RESEARCH ARTICLE

BRCA1 and BRCA2 Common Mutations in Iranian Breast Cancer Patients: a Meta Analysis

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Abstract

__Background__: To date several common mutations in BRCA1 and BRCA2 associated with breast cancer have been reported in different populations. However, the common BRCA1 and BRCA2 mutations among breast cancer patients in Iran have not been described in detail. __Materials and Methods__: To comprehensively assess the frequency and distribution of the most common BRCA1 and BRCA2 mutations in Iranian breast cancer patients, we conducted this meta-analysis on 13 relevant published studies indentified in a literature search on PubMed and SID. __Results__: A total of 11 BRCA1 and BRCA2 distinct common mutations were identified, reported twice or more in the articles, of which 10 (c.2311T>C, c.3113A>G, c.4308T>C, c.4837A>G, c.2612C>T, c.3119G>A, c.3548A>G, c.5213G>A c.IVS16-92A/G, and c.IVS16-68A/G) mutations were in BRCA1, and 1 (c.4770A>G) was in BRCA2. The mutations were in exon 11, exon 13, intron 16, and exon 20 of BRCA1 and exon 11 of BRCA2. All have been previously reported in different populations. __Conclusions__: These meta analysis results should be helpful in understanding the possibility of any first true founder mutation of BRCA1/BRCA2 in the Iranian population. In addition, they will be of significance for diagnostic testing, genetic counseling and for epidemiological studies.

Keywords: Breast cancer - BRCA1 - BRCA2 - common mutations - Iran

Introduction

Breast cancer is the most common cause of mortality among women accounting for 23% all cancers (Perez et al., 2009). In recent years, the mortality rate from breast cancer has increased rapidly in all countries. Breast cancer is the most prevalent cancer in Iranian women with an increase in incidence rates in recent years. In Iran, even though the prevalence of breast cancer is lower compared to western countries, it is the most common malignancy among women (Rezaianzadeh et al., 2011). There is an increasing trend for breast cancer mortality in Iran during 1995 to 2004 from 1.40 to 3.52 per 100,000 (Taghavi et al., 2012). In the next decades, Iran will face an upsurge in the incidence of the disease (Dey and Soliman, 2010).

Breast-ovarian cancer (BOC)-causing mutations and other genetic variants are distributed along the entire coding and non-coding regions of BRCA1 and BRCA2, and more than 3400 gene variants have been described in the Breast Cancer Information Core (Solano et al., 2012). New variants continue to be detected worldwide, mostly in BRCA1. Individuals with an inherited inactivating mutation in BRCA1 (MIM# 113705) or BRCA2 (MIM# 600185) have an increased risk of developing early-onset breast and ovarian cancers (Welcsh and King et al., 2001). Inherited mutations in BRCA1 account for 40-45% of all hereditary BC cases, but approximately 80% of cases in families with multiple cases of breast and ovarian cancers (Easton et al., 1999).

The aim of this study was to survey the spectrum of most common mutations among Iranian breast cancer patients.

Materials and Methods

Search strategy

The electronic databases PubMed, EMBASE, and Scientific Information Database (SID) were searched up to October 30, 2014. The final search strategy used for each database was based on keywords "BRCA1," "BRCA2," "Iran," "Breast cancer," and "polymorphism." Synonyms and different styles of the search terms were also used in the search in order to obtain every relevant paper. Case-control studies containing available BRCA1 and BRCA2

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genes mutations frequencies were chosen. Only research articles were included and the language was not limited. Reference lists of the included studies on related topics were also screened for additional studies.

Data extraction

Data were carefully and independently extracted from the relevant papers by two of the authors (HN and MZS) using the same standardized form. The following data were collected from each study: first author, year of publication, source of controls, and genotype distribution. In case of disagreement, a third reviewer assessed the articles until an agreement was reached. The following items were collected from each article: first author, publication year, country or

Statistical analysis

The strength of association between common mutations in BRCA1 and BRCA2 and breast cancer risk was assessed for each study by frequency by using of crude ORs with 95%CIs. For all studies, only the frequency of mutation which repeatedly reported twice or more in different articles was evaluated. Frequency of each BRCA mutation carriers was more than 1% in meta-analyses by using the number of patients with event mutation and the total number of patients. The statistical heterogeneity among studies was assessed with the I2 test was used to quantify inconsistency. An I2 value≥50% was considered to represent significant statistical heterogeneity. The fixed-effects model (the Mantel-Haenszel method) was used to calculate the pooled OR with 95 % CI; Otherwise we applied the random effects model (the DerSimonian and Laird method) (Begg et al., 1994; Egger et al., 1997). These two models provided similar results when between studies heterogeneity was absent. Funnel plots and the linear regression asymmetry test by Egger et al., were used to evaluate potential publication bias (Egger et al., 1997). All statistical analyses were performed in Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC) and Review Manage (v.4.2; Oxford, England), using two-sided P values.

