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EPIDEMIOLOGY

The hOGG1 Ser326Cys polymorphism and breast cancer risk: a meta-analysis

Weiguang Yuan · Lidan Xu · Yuanxi Feng · Yue Yang · Wangyang Chen · Jingwei Wang · Da Pang · Dianjun Li

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Abstract It was reported that the functional polymorphism Ser326Cys in the human 8-oxoguanine DNA glycosylase gene was associated with breast cancer risk; however, the published studies have inconsistent conclusions. To elucidate the effect of hOGG1 Ser326Cys on the susceptibility to breast cancer, all available studies were collected in this meta-analysis. We extracted the data from 10 case–control studies that were published in the PubMed database from 2003 to 2008 using the search phrases "human 8-oxoguanine DNA glycosylase, hOGG1, OGG1, OGG, polymorphism, genetic variation, and breast cancer." This meta-analysis included 4,963 breast cancer cases and 4,776 control subjects. The results showed that individuals who carrying the hOGG1 326Cys allele in the additive model did not have significantly increased risk of breast cancer compared with those carrying the 326Ser allele ($P = 0.47$, OR = 1.02; 95% CI = 0.96–1.09); similarly, no significant association between the hOGG1 326Cys allele and breast cancer risk was found either in the recessive genetic model ($P = 0.34$, OR = 1.06; 95% CI = 0.94–1.18) for Cys/Cys versus Ser/Cys + Ser/Ser, or dominant genetic model ($P = 0.78$, OR = 1.01; 95% CI = 0.93–1.11) for Cys/Cys + Ser/Cys versus Ser/Ser. In the stratified analysis, the meta-analysis showed the association between hOGG1 326Cys allele in the additive model and breast cancer was significant in European subjects ($P = 0.04$, OR = 0.71; 95% CI = 0.51–0.98), and dominant genetic model ($P = 0.004$, OR = 0.44; 95% CI = 0.25–0.77). However, the association was not significant between this polymorphism and different menopausal status (premenopausal and postmenopausal) and the other ethnicities (Asians and Americans). The meta-analysis suggested that the hOGG1 326Cys allele plays a significant protective effect to breast cancer in European women.

Keywords hOGG1 · SNP · Breast cancer · Meta-analysis

Weiguang Yuan and Lidan Xu contributed equally to this work.

W. Yuan · Y. Yang · W. Chen · J. Wang · D. Pang (✉) · D. Li (✉)
Institute of Cancer Prevention and Treatment, Harbin Medical University, Baojian Road 6, Nangang District, 150081 Harbin, China
e-mail: pangdasir@163.com

D. Li
e-mail: dianjunli@163.com

W. Yuan · D. Li
Department of Immunology, Harbin Medical University, 150081 Harbin, China

L. Xu
Laboratory of Medical Genetics, Harbin Medical University, 150081 Harbin, China

Y. Feng
Department of Medical Oncology, The Third Affiliated Hospital of Harbin Medical University, 150081 Harbin, China

D. Pang
Department of Surgery, The Third Affiliated Hospital of Harbin Medical University, 150081 Harbin, China

Introduction

DNA damage plays an important role in the process of tumor generation and development. The base excision repair (BER) pathway, which was composed by many DNA repair genes, mainly removes DNA damage caused by ionizing radiation and reactive oxidative species [1]. Some polymorphisms in these DNA repair genes may

influent the ability of repairing damaged DNA and lead to the genetic instability and carcinogenesis [2].

The human 8-oxoguanine DNA glycosylase (hOGG1) gene, as a component of the BER pathway, is located on chromosome 3p26 and encodes the 8-oxoguanine DNA glycosylase. It is a key enzyme in the repair of 8-oxoguanine [3] and the removal of 8-oxodeoxyguanosine, which is one of the most common forms generated by oxidative stress and highly mutagenic [4].

Among many polymorphisms of the hOGG1 gene, the common functional polymorphism (Ser326Cys) was a hotspot in many studies. It is an amino acid substitution from serine (Ser) to cysteine (Cys) in exon 7 of the hOGG1 gene (rs1052133) [5, 6]. The functional studies showed that the 326Cys allele was associated with the reduced DNA repair activity [5], and increased the cancer risk, such as breast cancer [7], colon cancer [8], esophageal cancer [9], and lung cancer [10–12].

