT, HA/SSCP analysis,	5-year follow-up	Sporadic	59517	65	Ref
			OS	Non-BRCA2	284	73	RR: 1.02 (0.75-1.39)
				BRCA2 (+)	43	72	RR:0.78 (0.39-1.57)
Brekelmans/2007/The Netherlands	All female patients with primary, invasive breast cancer and available data on histopathology and follow-up that were diagnosed after 1st January 1980 in hereditary breast/ovarian cancer families undergoing DNA-analysis at the Family Cancer Clinic of the Erasmus MC	DGGE PTT MLPA	5-year follow-up	Sporadic	759	75	Not detected in the article
			OS	Non-BRCA1/2	238	83	
				BRCA2 (+)	90	75	
			BCSS	Sporadic	759	78	
				Non-BRCA1/2	238	87	
				BRCA2 (+)	90	80	
			DFS	Sporadic	759	64	
				Non-BRCA1/2	238	73	
				BRCA2 (+)	90	73	
			10-year follow-up				
			OS	Sporadic	759	55	
				Non-BRCA1/2	238	66	
				BRCA2 (+)	90	61	
			BCSS	Sporadic	759	59	
				Non-BRCA1/2	238	70	
				BRCA2 (+)	90	68	
			DFS	Sporadic	759	50	
				Non-BRCA1/2	238	61	
				BRCA2 (+)	90	61	
Moller/2007/Norway	Women with a family history of breast cancer diagnosed at collaborating centers in Norway and the UK up to the end of 2005	MLPA	5-year OS	Non-BRCA1/2	318	92	Not detected in the article
				BRCA2 (+)	35	96	
Syamala/2008/India	A total of 102 hereditary breast/ovarian cancer patients found eligible for the present study	PCR CSGE	10-year follow-up OS	Non-BRCA1/2	83	72	Not detected in the article
				BRCA2 (+)	19	46	
Goodwin/2012/American	In Ontario, patients with breast cancer diagnosed between January 1, 1996, and December 31, 1998; In northern California, patients with breast cancer diagnosed between January 1, 1995, and December 31, 2000; In Australia, patients with breast cancer diagnosed between June 1, 1991, and June 30, 1998 (Melbourne), or between January 1, 1996, and June 30, 1998 (Sydney) identified	DHPLC, Enzymatic mutation detection, PTT,	7.9-year follow-up				
			DFS	Sporadic	1523	81	
				BRCA2 (+)	70	73	1.63 (1.02-2.60)
			OS	Sporadic	1549	82	
				BRCA2 (+)	72	72	1.81 (1.15-2.86)

DGGE: denaturing gradient gel electrophoresis; DHPLC: DNA high-performance liquid chromatography; PTT: protein-truncation test; CSGE: conformation-sensitive gel electrophoresis; MLPA: multiplex ligation-dependent probe amplification

Table 2 Characteristics of the subjects in each study

Authors/ Year	BRCA mutation	Age Mean (SD)	Stage (%)				Histo-logical grade: low (%)	ER (+) *n* (%)	PR (+) *n* (%)	Chemother-apy(+) *n* (%)	Homone Therapy (+) *n* (%)
			T1	N0	M1	Total Stage I					
Loman/ 2000	BRCA2(+)	45.6 (11.6)	27/50 (54)	20/52 (38)	6/52 (12)	17/52 (33)	–	–	–	–	–
	Non-mutation	45.6 (11.6)	119/198 (60)	108/198 (55)	7/202 (3)	83/202 (41)					
Eerola/ 2001	BRCA2(+)	<50									
	Non–Mutation Sporadic	>50 >50	–	–	–	–	–	–	–	–	–
Brekelmans/ 2007	BRCA2(+)	44	39 (49)	37 (43)	2 (2)		21 (35)	56 (84)	35 (64)	18 (20)	43 (48)
	Non-Mutation	47	145 (63)	145 (63)	2 (1)	–	76 (39)	129 (73)	105 (74)	64 (27)	98 (41)
	Sporadic	43	343 (50)	343 (50)	26 (3)		195 (37)	367 (67)	274 (54)	119 (16)	329 (43)
Moller/ 2007	BRCA2(+)	46		20 (57)			12 (41)	16 (70)			
	Non-Mutation	50	–	172 (54)	–	–	145 (60)	150 (67)	–	–	–
Syamala/2008	BRCA2(+)			7 (36.8)	3 (15.8)		3 (27.3)	3 (33.3)	3 (33.3)		
	Non-Mutation	–	–	40 (48.2)	6 (7.2)	–	23 (45.1)	10 (21.7)	10 (25.6)	–	–
Goodwin/2012	BRCA2(+)	42.2 (9.7)	37 (51.4)	32 (44.4)	2 (2.8)	–	18 (25)	56 (77.8)	52 (72.2)	57 (79.2)	39 (54.2)
	Sporadic	45.7 (9.9)	968 (62.5)	857 (55.3)	27 (1.7)		851 (55)	1065 (68.7)	1036 (66.8)	930 (60)	701 (45.2)

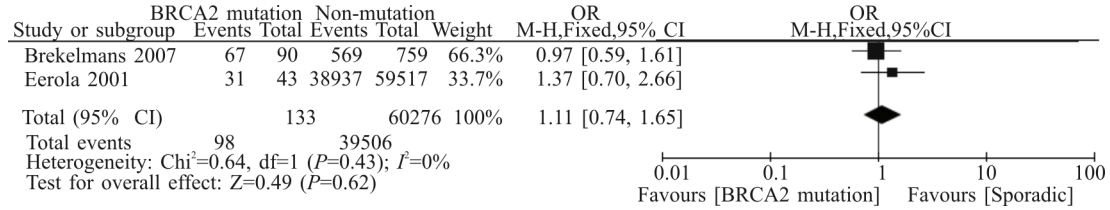

Fig. 4 Short-term OS between BRCA2 mutation carriers and patients with sporadic disease