Results

Study characteristics

Our systematic literature search identified 22 studies that met the inclusion criteria. After deduplication and exclusion of the clearly irrelevant studies, we eventually included 13 studies (Bar-Sade et al., 1998; Ghaderi et al., 2001; Yassaee et al., 2002; Moslehi et al., 2003; Pietschmann et al., 2005; Quintana-Murci et al., 2005; Mehdipour et al., 2006; Rassi et al., 2008; Fattahi et al., 2009; Saleh gohari et al., 2012, Keshavarzi et al., 2012; Keshavarzi et al., 2012; and Kooshyar et al., 2013) involving 1183 breast cancer patients. Figure 1 shows the study selection process.

Baseline characteristics of the 13 studies are summarized a synopsis of the included studies, briefly describing study population, mutation scanning method, mutation carriers information, and the enrollment criteria of families and subjects (Tables 1, 2). The 13 studies included report on 7 different screening methods for the detection of BRCA1 and BRCA2 mutations: In these
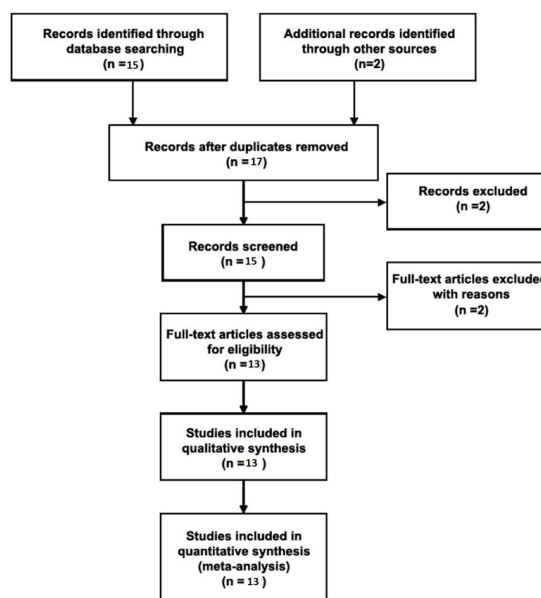

Figure 1. Flow Diagram of the Study Selection Process

Table 1. Characteristics of All 13 Studies Retrieved with the Searching Strategy for BRCA1

| Author	Year	Study population		Technique	Exo/Int
		NO.	Age(yr)		
Bar-Sade et al	1998	150 Iranian Jews	37	HA/Direct sequencing	2
Ghaderi et al	2001	22(BC) 18 (control)	42	Direct sequencing	11-2, 11-3a, 11-3b, 11-4, 13,16,IVS16,IVS16,IVS18
Yassaee et al	2002	83	<45	PTT, SSCP/HP	2, 11, 20
Moslehi et al	2003	1 Family with 4 cases (HOBS)	56	SSCP-PCR	
Murci et al	2005	442 (only males)	45-67	RFLP-PCR	2
Pietschmann et al	2005	10 high risk breast cancer families	<50	Direct sequencing	16, 17, 18, 24
Mehdipour et al	2006	396(Female), 4(Male)	48.8±11.3	PCR	2
Rassi et al	2008	16(FBC), 18(NFBC)	15-95, 25-80	Multiplex-PCR	2
Fattahi et al	2009	250 (SBC), 55(FBC), 200(HF)	45.1±9.2 32.0±7.3	Multiplex-PCR	2
Keshavarzi et al	2011	27 (BC), 50 (HF)	≤35	Direct sequencing	7, 9, 11, 13, 16, 20
Saleh-gohari et al	2012	22(female), 8 (male)	51	Direct sequencing	2, 11, 11
Keshavarzi et al	2012	36 (FBC), 49 (NFBC), 61 (Control)	≤35		IVS1, IVS1,2, IVS2, IVS5,6, 11, 13, 16, 20
Kooshyar et al	2013	39(BC) 29(HR)	49.3 23-72	SSCP-PCR	2, 11

