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Original Article

The C8092A polymorphism in the ERCC1 gene and breast carcinoma risk: a meta-analysis of case-control studies

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Abstract: The C8092A polymorphism in the ERCC1 (excision repair cross-complementation group 1) gene was shown to be associated with breast carcinoma risk. However, the results of different studies remain controversial. A meta-analysis including 3,308 cases and 3,242 controls from eight studies was performed to explore the association between the C8092A polymorphism in the ERCC1 gene and breast cancer risk. The pooled odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were evaluated by the random effects model. No significant association was detected in an allelic genetic model (OR: 1.081, 95% CI: 0.994-1.175, P=0.068, $P_{heterogeneity}$=0.331), a homozygote model (OR: 1.213, 95% CI: 0.926-1.589, P=0.160, $P_{heterogeneity}$=0.071), a heterozygote model (OR: 1.061, 95% CI: 0.958-1.176, P=0.256, $P_{heterogeneity}$=0.950), a dominant genetic model (OR: 1.082, 95% CI: 0.981-1.193, P=0.113, $P_{heterogeneity}$=0.816) and a recessive genetic model (OR: 1.181, 95% CI: 0.904-1.543, P=0.223, $P_{heterogeneity}$=0.060) between the C8092A polymorphism in the ERCC1 gene and breast tumor. A significant relationship between the C8092A polymorphism in the ERCC1 gene and breast tumor in Caucasian group was found in a homozygote genetic model (OR: 1.353, 95% CI: 1.009-1.815, P=0.044, $P_{heterogeneity}$=0.516) and a recessive genetic model (OR: 1.339, 95% CI: 1.004-1.785, P=0.047, $P_{heterogeneity}$=0.532). Individuals with the C8092A polymorphism in the ERCC1 gene have a higher risk of breast cancer in Caucasians, but not for Asians.

Keywords: Breast carcinoma, breast cancer, meta-analysis, ERCC1, polymorphism

Introduction

According to the cancer registry report released by National Central Cancer Registry (NCCR), the incidence and mortality of cancer have been rising gradually [1]. In Chinese urban areas, lung cancer was the most common cancer, followed by cancers of the breast, stomach, colorectum and liver. In females, breast cancer was the most common cancer, followed by cancers of the lung, colorectum, stomach and liver. In Chinese rural areas, lung cancer was the most common cancer, followed by cancers of the stomach, liver, esophagus and breast. In females, breast cancer was the most common cancer, followed by lung cancer, stomach cancer, esophageal cancer and liver cancer. According to the report from American Cancer Society, breast cancer alone is expected to account for 29% (232,670) of all new cancers among women in America [2]. Approximately 232,340 new cases of invasive breast cancers and 39,620 breast cancer deaths are expected to occur among US women in 2013 [3]. Breast cancer incidence rates increased slightly among African American women. Among females, breast cancer ranks first in women aged 20 years to 59 years, and lung cancer causes the most cancer deaths in those aged 60 years and older [4].

The primary risk factors for breast cancer are female sex and older age. Other potential risk factors are as follows: genetics, lack of childbearing or lack of breastfeeding, higher levels of certain hormones, certain dietary patterns,

and obesity. Recent studies have indicated that exposure to light pollution is a risk factor for the development of breast cancer.

Some genetic susceptibility may have a minor role in most cases. Overall, however, genetics is considered to be the foremost cause of 5-10% of all cases. In those with zero, one or two affected relatives, the risk of breast cancer before the age of 80 is 7.8%, 13.3%, and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively. Of those with a first degree relative with the disease, the risk of breast cancer between the age of 40 and 50 is double that of the general population. In less than 5% of cases, genetics plays a more important role by causing a hereditary breast-ovarian cancer syndrome. This includes those who carry the BRCA1 and BRCA2 gene mutation. These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60-80% for those affected. Other significant mutations include: p53, PTEN, and STK11, CHEK2, ATM, BRIP1, PALB2 and CXCL12 [5]. In 2012, researchers said that there are four genetically distinct types of breast cancer and that in each type, hallmark genetic changes lead to many cancers.

