META ANALYSIS

Genetic polymorphism in cytochrome P450 2E1 and alcoholic pancreatitis susceptibility: a meta-analysis

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Abstract

Background: The association between *cytochrome P450 2E1 (CYP2E1)* polymorphism and the risk of alcoholic pancreatitis is contentious. This meta-analysis aimed to demonstrate the association between *CYP2E1* RsaI/PstI, or DraI polymorphisms and the susceptibility of alcoholic pancreatitis.

Materials and Methods: We searched for sources and background in Pubmed, Medline, Web of science and CNKI (Chinese national knowledge infrastructure), using the following keywords: "cytochrome P450 2E1" or "CYP2E1", "polymorphism" or "genotype", in combination with "alcoholic pancreatitis". All meta-analyses were performed with Stata 12.0. Subgroup analyses on ethnicity and type of alcoholic pancreatitis were conducted as well.

Results: Eleven articles, which met the inclusion criteria, included 595 patients with alcoholic pancreatitis, and 1767 controls. For the general population, our analysis suggested no obvious association between *CYP2E1* RsaI/PstI or DraI polymorphisms and the risk of alcoholic pancreatitis. However, in the non-Asian subgroup, significant associations were found between the risk for alcoholic pancreatitis and *CYP2E1* RsaI/PstI polymorphism [dominant model: odds ratio (OR) =1.92, 95 % confidence interval (CI): 1.25-2.95, p =0.003; allelic contrast model: OR =1.99, 95 % CI: 1.35-2.92, p <0.001. There was not a significant association found within the Asian group. Meanwhile, the susceptibilities of chronic alcoholic pancreatitis were significantly increased for dominant and allelic contrast models of *CYP2E1* RsaI/PstI polymorphism [OR =1.62, 95 % CI: 1.12-2.34; p =0.011; OR =1.62, 95 % CI: 1.17-2.24, p = 0.004, respectively] but not for acute alcoholic pancreatitis for all population.

Conclusions: *CYP2E1* RsaI/PstI polymorphism may increase the risk of alcoholic pancreatitis in the non-Asian population. Additionally, the *CYP2E1* RsaI/PstI polymorphism may increase the susceptibility for chronic alcoholic pancreatitis for all population. HIPPOKRATIA 2018, 22(2): 60-67.

Keywords: Cytochrome P450 2E1, CYP2E1, polymorphism, alcoholic pancreatitis, meta-analysis

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Introduction

Alcohol abuse is a severe medical and socioeconomic problem[1], which is known to cause pancreatitis, a type of inflammation of the pancreas. There are two forms of alcoholic pancreatitis, acute and chronic. They are essentially the same disease but at different stages. Alcohol is the leading cause of chronic pancreatitis in approximately 70 % to 80 % of the patients living in developed societies[2,3]. It was reported that characterization of intestinal microbiota contributed to the occurrence of pancreatitis in alcoholics[4]. In addition, genetic factors also play a significant role in the risk of pancreatic injury, and the inflammatory processes[5,6].

Cytochrome P450 2E1 (CYP2E1), a member of CYP family, metabolizes low-molecular-weight compounds, such as endogenous substrates, centrally acting drugs, and bio-activating toxins[7,8]. CYP2E1 is primarily expressed in the liver, but also exists in the pancreas[9]. The human *CYP2E1* gene exhibits two point mutations in the 5'flanking region (RsaI/PstI), which are in complete linkage disequilibrium, and one mutation in 6' flanking region (DraI, alleles D and C). *CYP2E1* polymorphisms also play a role in transcriptional activation of the *CYP2E1* gene[10]. Previous meta-analyses suggested that *CYP2E1* polymorphisms were significantly associated with the susceptibilities of many diseases, such as lung cancer, gastric cancer, cervical neoplasia, and breast cancer[11-14].

Plenty of studies investigated the association of *CYP2E1* RsaI/PstI and DraI polymorphisms with the

risk of alcoholic pancreatitis. Despite this effort, whether CYP2E1 genetic polymorphism can influence the risk of alcoholic pancreatitis remains unclear. Therefore, this meta-analysis was performed to explicate this relationship.