Table 2. Characteristics of All 13 Studies Retrieved with the Searching Strategy for BRCA2

Author	Year	Study population		Technique	Exo/Int
		NO.	Age(yr)		
Yassaee et al	2002	83	<45	PTT, DS, SSCP/HA	11, 17, 18, 23
Moslehi et al	2003	1 Family with 4 cases (HOBS)	56 45-67	PTT	11
Pietschmann et al	2005	20 250 (SBC)	50 45.1±9.2	Direct sequencing Multiplex-PCR	2, 8, 10, 11, 14, 16, 21
Fattahi et al	2009	55(FBC) 200(HF)	32.0±7.3		
keshavarzi et al	2011	27 (BC) 50 (HF)	≤35	Direct sequencing	10, 11
keshavarzi et al	2012	36 (FBC) 49 (NFBC) 61 (Control)	≤35	Direct sequencing	IVS6, 11

Table 3. BRCA1 and BRCA2 Common Mutations Identified in 13 Studies

BRCA mutation	Exon /intron	Mutation effect	n/Na	Frequency	References
BRCA1					
c.2311T>C	11	Synonymous	17/154	0.131	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011; Keshavarzi et al., 2012
c.2612C>T	11	Misssense	18/69	0.269	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011
c.3113A>G	11	Misssense	35/105	0.334	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011; Keshavarzi et al., 2012
c.3119G>A	11	Misssense	26/132	0.202	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011
c.3548A>G	11	Misssense	Oct-42	0.243	Ghaderi et al., 2001; Pietschmann et al., 2005
c.4308T>C	13	Synonymous	26/154	0.175	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011; Keshavarzi et al., 2012
c.4837A>G	16	Misssense	30/154	0.201	Ghaderi et al., 2001; Pietschmann et al., 2005; Keshavarzi et al., 2011; Keshavarzi et al., 2012
IVS16-92A/G	16	Unknown	6/42	0.147	Ghaderi et al., 2001; Pietschmann et al., 2005;
IVS16-68A/G	16	Unknown	9/44	0.219	Ghaderi et al., 2001; Pietschmann et al., 2005
c.5213G>A	20	Misssense	9/112	0.096	Keshavarzi et al., 2011; Keshavarzi et al., 2012
BRCA2					
4075delGT	11	Synonymous	5/122	0.045	Keshavarzi et al., 2011; Keshavarzi et al., 2012

[a] n referred to the number of patients with event mutation, N referred to the total number of patients in total families; [b] These data were calculated through cumulative outcomes from all related articles; [c] These frequencies were obtained from meta-analysis results from all related articles
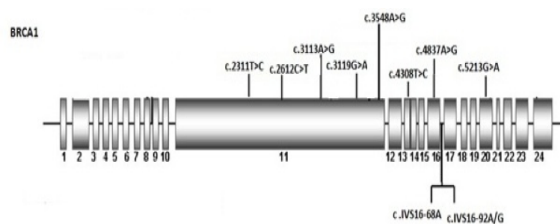
Figure 2. Position of Common Mutations with in BRCA1 in Iranian BC Patients

methods, Direct sequencing was more than one evaluation study identified and the distribution of these screening methods was as follows: 9 DHPLC, 7 SSCP, 6 PTT, 4 HA, 2 DGGE, 2 CSGE and 4 studies conducted sequencing to confirm each germline BRCA1/2 variant.

As shown in Figure 2, 11 common mutations were identified from all 13 studies, at exon 11, exon 13, intron 16, and exon 20 of BRCA1 and exon 11 of BRCA2.