Some previous work and studies have demonstrated that Excision repair cross complementation group 1 (ERCC1) protein in breast cancer which encoded by ERCC1 gene expressed is a key player in nucleotide excision repair. In recent years, the expression of ERCC1 was extensively studied in endometrial cancer, ovarian cancer, non-small cell lung cancer, nasopharyngeal cancer and thymic cancer. It was deemed to predict response to anti-cancer treatment and possibly have a prognostic role. Recently, some studies have reported increasing breast cancer risks associated with single nucleotide polymorphisms (SNPs) of ERCC1.

The association of ERCC1 polymorphism with breast cancer risk has been investigated in several studies, while the conclusion is still inconclusive. For example, data from Lee's study provide the first evidence that genetic polymorphisms of ERCC1 may be associated with breast cancer risk in Korean women [6], and Crew et al. found a statistically significant increase of 92% in the OR for the association between the homozygous variant genotype (AA) for the ERCC1 polymorphism (3'-untranslated region 8092C/A) and breast cancer risk [7]. However, Pei's study did not find a statistically significant association between the variants of C8092A in ERCC1 gene and risk of breast cancer [8].

To ascertain the relationship between the C8092A polymorphism in the ERCC1 gene and breast cancer risk, we performed this meta-analysis by pooling all the eligible studies.

Materials and methods

Publication search and inclusion/exclusion criteria

The following keywords were searched in PubMed database without a language limitation: "cancer of breast", "breast cancer" "breast carcinoma", "carcinoma of breast", "breast neoplasms", "breast neoplasms", "ERCC1", "excision repair cross-complementation group 1", "genetic variation", and "polymorphism". Additional relevant studies were also found in the indexed references of the retrieved literatures. The latest research was updated on June 3, 2014, with publication years ranging from 2000 to 2014.

The studies were selected based on the following inclusion criteria: studies that evaluate ERCC1 gene polymorphism and breast cancer, studies that diagnosis of cancer was confirmed by a histopathological analysis, case-control or cohort studies published in official journals. All records were selected by two authors independently according to the inclusion criteria and reached consensus on each record.

The main reasons for exclusion of studies were: animal studies; duplicated publications; no control population; pure cell studies; the study only involved a case population; not concerned with carcinoma risk; and no usable data described. All records were chosen by all the authors independently according to the inclusion criteria and reached consensus on each record.

Data extraction

The data were abstracted according to a standard protocol. Studies that did not follow the inclusion criteria, those considered double publications, or those that provided inadequate data were excluded. If the same data appeared in different studies, the data were intended for use only once. The abstracted data comprised

