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RESEARCH ARTICLE

Association of *OGG1* Ser326Cys polymorphism and pancreatic cancer susceptibility: evidence from a meta-analysis

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Abstract The 8-oxoguanine DNA glycosylase (*OGG1*) gene has been considered to be associated with cancer susceptibility. The *OGG1* Ser326Cys polymorphism has been reported to be associated with pancreatic cancer (PC), but the published studies have yielded inconsistent results. For better understanding of the effect of *OGG1* Ser326Cys polymorphism on PC susceptibility, a meta-analysis was performed. All eligible studies were identified through a search of PubMed, Excerpta Medica Database (Embase), Elsevier Science Direct, and Chinese Biomedical Literature Database before May 2013. The association between the *OGG1* Ser326Cys polymorphism and PC risk was conducted by odds ratios (ORs) and 95 % confidence intervals (CIs). A total of five case–control studies with 1,690 cases and 3,650 controls were eventually collected. Overall, we found that *OGG1* Ser326Cys polymorphism was not associated with PC susceptibility (Cys/Cys vs. Ser/Ser: OR=0.95, 95 % CI=0.80–1.14; Cys/Cys vs. Ser/Ser+Ser/Cys: OR=0.95, 95 % CI=0.78–1.14; Cys/Cys+Ser/Cys vs. Ser/Ser (OR=1.00, 95 % CI=0.89–1.12)). In the subgroup analysis based on ethnicity, source of control, sample size, and genotyping method, no significant association was found in any genetic models. This meta-analysis suggests that the *OGG1* Ser326Cys polymorphism may not associated with PC susceptibility. Considering the limited sample size and ethnicity included in the meta-analysis, further larger scaled and well-designed studies are needed to confirm our results.

Keywords *OGG1* · Pancreatic cancer · Polymorphism · Meta-analysis

Introduction

Pancreatic cancer (PC) is one of the most fatal malignant tumors among human; although infrequent, it takes up 3 % of all reported cases of cancer and it is the fourth most common cause of cancer-related deaths in the USA and the eighth worldwide [1–3]. What was worse, the prognosis of PC is very poor; the 5-year survival rate is less than 5 % even with the surgical and chemotherapy intervention. There were 44,000 new cases diagnosed and 37,000 deaths from PC in 2012 [4–6]. The situation has not significantly changed over the past several decades [7]. It is extremely important for us to find more effective methods to treat PC. So, having a good knowledge of the molecular basis of PC is necessary [8, 9]. A large number of studies have been carried out to explore potential risk factors of PC. Several factors have been considered as risk factors, such as diabetes [9], heavy alcohol consumption [10], smoking [11], and sucrose intake [12]. However, not all people exposed to those risk factors develop PC, suggesting a genetic contribution to the development of PC [13, 14].

The 8-oxoguanine DNA glycosylase (*OGG1*) gene, located on chromosome 3p26, is one of the component of

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BER pathway, plays a key role in repairing damaged DNA. It performs the initial step of recognizing the 8-hydroxyguanine damage which is highly mutagenic and a major form of oxidative DNA damage [15, 16]. The *OGG1* gene has at least 20 validated sequence variants, and one of the most studied functional polymorphism is Ser326Cys (exon 7 of the *OGG1* gene, rs1052133), which with an acid substitution of serine (Ser) with cysteine (Cys) at codon 326, resulting from a C to G transversion at 1245 position, has been reported to affect the *OGG1* function and to be associated with cancer susceptibility [17–21]. It is reported that the 326Cys allele had reduced DNA repair activity and was related with cancer risk [20, 21]. Up to now, many reports have evaluated the relationship between the *OGG1* Ser326Cys polymorphism and PC risk. However, the results from these studies were inconsistent [22–26]. In order to assess the association between the *OGG1* Ser326Cys polymorphism and PC risk accurately, we carried out a meta-analysis.