Breast cancer is one of the most frequently diagnosed cancers in women [13], and the mortality rate was high in the worldwide women [14, 15]. It is well-established that breast cancer was induced by many endogenous and exogenous factors, such as the level of hormone, the capacity to repair damaged DNA, and different genetic background [16]. Many studies have revealed the association between hOGG1 Ser326Cys polymorphism and breast cancer risk. However, these results was conflicting, including an increased risk for breast cancer [1], a reduced risk [17], and other studies [4, 7, 18–21].

To draw a conclusive result, a meta-analysis was performed to evaluate the association between hOGG1 Ser326Cys polymorphism and breast cancer risk. The stratified analysis was performed to examine the interaction between hOGG1 Ser326Cys polymorphism and breast cancer risk in different menopausal status and different ethnicities in this meta-analysis.

Materials and methods

Study identification and selection

To identify all articles that examined the association between hOGG1 Ser326Cys polymorphism and breast cancer risk, we conducted a literature search in the PubMed database (before 27 June, 2009) using the terms including human 8-oxoguanine DNA glycosylase, hOGG1, OGG1, OGG, polymorphism, genetic variation, and breast cancer. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis. The references cited in all studies were also reviewed to identify additional published work, which was not indexed by PubMed database. Conference abstracts, case reports, editorials, review articles, and letters were excluded. Studies included in this meta-analysis had to meet the following criteria: an unrelated case–control design was used, and genotype frequency was available.

Data extraction

The following information was extracted from each literature: first author, year of publication, country of study population, genotyping method, genotype frequency, and the design of experiment for hOGG1 Ser326Cys polymorphism.

Statistical analysis

This meta-analysis evaluated the overall association between hOGG1 Ser326Cys and the risk of breast cancer, including the additive model (326Cys allele versus 326Ser allele), which means the additive effect of having one additional copy of the 326Cys allele (model includes a variable with three levels—having 0, 1, or 2 copies of the 326Cys allele), the homozygote contrast (Cys/Cys versus Ser/Ser), the recessive genetic (Cys/Cys versus Cys/Ser + Ser/Ser) and the dominant model (Cys/Cys + Cys/Ser versus Ser/Ser). The effect of association was indicated as odds ratio (OR) with the corresponding 95% confidence interval (CI). The combined OR was estimated using fixed effects (FE) models (Mantel–Haenszel) and random-effects (RE) models (DerSimonian and Laird) [22]. The heterogeneity between these studies was tested by Q statistic [23], and it was considered statistically significant with $P < 0.10$. The heterogeneity was quantified by I^2 metric, which is independent of the number of studies in the meta-analysis ($I^2 < 25\%$ no heterogeneity; $I^2 = 25$–50% moderate heterogeneity; $I^2 > 50\%$ extreme heterogeneity) [24]. Publication bias was investigated by funnel plot, which was assessed by Egger's linear regression test [25]. The significant of asymmetry was determined by t test and $P < 0.05$ was considered a significant publication bias.

Hardy–Weinberg equilibrium (HWE) was tested by the Chi-square test. Meta-analysis was performed using the Review Manager 5.0 software.

Results

Eligible studies

The studies focusing on the association between hOGG1 Ser326Cys polymorphism and breast cancer risk were selected. In a total of 13 retrieved studies, only nine articles

met the inclusion criteria, which had a case–control design and available genotype frequency. Among the nine studies, two populations (Korean and Japanese) were included in one study [7], so we divided the relevant data into two studies. In Vogel et al's study, they only provide the data of the postmenopausal women, and the study was still included in this meta-analysis. In all studies, the cases were histologically confirmed and the controls were free of breast cancer and were matched for age and gender.

In the ten eligible studies, five studies provided the data of premenopausal women, and six data of postmenopausal women. First, these studies were treated as a mixed study, and then they were analyzed for different menopausal status.

These studies were conducted in different populations of various ethnicities: three studies were involved in the European populations [17, 20, 26], four studies were involved in the Asian populations [1, 7, 18, 19], and two studies were involved in the American populations [4, 21]. The subgroup analysis for different ethnicities (Asians, Americans, and Europeans) was conducted in this meta-analysis.