Materials and methods

Data sources and search strategy

In the literature review process, we searched for articles in Pubmed, Medline, Web of science, and CNKI (Chinese national knowledge infrastructure) (ended on May 2018), using the following keywords: "cytochrome P450 2E1" or "CYP2E1", "polymorphism" or "genotype", in combination with "alcoholic pancreatitis". All studies that met the inclusion criteria were then manually screened by two authors, according to the titles and abstracts. Then, the full texts of these articles were retrieved and independently reviewed by two authors and then referred to another author in the instance of disagreements.

Inclusion and exclusion criteria

Studies were searched to fulfill all of the following criteria: First, the study's primary focus had to pertain to the association of alcoholic pancreatitis and polymorphism of *CYP2E1*. Secondly, it had to be an observational study. Lastly, the study must have provided information about the sample size, ethnicity, and genetic distribution of the sample group. Exclusion criteria included: unrelated theme, absence of control subjects, and undetectable mutant type.

Data extraction

Two investigators independently extracted data. If necessary, a discussion and re-examination were conducted to achieve an agreement. When same authors published an additional article using the same case series, the most complete and recent publication was selected. When studies involved several separate control groups (healthy alcoholics, healthy non-alcoholic volunteers or blood donors, respectively), pooled data of these three control groups were considered as one control group for analysis. Data were extracted from the included studies as follows: the first author, year of publication, number of cases, country, race, control type, age, and type of alcoholic pancreatitis.

Statistical analysis

Our meta-analysis followed the recommendations of the PRISMA statement. Newcastle-Ottawa Scale (NOS) criteria were used to assess the study quality. Those studies that met five or more NOS criteria were considered of high quality. The odds ratio (OR) was plotted to measure any possible sample size bias. Heterogeneity analysis was performed using I^2 value. Results were summarized using forest plots. Egger's test and the funnel plot were performed to evaluate the publication bias. Subgroup analyses were also performed on race and type of alcoholic pancreatitis. STATA 12.0 software was used to perform all the statistical analyses (Stata Corp., Texas, USA).

Results

Study characteristics

As shown in Figure 1, we identified for this meta-analysis 38 publications, 18 irrelevant papers, four review articles[15-18], and two papers on animal studies[19,20] that were discarded. One conference paper[21] was discarded because it did not show any genotype results. After the entire exclusion process, 13 observational studies met the inclusion criteria. Four of these 13 studies[22-25] used the same two case series, so the most recent publications were included[22,25]. Ultimately, 11 publications were included[6,22,25-33], including 595 patients with alcoholic pancreatitis, and 1767 controls.

Nine out of 11 studies were published in English[6,22,25,26,28-31,33], one in Russian[32], and one in Korean language[27]. The detailed information is shown in Table 1.

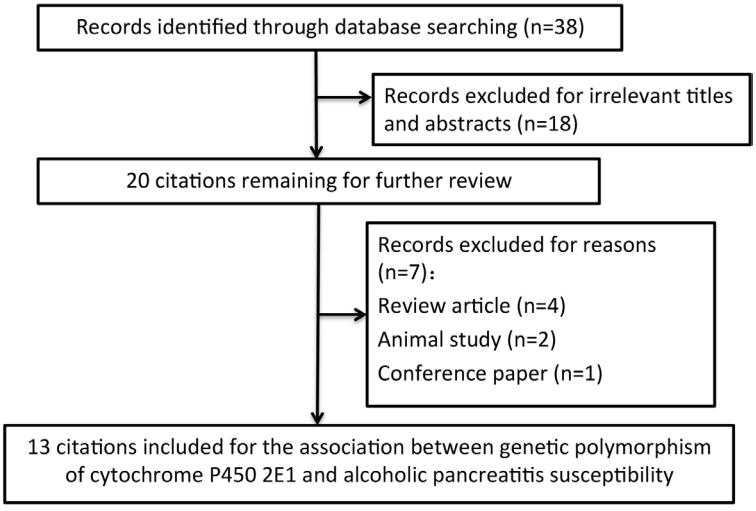

Figure 1: Flow diagram of the search strategy and study selection of the present Meta-Analysis.