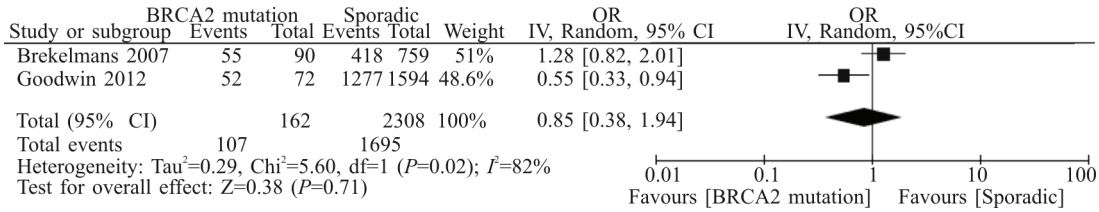

Fig. 5 Long-term OS between BRCA2 mutation carriers and sporadic disease

2.2 BC-specific survival (BCSS) and DFS Rates

As shown in fig. 6, we identified 2 studies that assessed long term BCSS of BRCA2 mutation carriers compared to non-mutation group, and summary OR was 0.61 (95% CI, 0.28–1.34) for long-term BCSS. For long-term DFS, we identified 2 studies that assessed BRCA2 mutation carriers and patients with sporadic disease, and the summary OR was 1.0 (95% CI, 0.41–2.47) (fig. 7).

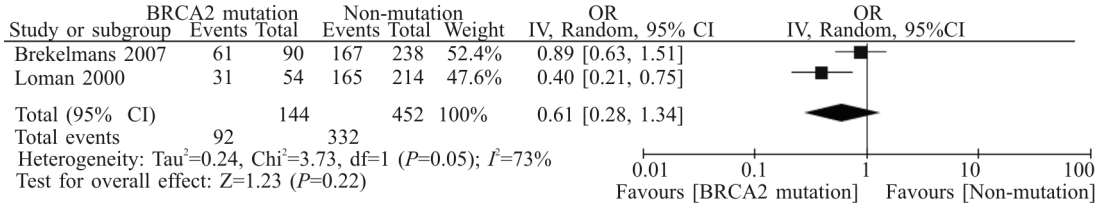

Fig. 6 BC-special survival between BRCA2 mutation carriers and non-carriers

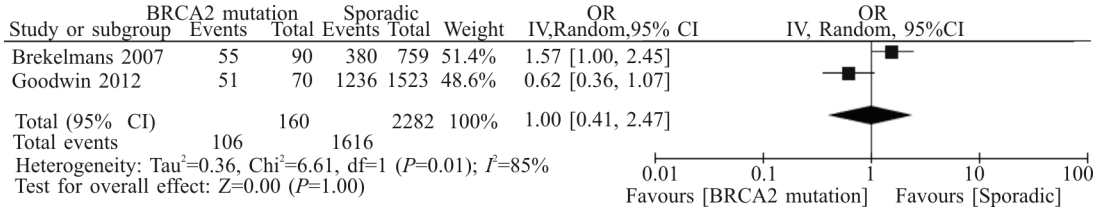

Fig. 7 Disease-free survival between BRCA2 mutation carriers and sporadic disease

3 DISCUSSION

Germline mutations in BRCA1 or BRCA2 may account for up to 5%–10% of BCs. Our systematic review of the literatures and meta-analysis demonstrated an improved prognosis in hereditary BC patients whose BC displays BRCA2 mutation, relative to those whose BC displays normal BRCA function. This meta-analysis assessed whether BRCA2 mutation could show similar effects on prognosis of non-mutation and sporadic disease.

In our study, patients whose BC displayed BRCA2 mutation had a favorable long-term survival and prognosis as compared to non-mutation rather than sporadic disease. BRCA gene products play a pivotal role in DNA repair mechanisms. The better prognosis of patients with BRCA dysfunction may be explained by their inability to repair double-strand DNA breaks caused by platinum-based chemotherapy. Several research groups found that BRCA2-mutated cells are recombination deficient and undergo significantly reduced homologous recombination repair of DNA doublestrand breaks[21, 22]. BRCA2 mutation-positive BC patients are more likely ER-positive than either mutation negative cases or patients with sporadic disease. The ER-negative BC patients have worse short-term prognosis than ER-positive cancer patients and tend to recur earlier after first treatment[23]. The lower risk in death or recurrence within 10 years of BRCA2-mutated BCs may be related to ER positivity.

Our results may have important implications for the clinical management of BC. BC is clinically highly heterogeneous. Our study revealed that BRCA2 mutation was associated with favorable survival in familial BC, and these BRCA2 statuses can guide choice of postoperative treatment decisions. It has been demonstrated that a deficiency of the BRCA gene confers substantial sensitivity to a new class of agents, namely poly-ADP-ribose polymerase-1 (PARP1) inhibitors[22, 24], which have been successfully applied to BRCA1/2 mutation carries of ovarian cancer and BC in preclinical studies[25]. So, routinely testing BRCA1/2 germline mutation status of BC patients may now be warranted. The majority of families remained negative for mutations in the BRCA1/2 gene even though many showed a clear predisposition for BC. Further work is needed to investigate other mutation mechanisms which may have been missed.

In conclusion, family BC patients with BRCA2 mutations have better outcomes, but more fundamental studies and further prospective clinical studies are urgently needed. Furthermore, family BC should be stratified by different BRCA2 status to specifically define the most effective treatment for the separate patient groups in further clinical studies.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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