RESEARCH ARTICLE

Association of Functional Polymorphisms of the XRCC4 Gene with the Risk of Breast Cancer: A Meta-analysis

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Abstract

Objective: X-ray cross-complementing group 4 (XRCC4) is a major repair gene for DNA double-strand breaks (DSB) in the non-homologous end-joining (NHEJ) pathway. Several potentially functional polymorphisms of the XRCC4 gene have been implicated in breast cancer risk, but individually published studies showed inconclusive results. The aim of this meta-analysis was to investigate the association between XRCC4 polymorphisms and the risk of breast cancer. Methods: The MEDLINE, EMBASE, Web of science and CBM databases were searched for all relevant articles published up to June 20, 2012. Potential associations were assessed with comparisons of the total mutation rate (TMR), complete mutation rate (CMR) and partial mutation rate (PMR) in cases and controls. Statistical analyses were performed using RevMan 5.1.6 and STATA 12.0 software. Results: Five studies were included with a total of 5,165 breast cancer cases and 4,839 healthy controls. Meta-analysis results showed that mutations of rs2075686 (C>T) and rs6869366 (G>T) in the XRCC4 gene were associated with increased risk of breast cancer, while rs2075685 (G>T) and rs10057194 (A>G) might decrease the risk of breast cancer. However, rs1805377 (A>G), rs1056503 (G>T), rs28360317 (ins>del) and rs3734091 (A>G) polymorphisms of XRCC4 gene did not appear to have an influence on breast cancer susceptibility. Conclusion: Results from the current meta-analysis suggest that the rs2075685 (G>T) and rs6869366 (G>T) polymorphisms of the XRCC4 gene might increase the risk of breast cancer, whereas rs2075685 (G>T) and rs10057194 (A>G) might be protective factors.

Keywords: XRCC4 - polymorphism - mutation - breast cancer - meta-analysis

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Introduction

Breast cancer, malignant breast neoplasm, is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (Sariego et al., 2010). It is the most common cancer among women worldwide (Smigal et al., 2006). Breast cancer comprises 23% of invasive cancers in women and 16% of all female cancers. In 2008, breast cancer caused 458503 deaths worldwide (13.7% of cancer deaths in women and 6.0% of all cancer deaths for men and women together) (Kelsey et al., 1993). The incidence of breast cancer varies greatly around the world for it is the lowest in developing countries and greatest in the developed countries (Stewart et al., 2003; Laurance et al., 2006). Epidemiological studies suggest that the etiology of breast cancer is multifactorial, including exposure to ionizing, high-fat dietary intake, alcohol consumption and use of hormones or oral contraceptives. However, only a small proportion of women exposed to these external factors develop breast cancer (Singletary et al., 2003; Dumitrescu et al., 2005). In addition, it is believed that breast cancer is resulted from a series of genetic alterations leading to progressive disorder of the normal mechanisms controlling cell proliferation, differentiation, death, and/or genomic stability (Wu et al., 2008). All of these suggest that genetic susceptibility plays a critical role in the individual risk of breast carcinogenesis (Teare et al., 1994). The response of the cell to genetic injury and its ability to maintain genomic stability by means of a variety of DNA repair mechanisms which are essential in preventing tumor initiation and progression (Bau et al., 2011). Mutations or defects in the DNA repairing system may promote tumorigenesis (Vogelstein et al., 2002).

One of the most deleterious DNA damaging types is double strand break (DSB), which should be repaired in eukaryotes by two major pathways, namely homologous recombination (HR) and non-homologous end-joining (NHEJ). HR is a template guided, error-free pathway predominantly operating in the S and G2 phases of the cell cycle (Valerie et al., 2003). In the NHEJ repair pathway, the broken DNA termini are first processed to make them compatible and the sealed by a ligation step. In most cases, NHEJ results in the loss of a few nucleotides at