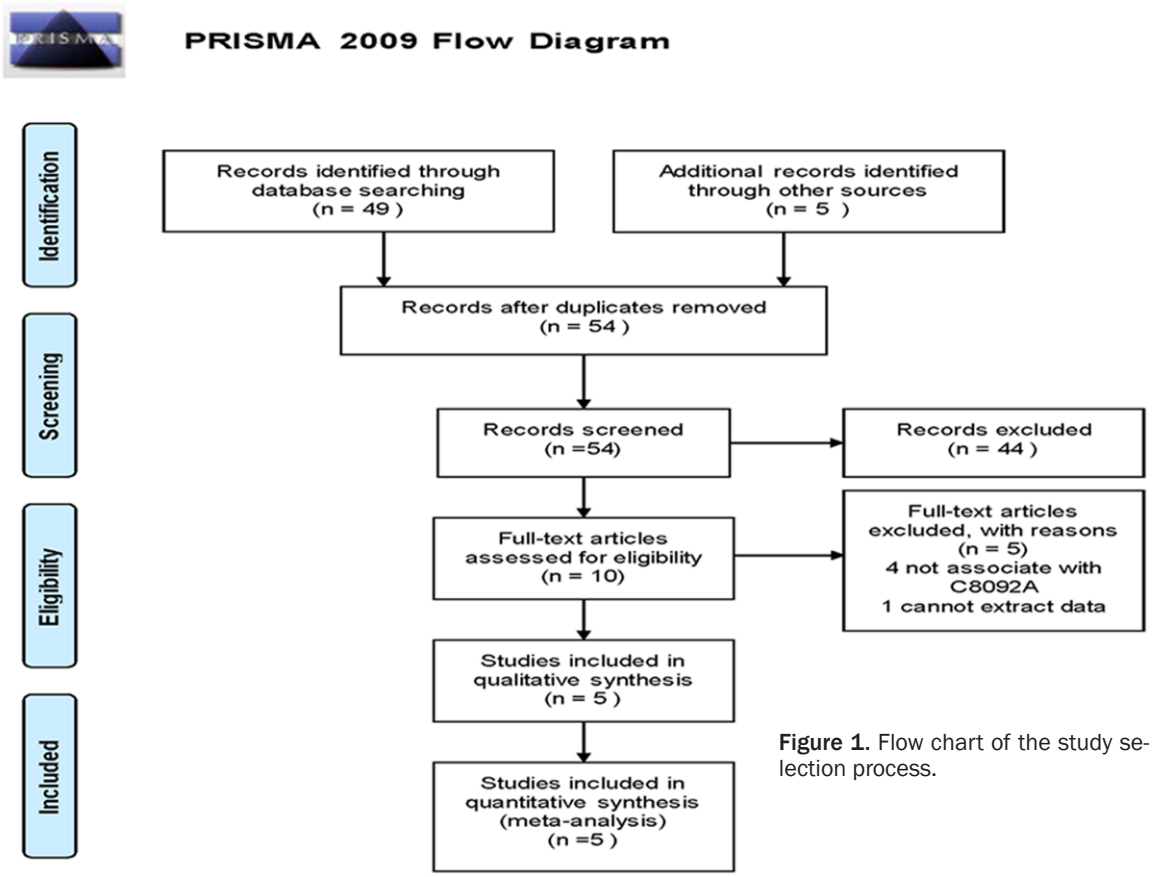

Figure 1. Flow chart of the study selection process.

the following items: the first author's name, publication year, region, the number of genotypes, genotyping, study design, total number of cases and controls and HWE.

Statistical analyses

STATA 12.0 software was utilized for performing the statistical analyses (Stata Corp, College Station, TX, USA). Five genetic models were used, including allelic (distribution of allelic frequency of the C8092A polymorphism in the ERCC1 gene, allelic model: A allele vs. C allele), homozygous (AA vs. CC), heterozygous (AC vs. CC) and recessive (AA vs. AC + CC) and dominant (AA + AC vs. CC) models [9]. The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were used to compare the association between the C8092A polymorphism in the ERCC1 gene and breast cancer. Chi-square-based Q-tests were used to calculate the heterogeneity between the individual studies with significance set at $P<0.05$ level [10]. The random-effect model was used to assess the pooled OR (Der Simonian and Laird method) if there was heterogeneity among the individual studies [11]. Otherwise, the fixed-effect model was used (the Mantel Haenszel method). The pooled OR was determined through Z test with significance set at $P<0.05$ level.

Fisher's exact test was used to evaluate the HWE, and significance was set at the $P<0.05$ level. The funnel plot was used to estimate the potential publication bias [12]. Egger's linear regression test on the natural logarithm scale of the OR was used to assess the funnel plot asymmetry with significance set at the $P<0.05$ level [13].