Table 1: Characteristics of the studies included in the present meta-analysis.

First author	Publication year	Country	Racial decent	Number of cases (M/F)	Number of controls (M/F)	Type of controls	Median (or mean) age, (range or SD)year (Cases/ Controls)	Studied genes
Matsumot[o2]8	1996	Japan	Japanese	52 (48/4)	244 (214/30)	Healthy alcoholics	48±11/51±11	RsaI/PstI
Chao[25]	1997	China	Chinese	48 (42/6)	119 (119/0)	Healthy alcoholics and non-drinker healthy volunteers	41.6±10.8/26.8±? *	RsaI/PstI
Maruyama[33]	1999	Japan	Japanese	54 (NM)	46 (NM)	Healthy alcoholics	NM	RsaI/PstI
Yang[31]	2001	England	Caucasian	57 (NM)	201 (NM)	Alcoholic controls and normal controls	NM	RsaI/ PstIDraI
Frenzer[26]	2002	Australia	Caucasian	71 (61/10)	257(166/91)	Healthy alcoholics and blood donors	53±NM/48±NM	RsaI/PstI DraI
Verlaan[29]	2004	Dutch	Caucasian	82 (56/26)	221 (139/82)	Alcoholics controls and healthy subjects	50±9/45±? *	RsaI/PstI DraI
Kim[27]	2004	Korea	Korean	29 (27/2)	100 (44/56)	Healthy blood donors	50.4±26.6/49.2±20.3	RsaI/PstI
Burim[30]	2004	Brazil	Brazilian	14 (NM)	262 (NM)	Healthy alcoholics and non-alcoholics controls	NM	RsaI/PstI
Cichoz-Lach[22]	2008	Poland	Polish	44 (8/36)	97 (22/75)	Healthy alcoholics and non-drinker healthy volunteers	45.00±9.44/ 47.05±?*	RsaI/PstI
Gubergrits[32]	2014	Russia	Russian	72	80	Healthy individuals	NM	RsaI/PstI
Singh[6]	2015	India	Indian	72 (72/0)	140 (100/40)	alcoholic control and healthy control	38.5±8.3/33.15±?*	DraI

M: male, F: female, *: The standard deviation (SD) cannot be decided for controls included 2 separated groups, NM: not mentioned.

Table 2: Distribution of *cytochrome P450 2E1* (*CYP2E1*) RsaI/PstI genotype among alcoholic pancreatitis cases and controls included in the meta-analysis.

First author	Year	Type of AP	Controls			HWE (p value)	Cases			Controls		Cases	
			c1/c1	c1/c2	c2/c2		c1/c1	c1/c2	c2/c2	c1	c2	c1	c2
Matsumoto[28]	1996	CAP	39	21	2	>0.05	9	2	0	99	25	20	2
Chao[25]	1997	AAP	68	43	8	>0.05	30	15	3	179	59	75	21
Maruyama[33]	1999	CAP	30	15	1	>0.05	30	21	2	75	17	81	25
Yang[31]	2001	CAP	192	9	0	>0.05	37	1	0	393	9	75	1
Frenzer[26]	2002	AAP	192	9	0	>0.05	18	1	0	393	9	37	1
		CAP	242	15	0	>0.05	65	6	0	499	15	136	6
Burim[30]	2004	CAP	234	27	1	>0.05	11	3	0	495	29	25	3
Kim[27]	2004	NM	51	34	15	>0.05	17	11	1	136	64	45	13
Verlaan[29]	2004	CAP	122	6	0	>0.05	75	7	0	250	6	157	7
Cichoz-Lach[22]	2008	CAP	97	0	0	>0.05	42	2	0	194	0	86	2
Gubergrits[32]	2014	CAP	55	22	3	>0.05	36	26	10	132	28	98	46

HWE: Hardy-Weinberg Equilibrium, AP: alcoholic pancreatitis, CAP: chronic alcoholic pancreatitis, AAP: acute alcoholic pancreatitis, NM: not mentioned.