Materials and methods

Literature search

We searched the relevant articles through the search engines such as PubMed, Excerpta Medica Database (Embase), Elsevier Science Direct, and Chinese Biomedical Literature Database using the search terms: "*OGG1*, *OGH1*, or *OGG1*", "variant or variation or polymorphism", and "pancreatic cancer" (last search was updated on 30 May 2013) without language restrict.

Inclusion and exclusion criteria

Studies were selected if they satisfied the following criteria: (1) estimating the association of *OGG1* Ser326Cys polymorphisms with PC risk, (2) case–control studies, (3) offering enough information for estimating the odds ratios (ORs) with the corresponding 95 % confidence intervals (CIs). The exclusion criteria were: (1) not case–control studies that evaluated the association between *OGG1* polymorphism and PC risk; (2) case reports, letters, and reviews; and (3) controls were not consistent in HWE.

Data extraction

All the data were extracted by two investigators (YY and XC) independently and the result was reviewed by a third investigator (HL). From each study, the following information were collected: first author, year of publication, country and ethnicity of the study population, the number of cases and controls, genotyping methods and genotype distribution of cases and controls, and source of control.

Statistical analysis

To test whether the population of control conformed to Hardy–Weinberg equilibrium, a chi-square test was applied. The homogeneity among the studies was verified by Chi square-based Q test [27] if there is a significant Q statistic ($P<0.10$) that indicated heterogeneity across studies, the pooled OR estimate of all studies would be calculated by the fixed-effects model (the Mantel–Haenszel method) [28]; otherwise, a random effects model (the DerSimonian and Laird method) would be used [29]. The strength of the association between *OGG1* Ser326Cys polymorphism and PC risk was measured by OR with 95 % CI. The statistical significance of the summary OR was determined with the Z test. The publication bias was tested by funnel plot and Egger's linear regression test [30, 31]. Sensitivity was analysis by sequential omission of individual study one a time or by omitting studies without high quality was performed to assess the stability of the results [32]. All statistical tests for this meta-analysis were performed with STATA version 9.0 (Stata Corporation, College Station, TX, USA).

Results

Studies characteristics

The general characteristics of eligible studies were listed in Table 1. After selecting based on the inclusion and exclusion criteria listed above, a total of five eligible studies with 1,690 cases and 3,650 controls were included in our meta-analysis [22–26]. The population of controls in each study was consistent with HWE ($P>0.05$).

Table 1 Main characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Genotyping method	Source of control	Cases/controls	HWE control
Nakao	2012	Japan	Asian	Taq Man	HB	185/1,465	Yes
Li	2009	USA	Caucasians	Taq Man	HB	722/773	Yes
Duell	2008	USA	Caucasians	Masscode	PB	126/330	Yes
McWilliams	2008	USA	Caucasians	SNPstream	PB	469/599	Yes
Zhang	2011	USA	Caucasians	Taq Man	PB	188/483	Yes