Results

Characteristics of eligible studies

Of the 54 articles that were initially identified in the search strategy, 44 articles were removed during the title/abstract review, and 5 articles [14-18] during the full-text review (**Figure 1**). Eight studies from five articles satisfied all of the criteria and were included in this report [6-8, 19, 20]. There were three studies of

Table 1. Characteristics of studies of the ERCC1 C8092A polymorphism included in this pooled analysis

Author	Year	Region	Ethnicity	Cases			Controls			Genotyping	Study design	Matching criteria	Sample size		HWE
				AA	CA	CC	AA	CA	CC				Case	Control	
Lee	2005	Korean	Asian	51	310	417	56	216	319	MALDI-TOF MS	Case-control	Age, BMI, Ethnicity	778	591	0.031
Shen	2006	USA	Caucasian	10	62	84	11	55	86	Taqman	Case-control	Age, BMI, Ethnicity	156	152	0.592
Crew	2007	USA	Caucasian	14	90	119	20	119	151	FP	Case-control	Age, ethnicity	223	290	0.597
Crew	2007	USA	Caucasian	45	251	340	30	258	356	FP	Case-control	Age, ethnicity	636	644	0.050
Crew	2007	USA	Caucasian	26	129	170	15	122	184	FP	Case-control	Age, ethnicity	325	321	0.355
Crew	2007	USA	Caucasian	19	122	170	15	136	172	FP	Case-control	Age, ethnicity	311	323	0.065
Yang	2013	China	Asian	48	177	236	45	189	270	MALDI-TOF MS	Case-control	Age, BMI, ethnicity	461	504	0.155
Pei	2014	China	Asian	60	161	197	40	155	222	MALDI-TOF MS	Case-control	Age, BMI, ethnicity	418	417	0.095

ERCC1: Excision Repair Cross-Complementation Group 1; BC: Breast carcinoma; PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; FP: Fluorescence Polarization; HWE: Hardy-Weinberg Equilibrium; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry; BMI: Body Mass Index.

Table 2. Meta-analysis of the association between the C8092A polymorphism in the ERCC1 gene and breast cancer risk

Polymorphism	Population	Number of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*P* value	Model	*P* value	I^2
A verse C	Asian	3	1.091	0.909-1.310	0.350	REM	0.064	63.6%
	Caucasian	5	1.084	0.972-1.209	0.146	REM	0.642	0.0%
	Overall	8	1.081	0.994-1.175	0.068	REM	0.331	12.7%
AA versus CC	Asian	3	1.121	0.668-1.881	0.665	REM	0.013	76.9%
	Caucasian	5	1.353	1.009-1.815	0.044	REM	0.516	0.0%
	Overall	8	1.213	0.926-1.589	0.160	REM	0.071	46.4%
AC versus CC	Asian	3	1.108	0.954-1.286	0.178	REM	0.904	0.0%
	Caucasian	5	1.021	0.887-1.176	0.772	REM	0.852	0.0%
	Overall	8	1.061	0.958-1.176	0.256	REM	0.950	0.0%
AA + AC versus CC	Asian	3	1.106	0.961-1.273	0.159	REM	0.430	0.0%
	Caucasian	5	1.060	0.925-1.214	0.401	REM	0.772	0.0%
	Overall	8	1.082	0.981-1.193	0.113	REM	0.816	0.0%
AA versus AC + CC	Asian	3	1.073	0.648-1.776	0.784	REM	0.012	77.3%
	Caucasian	5	1.339	1.004-1.785	0.047	REM	0.532	0.0%
	Overall	8	1.181	0.904-1.543	0.223	REM	0.060	48.3%

OR, odds ratio; CI, confidence interval; REM, random effects model.