Summary statistics

A total of 4,963 cases and 4,776 controls for hOGG1 Ser326Cys polymorphism were included in this study. Details of the cases and controls were listed in Table 1. Frequencies of genotype and allele were shown in Table 2. The frequency of 326Cys allele was 38.34 and 39.40% in case and control, respectively. Distribution of genotype and allele in different menopausal status (premenopausal and postmenopausal) was shown in Tables 3 and 4. Among the premenopausal women, the 326Cys allele frequency was 45.51 and 46.79% in case and control, respectively. Among postmenopausal women, the frequency of 326Cys allele was 35.30 and 35.70% in case and control, respectively. All the studies were in HWE ($P > 0.05$).

Main results of allele and subgroup analysis

To summarize the published data, we did a comprehensive meta-analysis. The data was extracted from ten case–control studies which were published in the PubMed database. The meta-analysis included 4,963 breast cancer cases and 4,776 control subjects. The heterogeneity results and the effect of the association between hOGG1 326Cys polymorphism and breast cancer risk were shown in Table 5. There was no heterogeneity among these studies ($I^2 = 40\%$, $P_{\text{heterogeneity}} = 0.10$).

The overall results showed that the individuals who carrying Cys/Cys genotype did not significantly increased breast cancer risk ($P = 0.44$, OR = 1.06; 95% CI = 0.92–1.21) compared with those who carrying the Ser/Ser genotype; similarly, no significant association was found in the recessive genetic model ($P = 0.34$, OR = 1.06; 95% CI = 0.94–1.18), and dominant genetic model ($P = 0.78$, OR = 1.01; 95% CI = 0.93–1.11) (Table 5). Then, the ten studies were analyzed by stratified based on menopausal status and ethnicity. In the stratified analyses of menopausal status, no significant association was found between hOGG1 326Cys allele in the additive model and breast cancer risk among both premenopausal women ($P = 0.34$, OR = 1.06; 95% CI = 0.94–1.18) and postmenopausal women ($P = 0.29$, OR = 1.05; 95% CI = 0.96–1.16) (Table 5). In the subgroup analysis of ethnicity, the association was significant between the hOGG1 326Cys allele in the additive model and the breast cancer risk in European subjects ($P = 0.04$, OR = 0.71; 95% CI = 0.51–0.98). The similar result was found in the homozygote contrast ($P = 0.03$, OR = 0.49; 95% CI = 0.26–0.94) and the dominant model ($P = 0.004$, OR = 0.44; 95%

Table 1 Characteristics of included studies in the meta-analysis

First author	Country	Genotyping method	Cases (age)	Controls (age)	Design of experiment
Cai [18]	China	TaqMan	$N = 1102$ (25–64 years)	$N = 1167$ (age frequency-matched controls)	Population-based
Choi [7]	Korea	PCR-RFLP	$N = 271$(NA)	$N = 314$ (NA)	Hospital-based
Choi [7]	Japan	PCR-CTTP	$N = 204$ (≤70 years)	$N = 186$ (frequency-matched controls)	Hospital-based
Huang [19]	Taiwan	PCR-RFLP	$N = 136$ (35–80 years)	$N = 232$ (frequency-matched controls)	Hospital-based
Romanowicz-Makowska [20]	Poland	PCR-RFLP	$N = 100$ (54–82 years, median age 58 years)	$N = 106$ (age-matched healthy women)	NA
Rossner [4]	USA	FP-TDI[a]	$N = 1058$ (NA)	$N = 1102$ (< 65 years of age)	Population-based
Sangrajrang [1]	Thailand	Capillary PCR	$N = 506$ (48.0 ± 10.0)	$N = 424$ (45.3 ± 12.2)	Hospital-based
Synowiec [17]	Poland	PCR-RFLP	$N = 41$ (mean age 58 years)	$N = 48$ (age-matched healthy women)	NA
Vogel [26]	Denmark	Real-time PCR	$N = 425$ (50–64 years)	$N = 434$ (age-matched healthy women)	Hospital-based
Zhang [21]	USA	TaqMan	$N = 1571$ (20–74 years)	$N = 1244$ (20–64 years and 65–74 years)	Population-based