HWE Hardy–Weinberg equilibrium, *HB* hospital based, *PB* population based

Table 2 Meta-analysis of *OGG1* Ser326Cys polymorphism with the PC risk

Study group	*N*	Cys vs Ser		Cys/Cys vs Ser/Ser		Cys/Cys vs Ser/Ser+Ser/Cys		Cys/Cys+Ser/Cys vs Ser/Ser	
		OR (95 % CI)	I^2	OR (95 % CI)	I^2	OR (95 % CI)	I^2	OR (95 % CI)	I^2
Overall	5	0.98 (0.95–1.05)	25.4	0.95 (0.80–1.14)	0.0	0.95 (0.78–1.14)	0.0	1.00 (0.89–1.12)	66.3
Ethnicity									
Caucasians	4	0.98 (0.90–1.17)	43.9	0.96 (0.74–1.23)	0.0	0.94 (0.73–1.21)	0.0	1.00 (0.85–1.18)	73.7
Asian	1	0.98 (0.87–1.09)	-	0.95 (0.75–1.21)	–	0.96 (0.73–1.26)	–	0.98 (0.89–1.08)	–
Control population									
Population-based	3	0.93 (0.79–1.11)	54.1	0.95 (0.73–1.33)	28.7	0.98 (0.72–1.34)	0.0	0.96 (0.74–1.26)	81.9
Hospital-based	2	1.01 (0.92–1.10)	0.0	0.94 (0.76–1.16)	0.0	0.93 (0.73–1.17)	0.0	1.03 (0.95–1.11)	3.0
Sample size									
>500 subjects	4	1.00 (0.93–1.08)	0.0	0.97 (0.81–1.16)	0.0	0.95 (0.78–1.15)	0.0	1.04 (0.97–1.11)	38.3
≤500 subjects	1	0.73 (0.55–0.97)	–	0.80 (0.49–1.32)	-	0.97 (0.48–1.95)	–	0.69 (0.52–0.92)	–
Genotyping method									
TaqMan	3	1.02 (0.94–1.10)	0.0	1.01 (0.83–1.22)	0.0	0.98 (0.79–1.21)	0.0	1.08 (0.95–1.19)	56.1
Non-TaqMan	2	0.86 (0.66–1.12)	64.4	0.80 (0.54–1.20)	0.0	0.85 (0.56–1.28)	0.0	0.84 (0.60–1.20)	79.6

N number of studies, *P* the *P* value used to test the heterogeneity, *CI* confidence interval