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the broken ends, making this pathway error-prone but it is still considered to be the major repair pathway of DSB in eukaryotic cells during most phases of the cell cycle (Pfeiffer et al., 2004). Ongoing studies have provided evidence that some genetic variants of DNA repair genes, such as X-ray cross-complementing group 4 (XRCC4) gene, might contribute to breast cancer pathogenesis (Chiu et al., 2008). XRCC4 gene, located on the chromosomal 5q14.2, is found to restore DNA DSB repair (Li et al., 1995). This kind of gene product directly interacts with Ku70/Ku80, and it is hypothesized that XRCC4 serves as a flexible tether between Ku70/Ku80 and its associated protein, ligase 4 (Mari et al., 2006). Since XRCC4 repair gene alterations have been shown to cause a reduction in DNA repair capacity, we hypothesized that XRCC4 gene polymorphisms may be risk factors for breast cancer. To test this hypothesis, we performed a meta-analysis by including the most recent and relevant articles to identify statistical evidences of the associations between XRCC4 gene polymorphisms and the risk of breast cancer that have been investigated.

Materials and Methods

Literature Search

Relevant papers published before June 20, 2012 were identified through a search of MEDLINE, EMBASE, Web of science and CBM databases using the following terms including ("XRCC4" OR "DNA repair protein XRCC4" OR "X-ray repair cross-complementing protein 4") AND ("Breast neoplasms" OR "Breast cancer" OR "Breast tumor" OR "Breast carcinoma") AND ("Genetic polymorphism" OR "Single nucleotide polymorphism" OR "SNP" OR "Mutant" OR "Gene variation" OR "Gene mutation"). The references of the eligible articles or textbooks were also reviewed to check through manual searches to find other potentially studies.

Inclusion and Exclusion Criteria

Studies included in our meta-analysis have to meet the following criteria: (i) case-control study focused on associations between XRCC4 gene polymorphisms and breast cancer risk; (ii) all patients with the diagnosis of malignant tumor confirmed by pathological or histological examination; (iii) the frequencies of alleles or genotypes in case and control groups could be extracted; (iv) published in English or Chinese language. Studies were excluded when they were: (i) no control population; (ii) duplicate of previous publication; (iii) based on incomplete data; (iv) investigations in subjects with family cancer risks or cancer-prone disposition; (v) meta-analyses, letters, reviews or editorial articles.

Data Extraction

Using a standardized form, data from published studies were extracted independently by two reviewers to populate the necessary information. The following information was extracted from each of the articles included: first author, year of publication, country, language, ethnicity, study design, source of cases and controls, number of cases and controls, mean age, sample, cancer type, genotype method, genotype frequency, the rate of mutation and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In case of conflicting evaluations, an agreement was reached following a discussion with a third reviewer.

Quality assessment of included studies

Two reviewers independently assessed the quality of papers according to modified STROBE quality score systems (von Elm et al., 2007; Zhang et al., 2011). Forty assessment items related with the quality appraisal were used in this meta-analysis, scores ranging from 0 to 40. Scores of 0-20, 20-30 and 30-40 were defined as low, moderate and high quality, respectively. Disagreement was resolved by discussion.

Statistical Analysis

The meta-analysis examined the association between XRCC4 gene polymorphisms and the risk of breast caner for the comparisons of mutation rates in cases and controls. The mutation rates can be classified into total mutation rate (TMR), the ratio of heterozygotes and mutant homozygotes to the total number of genotypes; complete mutation rate (CMR), the ratio of mutant homozygotes to the total number of genotypes; partial mutation rate (PMR), the ratio of heterozygotes to the total number of genotypes. The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using Review Manager Version 5.1.6 (provided by the Cochrane Collaboration, available at: http://ims.cochrane.org/revman/download) and STATA Version 12.0 (Stata Corp, College Station, TX) softwares. Between-study variations and heterogeneities were estimated using Cochran's Q-statistic (Higgins et al., 2002; Zintzaras et al., 2005) ($P \leq 0.05$ was considered to be manifestation of statistically significant heterogeneity). We also quantified the effect of heterogeneity by using I2 test, which ranges from 0 to 100% and represents the proportion of inter-study variability that can be contributed to heterogeneity rather than by chance. When a significant Q-test ($P \leq 0.05$) or $I^2 > 50\%$ indicated that heterogeneity among studies existed, the random effects model was conducted for meta-analysis. Otherwise, the fixed effects model was used. To establish the effect of heterogeneity on meta-analyses' conclusions, subgroup analysis was operated. We tested whether genotype frequencies of controls were in HWE using the χ^2 test. Funnel plots are often used to detect publication bias. However, due to its limitations caused by varied sample sizes and subjective reviews, Egger's linear regression test which measures funnel plot's asymmetry using a natural logarithm scale of OR was used to evaluate the publication bias (Peters et al., 2006). When the P value is less than 0.1, publication bias is considered significant. All the P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers populated the data in the statistical software programs independently and obtained the same results.