[a] Template-directed primer extension and detection by fluorescence polarization

Table 2 Distribution of the frequencies of hOGG1 Ser326Cys genotype and allele

First author (year)	Genotype						Allele				HWE (P)
	Cases *n* (%)			Controls *n* (%)			Cases *n* (%)		Controls *n* (%)		
	Ser/Ser	Ser/Cys	Cys/Cys	Ser/Ser	Ser/Cys	Cys/Cys	Ser	Cys	Ser	Cys	
Cai (2006) [18]	186 (16.88)	534 (48.46)	382 (34.66)	214 (18.34)	537 (46.02)	416 (35.65)	906 (41.11)	1298 (58.89)	965 (41.35)	1369 (58.65)	0.07
Choi (2003) [7]	48 (18.11)	132 (49.81)	85 (32.08)	49 (17.25)	155 (54.58)	80 (28.17)	228 (43.02)	302 (56.98)	253 (44.54)	315 (55.46)	0.07
Choi (2003) [7]	57 (28.36)	95 (47.26)	49 (24.38)	62 (33.70)	89 (48.37)	33 (17.93)	209 (51.99)	193 (48.01)	213 (57.88)	155 (42.12)	0.91
Huang (2004) [19]	25 (18.38)	63 (46.32)	48 (35.29)	38 (16.38)	106 (45.69)	88 (37.93)	113 (41.54)	159 (58.46)	182 (39.22)	282 (60.78)	0.53
Romanowicz-Makowska (2008) [20]	32 (32.00)	34 (34.00)	34 (34.00)	20 (18.87)	52 (49.06)	34 (32.08)	98 (49.00)	102 (51.00)	92 (43.40)	120 (56.60)	0.99
Rossner (2006) [4]	615 (59.08)	375 (36.02)	51 (4.90)	653 (59.74)	385 (35.22)	55 (5.03)	1605 (77.09)	477 (22.91)	1691 (77.36)	495 (22.64)	0.85
Sangrajrang (2008) [1]	112 (22.13)	232 (45.85)	162 (32.02)	104 (24.52)	217 (51.18)	103 (24.29)	456 (45.06)	556 (54.94)	425 (50.12)	423 (49.88)	0.63
Synowiec (2008) [17]	10 (24.39)	19 (46.34)	12 (29.27)	4 (8.33)	23 (47.92)	21 (43.75)	39 (47.56)	43 (52.44)	31 (32.30)	65 (67.71)	0.51
Zhang (2006) [21]	967 (61.55)	532 (33.86)	72 (4.58)	760 (61.09)	424 (34.08)	60 (4.82)	2466 (78.49)	676 (21.52)	1944 (78.14)	544 (21.87)	0.93
Total	2052 (41.35)	2016 (40.62)	895 (18.03)	1904 (39.82)	1988 (41.57)	890 (18.61)	6120 (61.66)	3806 (38.34)	5796 (60.60)	3768 (39.40)	

Table 3 Distribution of the frequencies of hOGG1 Ser326Cys genotype and allele among premenopausal women

First author (year)	Genotype						Allele			
	Cases *n* (%)			Controls *n* (%)			Cases *n* (%)		Controls *n* (%)	
	Ser/Ser	Ser/Cys	Cys/Cys	Ser/Ser	Ser/Cys	Cys/Cys	Ser	Cys	Ser	Cys
Cai (2006) [18]	130 (17.76)	347 (47.40)	255 (34.84)	138 (18.40)	344 (45.87)	268 (35.73)	607 (41.46)	857 (58.54)	620 (41.33)	880 (58.67)
Choi (2003) [7]	28 (15.38)	98 (53.85)	56 (30.77)	27 (15.79)	95 (55.56)	49 (28.66)	154 (42.31)	210 (57.69)	149 (43.57)	193 (56.43)
Choi (2003) [7]	30 (27.78)	51 (47.22)	27 (25.00)	24 (33.80)	37 (52.11)	10 (14.08)	111 (51.39)	105 (48.61)	85 (59.86)	57 (40.14)
Sangrajrang (2008) [1]	59 (22.01)	125 (46.64)	84 (31.34)	59 (24.08)	120 (48.98)	66 (26.94)	243 (45.34)	293 (54.66)	238 (48.57)	252 (51.43)
Zhang (2006) [21]	373 (61.86)	202 (33.50)	28 (4.64)	278 (62.33)	143 (32.06)	25 (5.61)	948 (78.61)	258 (21.39)	699 (78.36)	193 (21.64)
Total	620 (32.75)	823 (43.48)	450 (23.77)	526 (31.25)	739 (43.91)	418 (24.84)	2063 (54.49)	1723 (45.51)	1791 (53.21)	1575 (46.79)