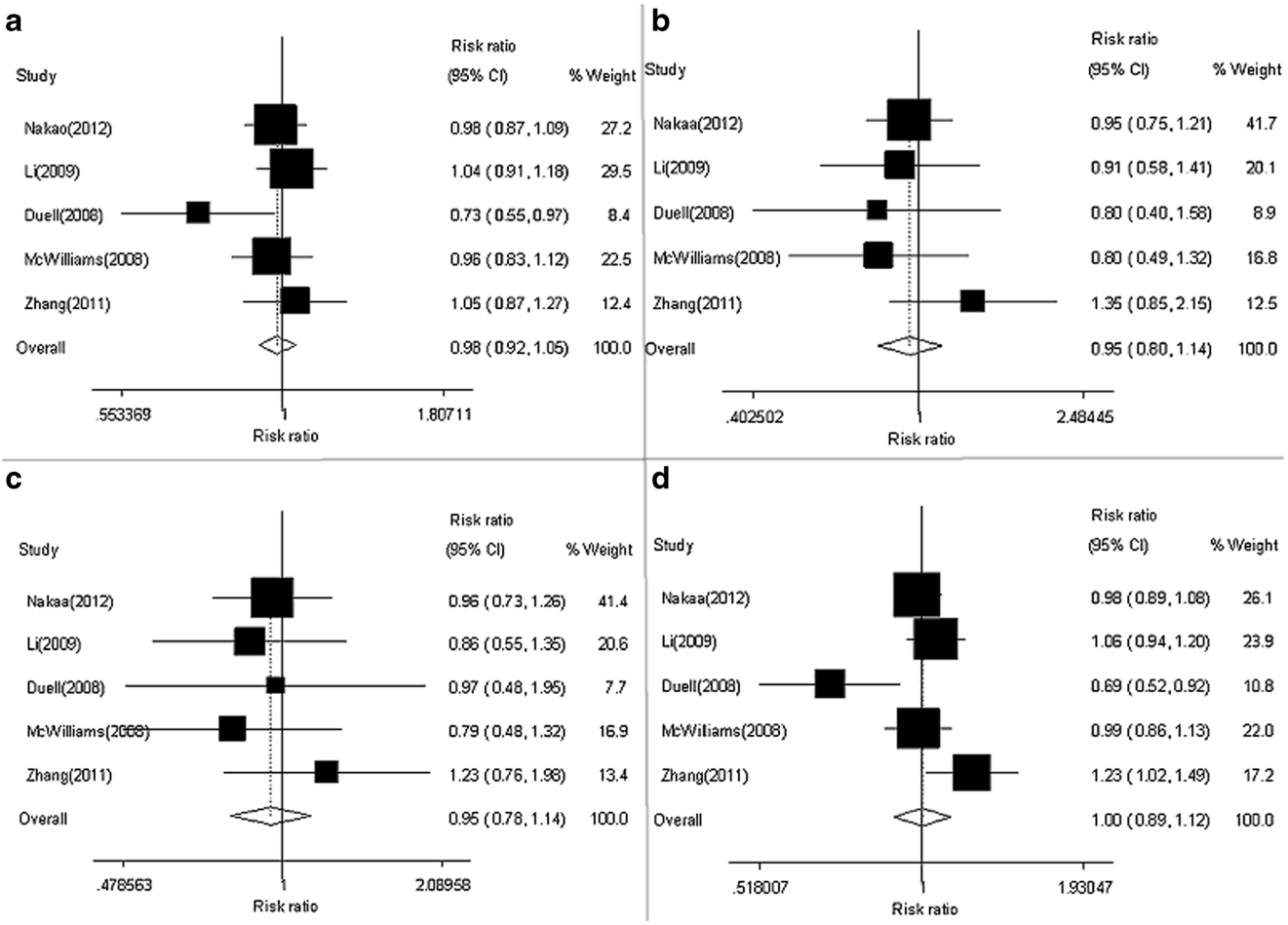

Fig. 1 Forest plots showed that OGG1 Ser326Cys polymorphism was not associated with PC susceptibility under all genetic models. **a** Allele contrast: Cys vs Ser; **b** homozygote model, Cys/Cys vs Ser/Ser; **c** recessive model, Cys/Cys vs Ser/Ser+Ser/Cys; **d** dominant model, Cys/Cys+Ser/Cys vs Ser/Ser

Meta-analysis

As shown in Table 2, there is no significant association between the *OGG1* Ser326Cys and PC risk was found in any of the genetic models. The results are as follow: Cys vs. Ser (OR=0.98, 95 % CI=0.95–1.05; Fig. 1a); Cys/Cys vs. Ser/Ser: OR=0.95, 95 % CI=0.80–1.14 (Fig. 1b); Cys/Cys vs. Ser/Ser+Ser/Cys: OR=0.95, 95 % CI=0.78–1.14 (Fig. 1c); Cys/Cys+Ser/Cys vs. Ser/Ser (OR=1.00, 95 % CI=0.89–1.12; Fig. 1d). Further subgroup analysis by ethnicity, source of controls, sample size, and genotyping method all yielded no statistically significant estimates (Table 2).

Test of heterogeneity

In the current study, significant heterogeneity was only found in dominant model (Cys/Cys+Ser/Cys vs Ser/Ser: $P=0.018$, $I^2=66.3$ %). Then, we assessed the source of heterogeneity by ethnicity (Caucasians or Asian), source of control (population- or hospital-based), sample size (>500 subjects or ≤500 subjects), and genotyping method (TaqMan or non-TaqMan). As a result, the source of control ($\chi^2=12.23$; $df=1$; $I^2=91.8$ %) and sample size ($\chi^2=2.10$; $df=1$; $I^2=52.3$ %) were found contribute substantial heterogeneity.

Sensitivity analyses and publication bias

Sensitivity analysis was carried out to evaluate the influence of each individual study on the pooled OR. The results indicated that no individual study significantly impact on the overall results. The publication bias was assessed by Egger's test and funnel plot. No publication bias was detected for *OGG1* Ser326Cys (the Egger's test result as follow: Cys vs. Ser: $P=0.256$, Cys/Cys vs. Ser/Ser: $P=0.877$, Cys/Cys vs. Ser/Ser+Ser/Cys: $P=0.982$, Cys/Cys+Ser/Cys vs. Ser/Ser= 0.643). The shape of the funnel plot did not indicate any evidence of obvious asymmetry too (Fig. 2).