Five studies were performed in Asia[22,24,25,30,31], and the other six outside of Asia[22,26,29-32]. Ten of the 11 studies focused on RsaI/PstI polymorphism of *CYP2E1* (523 patients and 1627 controls)[22,25-33], and four on DraI polymorphism (282 patients and 819 controls)[6,26,29,32]. All studies were considered of high quality according to NOS criteria. Distributions of the *CYP2E1* RsaI/PstI and DraI genotypes are presented in Table 2 and Table 3, respectively.

Test of heterogeneity

As shown in Figures 2-6, we analyzed the heterogeneity of the dominant (c2c2+c1c2 vs c1c1, or CD+CC

Table 3: Distribution of *cytochrome P450 2E1* (*CYP2E1*) DraI genotype among alcoholic pancreatitis cases and controls included in the meta-analysis.

First author	Year	Country	Race	Control			HWE (p value)	AP			Control		AP	
				DD	CD	CC		DD	CD	CC	D	C	D	C
Yang[31]	2001	England	Caucasian	152	38	1	>0.05	45	10	2	342	40	100	14
Frenzer[26]	2002	Australia	Caucasian	216	38	3	>0.05	54	17	0	470	44	125	17
Verlaan[29]	2004	Dutch	Caucasian	122	6	0	>0.05	75	7	0	250	6	157	7
Singh[6]	2015	India	Indian	101	29	0	>0.05	61	10	1	231	29	132	12

HWE: Hardy-Weinberg Equilibrium, AP: alcoholic pancreatitis.

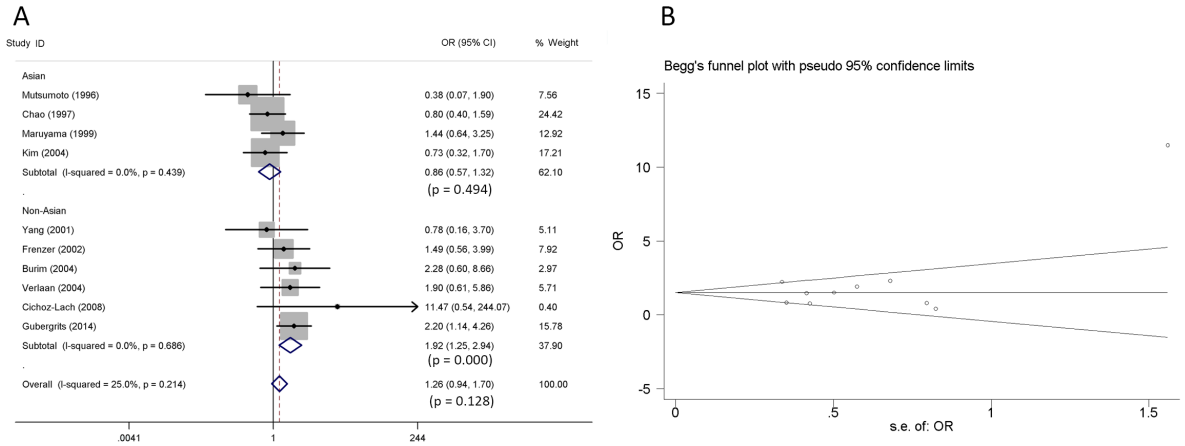

Figure 2: A) *Cytochrome P450 2E1* (*CYP2E1*) RsaI/PstI polymorphism was not associated with the risk of alcoholic pancreatitis for a dominant model (c2c2+c1c2 vs c1c1). B) There was no obvious publication bias test for this model by funnel plot.