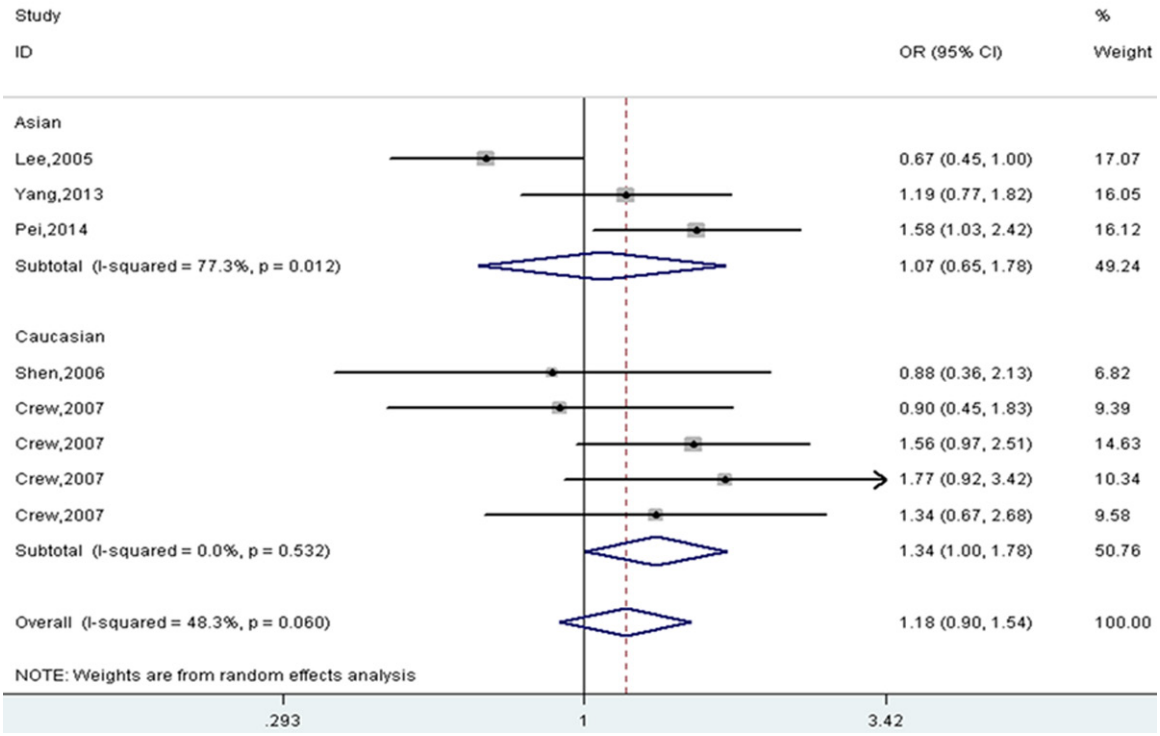

Figure 2. Forest plot of breast cancer associated with the C8092A polymorphism in the ERCC1 gene under a recessive genetic model.

Caucasians and two studies of Asians. The distribution of genotypes in the controls of all studies was in accord with HWE. The data were collected from 3,308 breast cancer cases and 3,242 controls in this meta-analysis (**Table 1**; **Figure 1**).

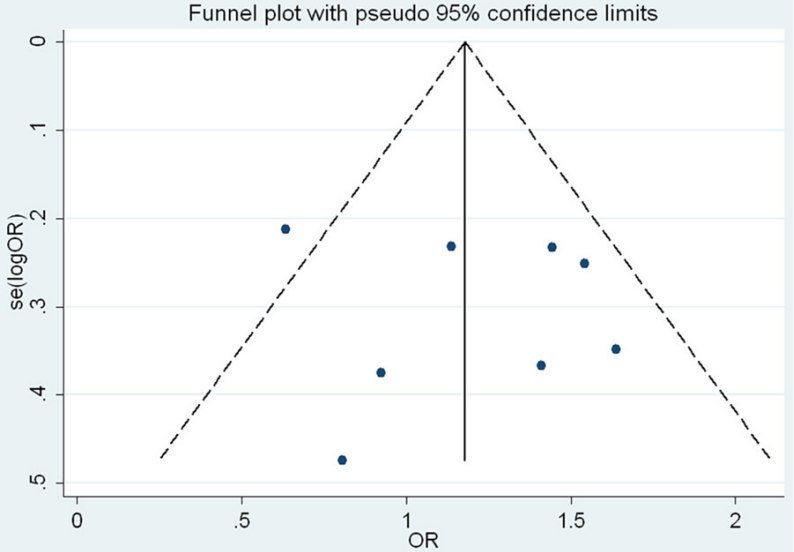

Figure 3. Funnel plot for studies of the association of breast cancer and the C8092A polymorphism in the ERCC1 gene.