Table 4 Distribution of the frequencies of hOGG1 Ser326Cys genotype and allele among postmenopausal women

First author (year)	Genotype						Allele			
	Cases *n* (%)			Controls *n* (%)			Cases *n* (%)		Controls *n* (%)	
	Ser/Ser	Ser/Cys	Cys/Cys	Ser/Ser	Ser/Cys	Cys/Cys	Ser	Cys	Ser	Cys
Cai (2006) [18]	54 (14.75)	186 (50.82)	126 (34.43)	74 (17.92)	191 (46.25)	148 (35.84)	294 (40.16)	438 (59.84)	339 (41.04)	487 (58.96)
Choi (2003) [7]	20 (24.10)	34 (40.96)	29 (34.94)	22 (19.82)	58 (52.25)	31 (27.93)	74 (44.58)	92 (55.42)	102 (45.95)	120 (54.05)
Choi (2003) [7]	27 (29.03)	44 (47.31)	22 (23.66)	38 (33.63)	52 (46.02)	23 (20.35)	98 (52.69)	88 (47.31)	128 (56.64)	98 (43.36)
Sangrajrang (2008) [1]	53 (22.27)	107 (44.96)	78 (32.77)	45 (25.14)	97 (54.19)	37 (20.67)	213 (44.75)	263 (55.25)	187 (52.23)	171(47.77)
Vogel (2003) [26]	256 (60.23)	147 (34.59)	22 (5.18)	245 (56.45)	169 (38.94)	20 (4.61)	659 (77.53)	191 (22.47)	659 (75.92)	209 (24.08)
Zhang (2006) [21]	516 (59.79)	306 (35.46)	41 (4.75)	422 (60.20)	250 (35.66)	29 (4.14)	1338 (77.52)	388 (22.48)	1094 (78.03)	308 (21.97)
Total	1852 (44.78)	1648 (39.85)	636 (15.38)	1692 (43.36)	1634 (41.88)	576 (14.76)	5352 (64.70)	2920 (35.30)	5018 (64.30)	2786 (35.70)

CI = 0.25–0.77). However, no significantly increased risk was found among Asian subjects ($P = 0.05$, OR = 1.09; 95% CI = 1.00–1.18) and American subjects ($P = 0.92$, OR = 1.00; 95% CI = 0.90–1.09) for the additive model (326Cys allele vs. 326Ser allele). The meta-analysis suggested that the hOGG1 326Cys allele plays an important role in the protective effect to breast cancer in European women (Tables 6, 7).

Sensitivity analysis

Sensitivity analysis was performed both by sequential remove (statistics of study remove) of individual studies and cumulative statistics under all comparisons in worldwide subjects and subgroups, respectively. The combined ORs of hOGG1 Ser326Cys polymorphism was not influenced by any individual study and it did not changed by removing any individual study on different menopausal status and different ethnicity.

Publication bias

Funnel plots and Egger's test were performed to assess the publication bias. The data suggested that there was no evidence of publication bias in hOGG1 Ser326Cys polymorphism ($t = 0.86$, $P = 0.420$) (data not shown).

Discussion

The previous study has conflicting results about the association between hOGG1 326Cys allele and the risk of breast cancer, which might be influenced by relatively small sample size and different genetic background. Meta-analysis is a powerful method for resolving inconsistent finding with a relatively large number of subjects. In this study, we analyzed the data from ten available case–control studies to evaluate the role of hOGG1 Ser326Cys polymorphism in relation to breast cancer risk, and its interaction with menopausal status and ethnic heterogeneity. After an analysis for combined data, we found that the association between hOGG1 Ser326Cys polymorphism and breast cancer was significant in European women and the hOGG1 326Cys allele in the additive model was associated with the decreased susceptibility to breast cancer in this population.