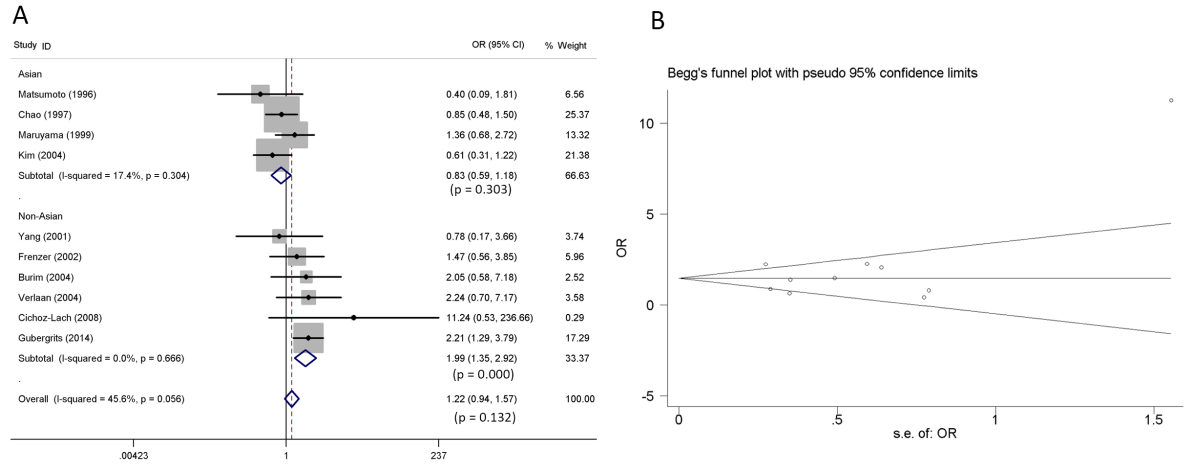

Figure 3: A) *Cytochrome P450 2E1* (*CYP2E1*) RsaI/PstI polymorphism was not associated with the risk of alcoholic pancreatitis for an allelic contrast model (c2 vs c1). B) There was no obvious publication bias test for this model by funnel plot. =1.92, 95 %

vs DD), and allelic contrast (c2 vs c1 allele, or C vs D allele) models for both *CYP2E1* RsaI/PstI and DraI polymorphisms. No significant heterogeneities were found in the dominant contrast *CYP2E1* RsaI/PstI polymorphism (c2c2+c1c2 vs c1c1: I^2 =25 %, p =0.214, Figure 2A) and in the allelic comparison model (c2 vs c1: I^2 =45.6 %, p =0.056, Figure 3A); this was also the case for the both DraI polymorphism models (CD+CC vs DD: I^2 =33.5 %, p =0.211, Figure 4A; C vs D: I^2 =0.0 %, p =0.398, Figure 6A). Subgroup analyses on the ethnicity and type of alcoholic pancreatitis showed that there was no significant heterogeneity (I^2 =0.0 %, p =0.568 for the Asian group, I^2 =0.0 %, p =0.666 for the non-Asian group, Figure 3A) in the subgroup analysis according to ethnicity, as well as in subgroup analysis according to the type of alcoholic pancreatitis [I^2 =16.1 %, p =0.307 for CAP group, I^2 =0.0 %, p =0.766 for the alcoholic acute pancreatitis (AAP) group, Figure 4B].