To evaluate the frequency of 11 common mutations which repeatedly reported twice or more in different articles, we conducted meta-analysis and the results were shown in Table 1. For those 11 mutations, 4 studies had repeatedly reported the c.2311T>C, c.3113A, c.4308T>C,

c.4837A>G, and c.2311T>C, 3 studies had repeatedly reported the c.2612C>T, and c.3119G>A, and 2 studies had repeatedly reported the c.3548A>G, c.IVS16-92A/G, c.IVS16-68A/G, and c.5213G>A. For those mutations which were not repeatedly reported in all 13 studies, we only selectively listed the common mutations (frequency more than 5%) in our study. For the BRCA1 (Figure 3), after conducting meta-analysis, we found that the overall frequency of c.3113A>G was 0.3 (95%CI 0.24-0.44, p=0.00 for heterogeneity test), the frequency of c.2311T>C was 0.13 (95%CI 0.08-0.20, p=0.00 for heterogeneity test), the frequency of c.2612C>T was 0.27 (95%CI 0.17-0.57, p=0.00 for heterogeneity test), the frequency of c.3548A>G was 0.24 (95%CI 0.01-0.13, p=0.00 for heterogeneity test), the frequency of c.4308T>C was 0.17 (95%CI 0.12-0.24, p=0.00 for heterogeneity test), the frequency of c.4837A>G was 0.20 (95%CI 0. 14-0.27, p=0.00 for heterogeneity test), the frequency of c.IVS16-92A/G was 0.22 (95%CI 0.10-0.40, p=0.00 for heterogeneity test), the frequency of c.IVS16-68A/G was 0.22 (95%CI 0.12-0.38, p=0.00 for heterogeneity test), the frequency of c.3119G>A was 0.20 (95%CI 0.14-0.28, p=0.00 for heterogeneity test), and the
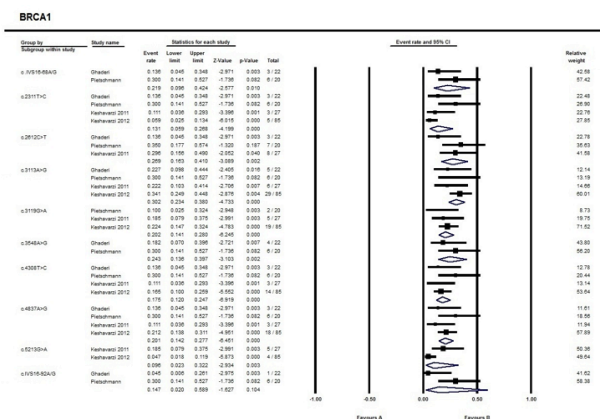
Figure 3. Forest Plot Showing the Odds Ratio of Each Study and the Pooled Estimate in BRCA1
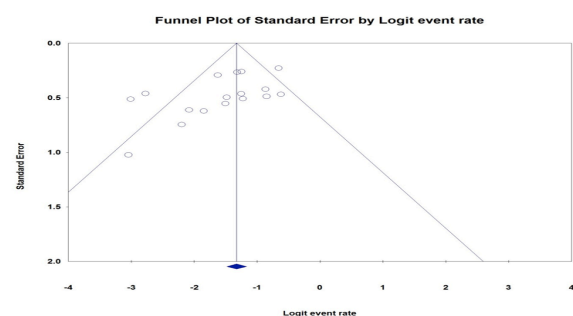

Figure 4. Funnel Plot of Standard Error by Log Odds Ratio Showing Analysis of Publication Bias of Studies in Spontaneously Aborted Embryos

frequency of c.5213G>A was 0.09 (95%CI 0.05-0.17, p=0.00 for heterogeneity test).

For the BRCA2, the overall frequency of 4075delGT was 0.02 (95%CI 0.019-0.103, p=0.00 for heterogeneity test).

Publication bias

Egger test for intercept showed no evidence of publication bias (intercept = -1.85; SE = 0.67; 95%CI = -3.23-0.47; P2-tailed = 0.01). Classic Fail-Safe "N"= 4, missing from the analysis for every published study included, which further supports absence of publication bias. A funnel plot of SE by log OR was generated. Almost symmetric distribution of studies on the funnel plot shows absence of publication bias (Figure 4).

Discussion

To date, no reports have been published about BRCA1 and BRCA2 most common mutations in the Iranian population. To determine frequent mutations within the Iranian population, we analyzed together the other 13 studies for this population and calculated pooled mutation frequencies. We believe that this Meta-analysis result will be of significance both for diagnostic testing and for epidemiological studies. BRCA1 and BRCA2 are both large genes, and complete analysis of the coding regions is expensive and time-consuming. The identification of recurrent mutations allows for the rapid diagnosis of BRCA1-mutation carriers in Iranian individuals with relatively high sensitivity.