Results

Characteristics of Eligible Studies

According to the inclusion criteria, five studies were included (Fu et al., 2003; Lee et al., 2005; García-Closas

Table 1. Characteristics of Included Studies in this Meta-analysis

First author	Year	Country	Ethnicity	Number Case	Number Control	Source of control	Sample	Genotype method	SNP	Quality scores
Fu et al	2003	China	Asian	254	379	Population-based	Blood	MassArray	rs1805377 (A>G) rs2075685 (G>T) rs2075686 (C>T)	25
Lee et al	2005	Korea	Asian	872	671	Population-based	Blood	MassArray	rs1056503 (G>T)	29
García-Closas et al	2006	USA	Caucasian	3368	2880	Population-based	Blood	MassArray	rs1805377 (A>G)	31
Chiu et al	2008	China	Asian	432	432	Population-based	Blood	PCR-RFLP	rs3734091 (A>C) rs6869366 (G>T) rs28360317 (ins>del)	28
Han et al	2009	USA	Caucasian	239	477	Population-based	Blood	AS-PCR	rs10057194 (A>G)	32

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; AS, allele specific

Table 2. The Genotype Distribution of XRCC4 Gene Polymorphisms in Case and Control Groups

First author	SNP	Case							Control							HWE test	
		Total	TM	CM	PM	TMR	CMR	PMR	Total	TM	CM	PM	TMR	CMR	PMR	χ^2	P
Fu et al (2003)	rs1805377 (A>G)	251	116	14	102	0.46	0.06	0.41	379	183	24	159	0.48	0.06	0.42	1.22	0.27
	rs2075685 (G>T)	254	47	3	44	0.19	0.01	0.17	378	106	9	97	0.28	0.02	0.26	0.01	0.92
	rs2075686 (C>T)	254	151	41	110	0.59	0.16	0.43	379	211	39	172	0.56	0.10	0.45	0.27	0.61
Lee et al (2005)	rs1056503 (G>T)	803	373	46	327	0.46	0.06	0.41	650	307	50	257	0.47	0.08	0.40	0.04	0.85
García-Closas et al (2006)	rs1805377 (A>G)	1536	305	20	285	0.20	0.01	0.19	1213	249	10	239	0.21	0.01	0.20	1.33	0.25
Chiu et al (2008)	rs3734091 (A>C)	432	22	3	19	0.05	0.01	0.04	432	15	0	15	0.03	0.00	0.03	0.14	0.71
	rs6869366 (G>T)	432	46	4	42	0.11	0.01	0.10	432	21	0	21	0.05	0.00	0.05	0.27	0.61
	rs28360317 (ins>del)	432	192	38	154	0.44	0.09	0.36	432	183	45	138	0.42	0.10	0.32	3.65	0.06
Han et al (2009)	rs10057194 (A>G)	237	20	2	18	0.08	0.01	0.08	471	67	4	63	0.14	0.01	0.13	0.77	0.38

TM, total mutation; CM, complete mutation; PM, partial mutation; TMR, the rate of total mutation; CMR, the rate of complete mutation; PMR, the rate of partial mutation; SNP, single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium

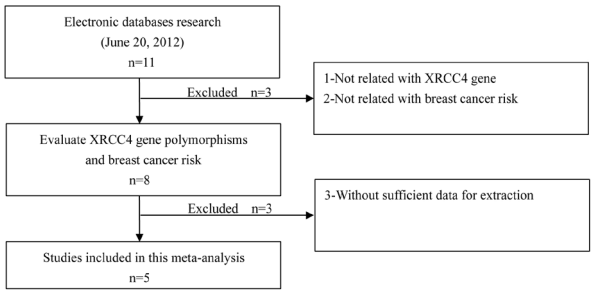

Figure 1. Flow Chart Shows Study Selection Procedure

et al., 2006; Chiu et al., 2008; Han et al., 2009) (Figure 1). The flow chart of study selection is shown in Figure 1. The total of breast cancer cases and healthy controls were 5165 and 4839 respectively in these five case-control studies, which evaluated the relationship between XRCC4 polymorphisms and breast cancer risk. The publication year of involved studies ranged from 2003 to 2009. All cases fulfilled the diagnosis criteria of breast cancer confirmed by pathological or histological examination. There were eight single nucleotide polymorphisms (SNP) of XRCC4 gene in these five studies, including rs1805377 (A>G), rs2075685 (G>T), rs2075686 (C>T), rs1056503 (G>T), rs3734091 (A>C), rs6869366 (G>T), rs28360317 (ins>del) and rs10057194 (A>G). Three of five case-control studies were conducted in Asians and two studies were conducted in Caucasians. The HWE test was performed on the genotype distribution of the controls in all included studies, all of them showed to be in HWE ($P<0.05$). The characteristics and methodological quality of the included studies are summarized in Table 1. The mutation genotypes of XRCC4 gene polymorphisms were presented in Table 2.

Table 3. Meta-analysis of the Association between XRCC Gene Polymorphisms and Breast Cancer Risk

Polymorphisms	Cancer n/N	Control n/N	OR [95%CI]	P	Effect model
rs1805377 (A>G)					
TMR	421/1787	432/1592	0.95 [0.81, 1.12]	0.53	Fixed
CMR	34/1787	34/1592	1.14 [0.70, 1.88]	0.59	
PMR	387/1787	398/1592	0.93 [0.79, 1.10]	0.41	
rs2075685 (G>T)					
TMR	47/254	106/378	0.58 [0.40, 0.86]	0.006	Fixed
CMR	3/254	9/378	0.49 [0.13, 1.83]	0.29	
PMR	44/254	97/378	0.61 [0.41, 0.90]	0.01	
rs2075686 (C>T)					
TMR	151/254	211/379	1.17 [0.85, 1.61]	0.35	Fixed
CMR	41/254	39/379	1.68 [1.05, 2.69]	0.03	
PMR	110/254	172/379	0.92 [0.67, 1.27]	0.61	
rs1056503 (G>T)					
TMR	373/803	307/650	0.97 [0.79, 1.19]	0.77	Fixed
CMR	46/803	50/650	0.73 [0.48, 1.10]	0.14	
PMR	327/803	257/650	1.05 [0.85, 1.30]	0.65	
rs3734091 (A>C)					
TMR	22/432	15/432	1.49 [0.76, 2.92]	0.24	Fixed
CMR	3/432	0/432	7.05 [0.36, 136.87]	0.20	
PMR	19/432	15/432	1.28 [0.64, 2.55]	0.48	
rs6869366 (G>T)					
TMR	46/432	21/432	2.33 [1.37, 3.98]	0.002	Fixed
CMR	4/432	0/432	9.08 [0.49, 169.24]	0.14	
PMR	42/432	21/432	2.11 [1.23, 3.62]	0.007	
rs28360317 (ins>del)					
TMR	192/432	183/432	1.09 [0.83, 1.42]	0.54	Fixed
CMR	38/432	45/432	0.83 [0.53, 1.31]	0.42	
PMR	154/432	138/432	1.18 [0.89, 1.57]	0.25	
rs10057194 (A>G)					
TMR	20/237	67/471	0.56 [0.33, 0.94]	0.03	Fixed
CMR	2/237	4/471	0.99 [0.18, 5.46]	0.99	
PMR	18/237	63/471	0.53 [0.31, 0.92]	0.02	

TMR, the rate of total mutation; CMR, the rate of complete mutation; PMR, the rate of partial mutation; OR, odds ratio; 95%CI, 95% confidence interval