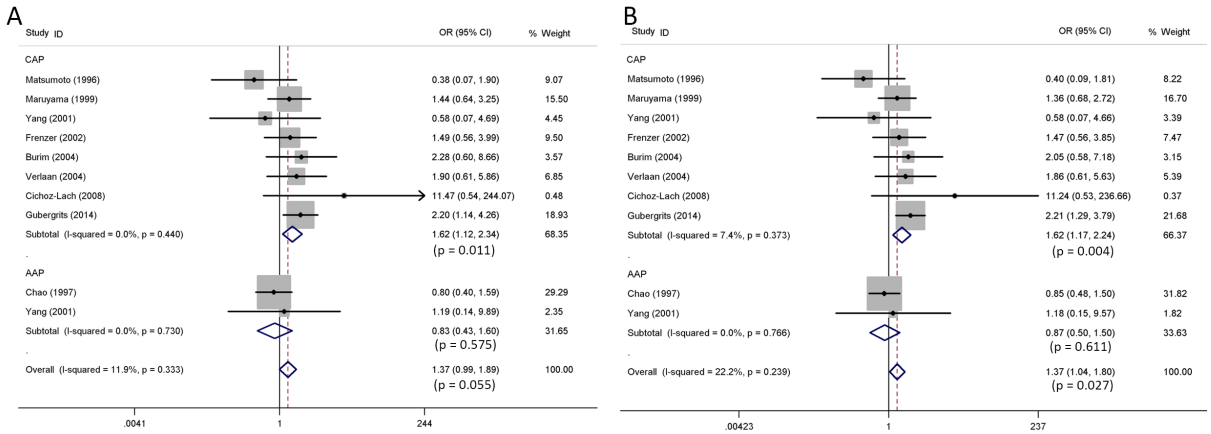

Figure 4: A) *Cytochrome P450 2E1* (*CYP2E1*) RsaI/PstI polymorphism was significant associated with the risk of chronic alcoholic pancreatitis (CAP) [odds ratio (OR) =1.62, 95 % confidence interval (CI): 1.12-2.34; p =0.011] but not among the acute alcoholic pancreatitis (AAP) group for a dominant model (c2c2+c1c2 vs c1c1); B) *CYP2E1* RsaI/PstI polymorphism was significant associated with the risk of CAP (OR =1.62, 95 % CI: 1.17-2.24, p =0.004), but not among the AAP group for an allelic contrast model (c2 vs c1).

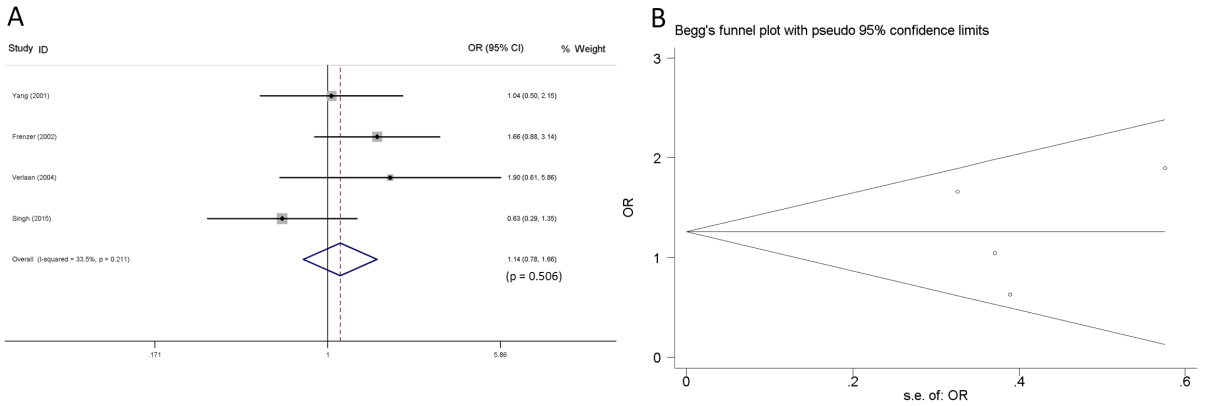

Figure 5: A) *Cytochrome P450 2E1* (*CYP2E1*) DraI polymorphism was not associated with the susceptibility of alcoholic pancreatitis risk for a dominant model (CC+CD vs DD). B) There was no obvious publication bias test for this model by funnel plot.