The majority of these 11 mutations described here are frequent in other populations. Recently, Medimegh et al., found that c.2082C>T, c.3113A>G, c.3119G>A, c.3548A>G and c.4837A>G SNPs were not associated with breast cancer disease (FBC or SBC) with P value>0.05.

The most commonly observed mutation in the present study was the c.3113A>G, which accounted for 29.8% of all common mutations. This mutation has previously been reported in various ethnic groups. However, Medimegh et al., have found c.3113A>G was not associated with breast cancer disease (Medimegh et al., 2014). In addition, Dombernowsky et al., in a large study, evaluated risk associated of breast and/or ovarian cancer by 9 missense polymorphisms in BRCA1 c.1067A>G, c.2612C>T, c.3113A>G, c.4837A>G, c.4956G>A and BRCA2 c.865A>C, c.1114A>C, c.4258G>T, and c.5744C>T. They found no association between heterozygosity or homozygosity for any of the nine polymorphisms and risk of breast and/or ovarian cancer in either study (Dombernowsky et al., 2009).

Medimegh et al., Wild-type alleles and genotypes of c.442-58 delT, c.2311T>C, c.2612 C>T and c.4308T>C are clearly associated with familial breast cancer with an odds ratio ranging from 2.49 to 4.66. They found that among the four associated SNPs to familial breast cancer, the c.2612 C>T variant could have an effect on the protein sequence with an amino acid change (Proline to Leucine) at position 871, suggesting an alteration on the protein function and an ambivalent role of wild allele to familial breast cancer susceptibility. However, Dombernowsky et al., found no association between c.2612 C>T and breast cancer (Dombernowsky et al., 2009).

The BRCA1 c.2311T>C missense mutation in exon 11 accounted for 4.5% of families with mutations. This mutation has previously been reported in various ethnic groups. Combination between TT genotype of c.2311T[C and miR-1179 over-expression could generate a lack of BRCA1 protein leading to a high risk of familial breast cancer with distant metastases.

Pilato et al. studied both transmission of BRCA1 and BRCA2 pathogenic mutations and polymorphic variants in breast cancer familial members. They found that SNPs BRCA1 c.3548A>G (p.Lys1183Arg) were more frequently present in breast cancer relatives belonging to families tested negative for BRCA1 and BRCA2 mutations (Pilato et al., 2011). Also, Cherbala et al., have reported that the c.3548A>G missense has high frequency in patients who were tested negative for BRCA1 and BRCA2 mutations in Algerian breast/ovarian cancer families (Cherbala et al., 2012).

We have found two unclassified intronic variants (IVS16-68 G>A, IVS16-92 G>A) that were reported twice or more in the studies. These two intronic mutations previously reported in Greek, Netherlands, Belgium, Argentina breast/ovarian cancer families and Singapore Malay women with early onset breast/ovarian cancer (Konstantopoulou et al., 2000; Sng et al., 2003). BRCA1 IVS16-68 G>A and IVS16-92 G>A have been reported previously in the BIC database, and they are among the top 20 mutation frequencies that have been described by

designation (Sng et al., 2003).

Nevertheless, this meta-analysis also had some limitations. Firstly, the samples size for the association about BRCA1/2 and breast cancer common mutations and articles about Iranian populations are too small to provide strong information and more original studies are needed to further confirm our findings. Secondly, previous study only screened particular region of the BRCA1/2 genes might naturally exclude many potential common polymorphism in other region, so our results may not have sufficient statistical power to identify and analysis common polymorphism in the Iranian breast cancer patients.

Although there are some limitations in this meta-analysis, values of this study should also be highlighted. Firstly, as far as we know, this is the first meta-analysis to examine the common mutation of the BRCA genes in the Iranian breast cancer patients. Finally, any obvious evidence of publication bias could be detected in all genetic models.

In conclusion, this Meta-analysis results will be helpful to understand the possibility of the first true founder mutation of BRCA1/BRCA2 identified in the Iranian population, establish a genetic screening strategy, to provide individual risk assessment, and to design better therapeutic strategies in the Iranian population. However, the relatively high frequency of these mutations in the Iranian breast cancer patients cannot be explained by founder effects and It is possible that we have not yet identified all recurrent mutations that occur in Iran. Therefore, further population surveys of BRCA mutations will be necessary.

Acknowledgements

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