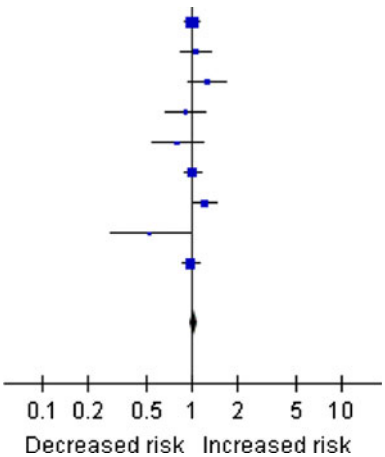
In this study, heterogeneity in the studies of hOGG1 Ser326Cys polymorphism were not significant ($I^2 = 40\%$, $P_{\text{heterogeneity}} = 0.10$). Publication bias was not observed ($t = 0.86$, $P = 0.420$). Moreover, sensitivity analysis conducted by removed and cumulative statistics have showed combined ORs of hOGG1 Ser326Cys polymorphism were not influenced by any individual study under

Table 5 The ORs of hOGG1 Ser326Cy polymorphism, ethnicity and menopausal status with breast cancer

Allele and genotype	Populations	OR	I^2 (%)	$P_{heterogeneity}$	P
326Cys allele (an additive model)	All populations	1.02 (0.96–1.09)	40	0.10	0.47
	American populations	1.00 (0.90–1.09)	0	0.71	0.92
	European populations	**0.71 (0.51–0.98)**	22	0.26	**0.04**
	Asian populations	1.09 (1.00–1.18)	7	0.37	0.05
	Premenopausal women	1.06 (0.94–1.18)	0	0.43	0.34
	Postmenopausal women	1.05 (0.96–1.16)	1	0.41	0.29
Cys/Cys versus Ser/Ser (homozygote contrast)	All populations	1.06 (0.92–1.21)	39	0.11	0.44
	American populations	1.00 (0.90–1.09)	0	0.71	0.92
	European populations	**0.49 (0.26–0.94)**	39	0.20	**0.03**
	Asian populations	1.16 (0.98–1.38)	14	0.33	0.09
	Premenopausal women	1.08 (0.88–1.34)	0	0.45	0.45
	Postmenopausal women	1.24 (0.98–1.56)	0	0.80	0.07
Cys/Cys versus Cys/Ser + Ser/Ser (recessive genetic model)	All populations	1.06 (0.94–1.18)	32	0.16	0.34
	American populations	1.00 (0.90–1.09)	0	0.71	0.92
	European populations	0.88 (0.54–1.42)	44	0.18	0.59
	Asian populations	1.09 (0.96–1.24)	54	0.07	0.17
	Premenopausal women	1.04 (0.89–1.23)	17	0.31	0.60
	Postmenopausal women	1.18 (0.98–1.42)	24	0.25	0.08
Cys/Cys + Cys/Ser versus Ser/Ser (dominant genetic model)	All populations	1.01 (0.93–1.11)	32	0.16	0.78
	American populations	1.00 (0.90–1.09)	0	0.71	0.92
	European populations	**0.44 (0.25–0.77)**	0	0.43	**0.004**
	Asian populations	1.10 (0.94–1.27)	0	0.79	0.23
	Premenopausal women	1.06 (0.91–1.24)	0	0.96	0.47
	Postmenopausal women	1.01 (0.89–1.16)	0	0.53	0.84

Table 6 Overall meta-analysis for 326Cys allele in the additive model in breast cancer risk