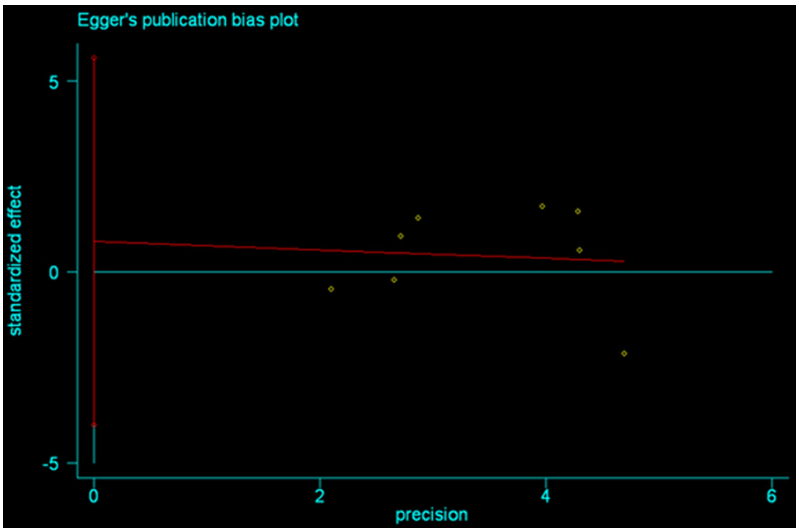

Figure 4. Egger's publication bias plot about studies of the association of breast cancer and the C8092A polymorphism in the ERCC1 gene.

Pooled analysis

No significant association was detected in an allelic genetic model (OR: 1.081, 95% CI: 0.994-1.175, P=0.068, $P_{heterogeneity}$=0.331), a homozygote model (OR: 1.213, 95% CI: 0.926-1.589, P=0.160, $P_{heterogeneity}$=0.071), a heterozygote model (OR: 1.061, 95% CI: 0.958-1.176, P=0.256, $P_{heterogeneity}$=0.950), a dominant genetic model (OR: 1.082, 95% CI: 0.981-1.193, P=0.113, $P_{heterogeneity}$=0.816) and a recessive genetic model (OR: 1.181, 95% CI: 0.904-1.543, P=0.223, $P_{heterogeneity}$=0.060) between the C8092A polymorphism in the ERCC1 gene and breast tumor as showed in **Table 2** and **Figure 2**.

A significant relationship between the C8092A polymorphism in the ERCC1 gene and breast tumor in Caucasian group was found in a homozygote genetic model (OR: 1.353, 95% CI: 1.009-1.815, P=0.044, Pheterogeneity=0.516) and a recessive genetic model (OR: 1.339, 95% CI: 1.004-1.785, P=0.047, $P_{heterogeneity}$=0.532). No significant association was detected in an allelic genetic model (OR: 1.084, 95% CI: 0.972-1.209, P=0.146, Pheterogeneity=0.642), a heterozygote model (OR: 1.108, 95% CI: 0.954-1.286, P=0.178, $P_{heterogeneity}$=0.904), and a dominant genetic model (OR: 1.106, 95% CI: 0.961-1.273, P=0.159, $P_{heterogeneity}$=0.430) between the C8092A polymorphism in the ERCC1 gene and breast tumor in Caucasian group as showed in **Table 2**.