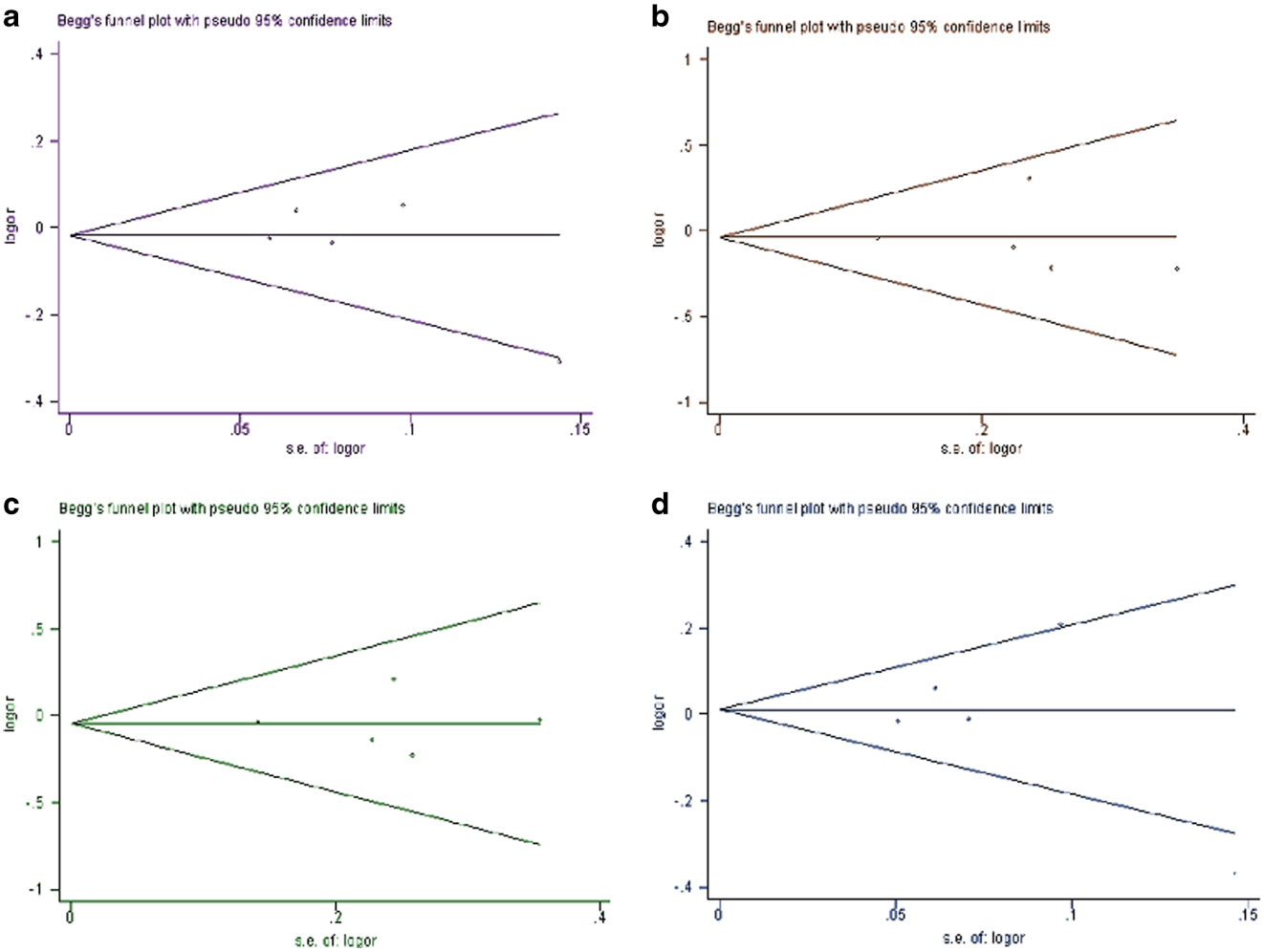

Fig. 2 Funnel plots did not indicate any evidence of obvious asymmetry under all genetic models. **a** Allele contrast, Cys vs Ser; **b** homozygote model: Cys/Cys vs Ser/Ser; **c** recessive model: Cys/Cys vs Ser/Ser+Ser/Cys; **d** dominant model: Cys/Cys+Ser/Cys vs Ser/Ser