Table 4. Additional Pooled Analysis and Subgroup Analysis by Ethnicity

Mutation genotypes	Case n/N	Control n/N	OR [95%CI]	P	Heterogeneity P	Heterogeneity I^2	Effect model
TMR	1272/3767	1342/3902	0.97 [0.80, 1.19]	0.80	0.007	72%	Random
Asians	947/1994	1026/2218	1.07 [0.82, 1.40]	0.63	0.01	78%	
Caucasians	325/1773	316/1684	0.77 [0.46, 1.30]	0.34	0.06	73%	
CMR	171/3767	181/3902	1.03 [0.83, 1.28]	0.81	0.31	17%	Fixed
Asians	149/1994	167/2218	0.98 [0.78, 1.24]	0.89	0.18	42%	
Caucasians	22/1773	14/1684	1.47 [0.74, 2.93]	0.27	0.62	0%	
PMR	1101/3767	1161/3902	0.97 [0.77, 1.21]	0.76	0.002	76%	Random
Asians	789/1994	859/2218	1.08 [0.80, 1.45]	0.62	0.004	82%	
Caucasians	303/1773	302/1684	0.75 [0.44, 1.27]	0.28	0.06	72%	

TMR, the rate of total mutation; CMR, the rate of complete mutation; PMR, the rate of partial mutation; OR, odds ratio; 95%CI, 95% confidence interval

Association between XRCC4 Polymorphisms and Breast Cancer Risk

A summary of the meta-analysis findings of the association between XRCC4 gene polymorphisms and breast cancer risk is provided in Table 3. No heterogeneity was found in all comparisons (all P>0.05), so the fixed effects model was used. The meta-analysis result showed that the rs2075686 (C>T) polymorphism in XRCC4 gene were associated with increased risk of breast cancer (for CMR: OR=1.68, 95%CI=1.50-2.69, P=0.03). Moreover, the rs6869366 (G>T) polymorphism might also increase the risk of breast cancer (for TMR: OR=2.33, 95%CI=1.37-3.98, P=0.002; for PMR: OR=2.11, 95%CI=1.23-3.62, P=0.007). Interestingly, the results showed that there were negative associations of the rs2075685 (G>T) polymorphism with breast cancer risk (for TMR: OR=0.58, 95%CI=0.40-0.86, P=0.006; for PMR: OR=0.61, 95%CI=0.41-0.90, P=0.01), as well as the rs10057194 (A>G) polymorphism (for TMR: OR=0.56, 95%CI=0.33-0.94, P=0.03; for PMR: OR=0.53, 95%CI=0.31-0.92, P=0.02). However, there was no evidence that the rs1805377 (A>G), rs1056503 (G>T), rs28360317 (ins>del) and rs3734091 (A>G) polymorphisms of XRCC4 gene associated with the risk of breast cancer (all P>0.05).

Additional a pooled analysis was conducted, we combined eight mutation variants in XRCC4 gene to investigate associations between the overall mutation rate of XRCC4 gene and the risk of breast cancer. The results of pooled analysis showed no association between XRCC4 gene mutations and breast cancer risk (for TMR: OR=0.97, 95%CI=0.80-1.19, P=0.80; for CMR: OR=1.03, 95%CI=0.83-1.28, P=0.81; for PMR: OR=0.97, 95%CI=0.77-1.21, P=0.76).

Further subgroup analysis was conducted by ethnicity, we also found no association between mutation rates of XRCC4 gene and breast cancer risk neither in Caucasians nor in Asians (all P>0.05) (Table 4). Sensitivity analysis was performed by sequential omission of individual studies under various contrasts. However, the significance of pooled OR in all individual analysis and subgroup analysis was not influenced excessively.