In the Asian subgroup analysis, no significant association was detected in an allelic genetic model (OR: 1.091, 95% CI: 0.909-1.310, P=0.350, $P_{heterogeneity}$=0.064), homozygote model (OR: 1.121, 95% CI: 0.668-1.881, P=0.665, $P_{heterogeneity}$=0.013), a heterozygote model (OR: 1.108, 95% CI: 0.954-1.286, P=0.178, $P_{heterogeneity}$=0.904), a dominant genetic model (OR: 1.106, 95% CI: 0.961-1.273, P=0.159, $P_{heterogeneity}$=0.430) and a recessive genetic model (OR: 1.073, 95% CI: 0.648-1.776, P=0.784, $P_{heterogeneity}$=0.012) as shown in **Table 2**.

Bias diagnosis

The publication bias of the studies was evaluated using the funnel plot and Egger's test.

Publication bias was not seen in the funnel plot (**Figure 3**). No statistically significant difference was discovered in the Egger's test (P=0.698), indicating low publication bias in the current meta-analysis (**Figure 4**).

Discussion

No significant association was detected in an allelic genetic model (OR: 1.081, 95% CI: 0.994-1.175, P=0.068, $P_{heterogeneity}$=0.331), a homozygote model (OR: 1.213, 95% CI: 0.926-1.589, P=0.160, $P_{heterogeneity}$=0.071), a heterozygote model (OR: 1.061, 95% CI: 0.958-1.176, P=0.256, $P_{heterogeneity}$=0.950), a dominant genetic model (OR: 1.082, 95% CI: 0.981-1.193, P=0.113, $P_{heterogeneity}$=0.816) and a recessive genetic model (OR: 1.181, 95% CI: 0.904-1.543, P=0.223, $P_{heterogeneity}$=0.060) between the C8092A polymorphism in the ERCC1 gene and breast tumor.

A significant relationship between the C8092A polymorphism in the ERCC1 gene and breast tumor in Caucasian group was found in a homozygote genetic model (OR: 1.353, 95% CI: 1.009-1.815, P=0.044, $P_{heterogeneity}$=0.516) and a recessive genetic model (OR: 1.339, 95% CI: 1.004-1.785, P=0.047, $P_{heterogeneity}$=0.532). The present study suggested no significant association was observed between the C8092A polymorphism in the ERCC1 gene and breast cancer risk in all the group. However, in the subgroup analysis, Individuals with the C8092A polymorphism in the ERCC1 gene have a higher risk of breast cancer in Caucasians populations, but not in Asian populations. This result was the strength of this meta-analysis.

Cancer is an illness in which abnormal cells grow in an uncontrolled way. Breast cancer is a cancerous growth that begins in the tissues of the breast. Breast cancer is the most common cancer in women, but it can also appear in men. In the U.S., it affects one in eight women.

There is information about factors that we know increase the risk, including cancer genes, as well as information about the factors that possibly increase the risk [5, 21]. Like most cancers, the risk of developing breast cancer increases as women get older. Having a mother or sister suffered from breast cancer approximately doubles the risk of breast cancer. However, more than 8 out of 10 women who have a close relative with breast cancer will never develop it. If you have a very strong family history, there may be a faulty gene in your family that increases your risk of breast cancer. There are likely several gene faults that can increase breast cancer risk. We can test for them. The female sex hormone, oestrogen, and the male hormone, testosterone, can have an impact on the development of breast cancer. In 2003, researchers from Cancer Research UK looked at hormone replacement therapy (HRT) and the risk of breast cancer in more than a million women. They showed clearly that HRT increases the risk of breast cancer while women take it and for up to 5 years afterwards. Other studies have also confirmed this. The million women study also showed that combined HRT (oestrogen and progesterone) is the most likely to cause breast cancer than oestrogen only HRT. Other risk factor including the contraceptive pill, having children or having them early in life, When you start and stop having periods, Ethnic group, A previous breast cancer, ductal carcinoma in situ or lobular carcinoma in situ, Benign breast disease, Having dense breast tissue, Alcohol intake and smoking, Your weight and height, Chest X-rays or radiotherapy, Diabetes, Medicines, Shift work, and so on [22].