First author	Case		Control		Weight (%)	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total			
Cai [18]	1,298	2,204	1,369	2,334	27.5	1.01 (0.90, 1.14)	
Choi [7]	302	530	315	568	6.6	1.06 (0.84, 1.35)	
Choi [7]	193	402	155	368	4.2	1.27 (0.95, 1.69)	
Huang [19]	159	272	282	464	4.4	0.91 (0.67, 1.23)	
Romanowicz-Makowska [20]	102	200	120	212	2.9	0.80 (0.54, 1.18)	
Rossner [4]	477	2,082	495	2,186	18.7	1.02 (0.88, 1.17)	
Sangrajrang [1]	556	1,012	423	848	10.4	1.23 (1.02, 1.47)	
Synowiec [17]	43	82	65	96	1.4	0.53 (0.29, 0.97)	
Zhang [21]	676	3,142	544	2,488	23.9	0.98 (0.86, 1.11)	
Total (95% CI)		9,926		9,564	100.0	1.02 (0.96, 1.09)	
Total events	3,806		3,768				

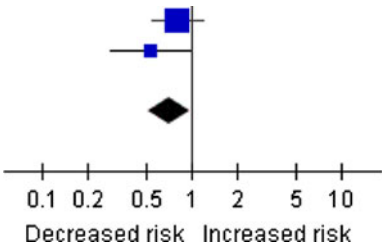


Heterogeneity: $\chi^2 = 13.28$, df = 8 ($P = 0.10$); $I^2 = 40\%$

Test for overall effect: $Z = 0.73$ ($P = 0.47$)

Table 7 Overall meta-analysis for 326Cys allele in the additive model in breast cancer risk in European women

First author	Case		Control		Weight (%)	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total			
Romanowicz-Makowska [20]	102	200	120	212	66.7	0.80 (0.54,1.18)	
Synowiec [17]	43	82	65	96	33.3	0.53 (0.29, 0.97)	
Total (95% CI)		282		308	100.0	0.71 (0.51, 0.98)	
Total events	145		185				



Heterogeneity: $\chi^2 = 1.28$, df $= 1(P = 0.26)$; $I^2 = 22\%$
Test for overall effect: $Z = 2.08$ $(P = 0.04)$

all comparisons in worldwide subjects and subgroups. It showed that the results of our meta-analysis are relatively reliable.

Epidemiological studies revealed that many factors were included in the pathology of breast cancer. The level of hormones is the major risk factor for breast cancer [27, 28]. In the published studies, one study has showed an significantly increased risk in dominant genetic model of the hOGG1 Ser326Cys of postmenopausal women [1], the other studies provided inconsistent results [7, 18, 21, 26]. So, the different menopausal status was considered in the stratified analysis. Our combined results showed that hOGG1 Ser326Cys polymorphism was not associated with breast cancer risk in both premenopausal and postmenopausal women. It was well known that the mechanism of the generation and development of breast cancer was complex. We presumed that the pathway of hormone and hOGG1 Ser326Cys polymorphism may be not consistent and the interaction was weak between hormone level and gene polymorphism.

The genetic heterogeneity plays an important role in the pathology of disease. The carcinogenesis of breast cancer is an interaction between environment factors and genetic background. The different ethnicities and environmental exposures may have influence the susceptibility to diseases [29].To clarify the association between the hOGG1 Ser326Cys polymorphism and breast cancer in different genetic background, the subgroups analysis was performed. Our results showed that the association was significant between the hOGG1 326Cys allele and breast cancer risk in Europeans, and the 326Cys allele play a protective effect on the carcinogenesis of breast cancer among them. Nevertheless, Functional studies in the previous study have showed that the 326Cys allele might associate with increased cancer risk [30]. The discrepancy might due to the small sample size in some studies, which are underpowered to detect a slight effect. Second, the genotyping method and the design of experiment in the included studies were different. Another possible reason is that the real function of the Ser326Cys polymorphism is unclear, and it may play an effect only under special conditions of cellular oxidative stress [31]. Therefore, the results of this study should be interpreted with caution. A meta-analysis of the hOGG1 Ser326Cys polymorphism for lung cancer risk has showed that the 326Cys allele significantly increased the risk in Asian populations in dominant genetic model [29]. It suggested that the different tumors involves different pathological pathways and target gene.

In summary, we demonstrated that the hOGG1 Ser326Cys polymorphism is significantly associated with breast cancer in European women, and the 326Cys allele play a protective role in the carcinogenesis of breast cancer.

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