Publication Bias

Publication bias of the literatures was accessed based on mutations of SNPs in XRCC4 gene by funnel plot and Egger's linear regression test. All graphical funnel plots

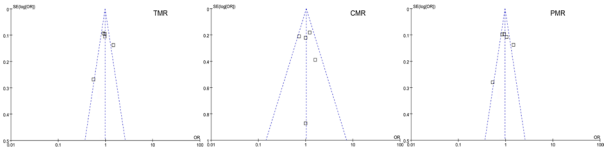

Figure 2. Begger's Funnel Plot of Publication Bias

of included studies appeared to be symmetrical (Figure 2). Egger's test also showed that there was no statistical significance for all evaluations of publication bias.

Discussion

DNA damage is the most important factor for carcinogenesis because exogenous carcinogens and endogenous oxygen species can induce DNA damage and genomic instability that may lead to carcinogenesis through activation of oncogenes and inactivation of tumor suppressor genes (Barnes et al., 2002). Thus, DNA repair is expected to play a role in maintaining genomic stability (Dixon et al., 2004). Repair of DNA damage can protect cells against carcinogenesis, and the polymorphisms of the DNA repair gene have been implicated as susceptibility factors in cancer development (Goode et al., 2002).

The DNA repair gene XRCC4, an important caretaker of the overall genome stability, is thought to play a major role in the human carcinogenesis (Chiu et al., 2008). It is believed that genetic polymorphisms of DNA repair genes seem to determine the DNA repair capacity (Qiao et al., 2002), which may affect the risk of breast cancer (Yu et al., 1999; Goode et al., 2002). Nevertheless, despite the past establishment of the important functions of XRCC4 gene, studies investigating the connection between polymorphisms of the XRCC4 gene and breast cancer risk have only recently begun to emerge. To date, several functional XRCC4 gene polymorphisms are considered as predisposing genetic factors for breast malignancies. Allen-Brady et al found that four tagging SNPs (rs1478485, rs13180316, rs963248 and rs1056503) in XRCC4 gene may play an important role in the development of breast cancer (Allen-Brady et al, 2006). Sehl et al have also reported that SNPs within or near a number of DNA DSB repair pathway genes including XRCC4 are associated with breast cancer in individuals from a high-risk population (Sehl et al., 2009). In addition, Fu et al confirmed that the rs2075685 (G>T) polymorphism in XRCC4 gene showed to be significantly associated with breast cancer risk in a Taiwanese breast

cancer case-control study (Fu et al., 2003). However, Lee et al did not find significance with breast cancer risk for carriage of the rare allele in XRCC4 rs1056503 (G>T) polymorphism (Lee et al., 2005).

Given controversial results in those previous studies, we conducted a meta-analysis to explore the associations between XRCC4 genetic polymorphisms and risk of breast cancer. In this meta-analysis, including a total of 5165 breast cancer cases and 4839 healthy controls from five independent publications, we mainly examined the association of eight polymorphisms in XRCC4 gene with breast cancer risk. We demonstrated that the mutations of rs2075686 (C>T) and rs6869366 (G>T) polymorphisms in XRCC4 gene were associated with increased risk of breast cancer, while the rs2075685 (G>T) and rs10057194 (A>G) might decrease the risk of breast cancer. However, the rs1805377 (A>G), rs1056503 (G>T), rs28360317 (ins>del) and rs3734091 (A>G) polymorphisms of XRCC4 gene did not appear to have an influence on breast cancer susceptibility. In interpreting our results of the current meta-analysis, some limitations need to be addressed. Firstly, although the funnel plot and Egger's test did not show any publication bias, selection bias could have occurred because only studies published in English or Chinese were included. Secondly, the numbers of published studies were still not sufficiently large for the analysis of some particular cancer types. Thirdly, our meta-analysis was based on unadjusted ORs estimates because not all published presented adjusted ORs or when they did, the ORs were not adjusted by the same potential confounders, such as pathological types, age, gender, geographic distribution, etc. In addiction, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results.

In summary, our meta-analysis of five case-control studies demonstrates that the rs2075685 (G>T) and rs6869366 (G>T) polymorphisms of XRCC4 gene might increase the risk of breast cancer, but the rs2075685 (G>T) and rs10057194 (A>G) might be protective factors for breast cancer. It is of great essentiality to carry out large sample studies so as to elucidate the influence of these polymorphisms on breast cancer risk.

Acknowledgements

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