Commonly occurring single nucleotide polymorphisms (SNPs) have been demonstrated to incrementally contribute to breast cancer risk. Although the effect of an individual SNP is generally small, the genetic effect of combinations of functionally relevant SNPs may additively or synergistically contribute to increased breast cancer risk. It is reported that ERCC1 is the rate-limiting member of the nucleotide excision repair pathway (NER), one of at least 5 overlapping biochemical pathways by which altered DNA sequences can be restored to base-line. Abrogation of these pathways has been both associated with carcinogenesis, and targeted as a therapeutic mechanism. The NER pathway functions to remove bulky DNA lesions, including tobacco-associated adducts formed by carcinogen exposure. Mechanisms of platinum cytotoxicity include forming bulky DNA adducts leading to both inter-and intrastrand cross-link generation, which results in apoptosis unless repaired. The critical role of ERCC1 in carcinogen and platinum adduct removal by NER has led to a number of studies reporting the rela-

tionship between ERCC1 status and survival in some cancers. In recent study, a current meta-analysis provides additional evidence supporting the hypothesis that the ERCC1 C8092A may be associated with increased adult glioma risk in Asians. ERCC1 C8092A can probably be used with other genetic markers together to identify individuals at a high risk of developing adult glioma. Whether ERCC1 is associated with breast cancer? The results of individual studies remain controversial. Here we will discuss the C8092A polymorphism in the ERCC1 and breast carcinoma risk. Overall, a significant association exists between the C8092A polymorphism in the ERCC1 gene and breast carcinoma risk. This finding indicates that the genetic variant in AURKA gene exon3 may crucially modify the susceptibility of cancers [23].

Meta-analysis is a retrospective research that is subject to the methodological deficiencies of the included studies and numerous specific details merit consideration in the current meta-analysis. A foremost consideration is that our results are based on unadjusted estimates and a more precise analysis stratified by different lifestyle related habits and different grades of breast cancer could be performed if individual data were available. A second consideration is that large-scale studies on the relationship between the C8092A polymorphism in the ERCC1 gene and breast cancer risk are still incompetent. AURKA is affected not only by gene polymorphism, but also by environmental factors. A third consideration is that all recruited case-control studies were from Asians and Caucasians; thus, our results may only be suitable for these populations. Considering the complexity of cancer etiology and the low penetrance cancer susceptibility gene effects from the C8092A polymorphism in the ERCC1 gene, these crucial environmental factors should not be ignored.

Nevertheless, the total number of subjects contained in the contemporary part of the analysis comprises the largest sample size so far. Finally, as with any meta-analysis of published results, the quality of our meta-analysis is dependent upon that of the individual studies. Ideally we would want to pool individual level data. However, this is not feasible in the present study. These considerations may distort our results.

Statistical surveys in America and England have shown that white women have a higher risk of breast cancer than women from other ethnic groups. This is at least partly due to lifestyle factors. To our surprise, the Ile/Ile homozygote frequency (rs2273535) in the Asian group in an allelic genetic model (OR: 1.124, 95% CI: 1.003-1.29, P=0.044, $P_{heterogeneity}$= 0.034) is much higher than in the control subjects, and also much higher than in Caucasian women in an allelic genetic model (OR: 1.047, 95% CI: 0.959-1.145, P=0.305, $P_{heterogeneity}$= 0.013), indicating that individuals with the C8092A polymorphism in the ERCC1 gene have a higher risk of breast cancer in Asian populations, but not in Caucasians.

To conclude, our meta-analysis demonstrated an association between the C8092A polymorphism in the ERCC1 gene and breast cancer risk. However, reserchers need to investigate gene-gene and gene-environment interactions on the C8092A polymorphism in the ERCC1 gene and breast cancer risk with large-scale and well-designed studies, which may eventually lead to better comprehensive understanding of the possible roles in tumorigenesis.

Disclosure of conflict of interest

None.

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