Discussion

In recent years, a number of studies have carried out to explore the *OGG1* Ser326Cys polymorphism with cancers risk including lung cancer, breast cancer, colorectal cancer, and PC. Unfortunately, previous findings of *OGG1* Ser326Cys polymorphism on cancer susceptibility were controversial or ambiguous. Therefore, some meta-analyses were performed to solve the phenomenon. Zhang et al. reported that the *OGG1* Ser326Cys polymorphism is not associated with CRC risk and Wang et al. concluded that the *OGG1* Ser326Cys polymorphism might not be a potential candidate risk factor for the development of gastric cancer [33, 34]. However, Yuan et al. suggested that the *OGG1* 326Cys allele plays a significant protective effect to breast cancer in European women and Duan et al. established solid statistical evidence for an association between the *OGG1* Cys/Cys genotype and lung cancer risk [35, 36]. This phenomenon indicates that the *OGG1* Ser326Cys polymorphism exerts different effect on various types of cancers. So, it is necessary for us to get a better understanding of *OGG1* Ser326Cys polymorphism on PC susceptibility, especially when inclusive and controversial findings still exist. In our present meta-analysis, *OGG1* Ser326Cys polymorphism was not significantly associated with PC risk. Subgroup analysis was based on ethnicity, source of control, sample size, and genotyping method; we could not achieve a significant association between *OGG1* Ser326Cys polymorphism and PC susceptibility.

When performing meta-analysis, testing the heterogeneity among studies is very important. In the current study, significant heterogeneity was only found in the dominant model. Then, we did subgroup analysis to search the source of heterogeneity. Interestingly, it seems that the ethnicity is not the source of heterogeneity, suggesting that *OGG1* Ser326Cys polymorphism may not have race-specific effects on PC susceptibility. We found that the source of control and sample size may contribute substantial heterogeneity. It is possible that some limitations of recruited studies may partially contribute to the observed heterogeneity. For this reason, we conducted analyses using the random effects model. In addition, publication bias is another aspect which may make a negative effect on our meta-analysis. Both funnel plot and Egger's test were applied to test the publication bias. Our results suggest that the publication bias have little effect on the results of our study, and the results of our meta-analysis are relatively stable.

Although comprehensive analysis was conducted to explore the association between *OGG1* Ser326Cys polymorphism and PC susceptibility, there are still some limitations. Firstly, the primary studies mainly provided data towards Caucasians; therefore, other ethnicities should be researched in future studies. Secondly, only three studies used controls that were population-based. Other articles used hospital-based controls, which may not be representative of the general population. Thirdly, the number of samples included in the meta-analysis was relatively small.

In spite of the shortages above, our meta-analysis also had several advantages. Firstly, strict searching strategy which combines computer-assisted with manual search makes the eligible studies included as much as possible. Secondly, the quality of case–control studies met our inclusion criteria and was satisfactory, and the sensitivity analysis and publication bias analysis indicated the stability and credibility of the meta-analysis, which leads to a more convincing result. More importantly, the process of literature selection, data extraction, and data analysis were well designed and conducted.

In conclusion, this is the first meta-analysis evaluating the association between *OGG1* Ser326Cys polymorphism and PC susceptibility. The pooled results suggest that the *OGG1* Ser326Cys polymorphism may not be associated with PC susceptibility. Considering the limited sample size and ethnicities included in the meta-analysis, further larger-scaled and well-designed studies are needed to confirm our results.

Conflicts of interest None.

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