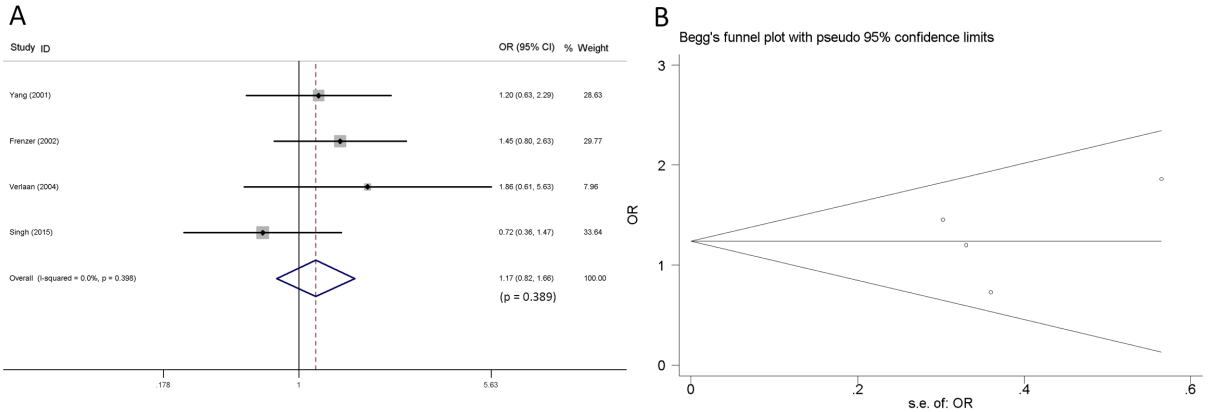

Figure 6: A) *Cytochrome P450 2E1* DraI polymorphism was not associated with the susceptibility of alcoholic pancreatitis risk for an allelic contrast model (C vs D). B) There was no obvious publication bias test for this model by funnel plot.

Results of Meta-Analysis

The meta-analysis showed that there was no significant association between *CYP2E1* RsaI/PstI polymorphism and alcoholic pancreatitis risk [OR =1.26, 95 % confidence interval (CI): 0.94-1.70, p =0.128, Figure 1A, and OR =1.22, 95 % CI: 0.94-1.57, p =0.132, Figure 3A], for the dominant, and allelic contrast models respectively. *CYP2E1* RsaI/PstI polymorphism was not associated with the risk of alcoholic pancreatitis (Figure 2A, and Figure 3A). Subgroup analysis based on ethnicity suggested that there was a significant increase in alcoholic

pancreatitis risk in the non-Asian subgroup. The dominant model demonstrated a significant relationship (OR =1.92, 95 % CI: 1.25-2.94, p =0.003), as well as the allelic contrast model (OR =1.99, 95 % CI: 1.35-2.92, p <0.001). The Asian group, however, was not significantly associated for either the dominant (OR =0.86, 95 % CI: 0.57-1.32, p =0.494), or the allelic contrast model (OR =0.83, 95 % CI: 0.59-1.18, p =0.303) (Figure 2A, and Figure 3A). The interaction of ethnicity with *CYP2E1* polymorphism may increase the risk of alcoholic pancreatitis. Subgroup analysis on the type of alcoholic pancreatitis suggests that there were significant increases in the chronic alcoholic pancreatitis (CAP) group for the dominant (OR =1.62, 95 % CI: 1.12-2.34, p =0.011) and the allelic (OR =1.62, 95 % CI: 1.17-2.24, p =0.004) contrast models, but not among the AAP group for the dominant (OR =0.83, 95 % CI: 0.43-1.60, p =0.575), or the allelic contrast model (OR =0.87, 95 % CI: 0.50-1.50, p =0.611) (Figure 4A and B). *CYP2E1* RsaI/PstI polymorphism may increase the risk of CAP, but not AAP.

Results of the meta-analysis of the association between *CYP2E1* DraI polymorphism and alcoholic pancreatitis risk showed that the ORs were 1.14 (95 % CI: 0.78-1.66, p =0.506), and 1.17 (95 % CI: 0.82-1.66, p =0.389), for the dominant, and allelic contrast models, respectively. *CYP2E1* DraI variations may not be associated with the risk of alcoholic pancreatitis (Figure 5A, and Figure 6A).

Sensitivity analysis and publication bias

The sensitivity analysis showed that, when altered according to the effect models, these two models did not show significant changes. When we omitted any given single study, the significances of the overall results did not change (data not shown), which indicated the stability of the results.

The results of the funnel plots indicated no obvious publication biases for the dominant (Figure 2B for RsaI/PstI polymorphism, and Figure 5B for DraI polymorphism), nor for the allelic contrast (Figure 3B for RsaI/PstI polymorphism, and Figure 6B for DraI polymorphism) models. The Egger's tests also suggested that there were no significant publication biases for RsaI/PstI polymorphism (dominant model: t =1.53, p= 0.164; allelic contrast model: t =1.29, p =0.232), and for DraI polymorphism (dominant model: t =0.50, p =0.667; allelic contrast model: t =0.61, p =0.603).

Discussion

Alcohol abuse is a severe medical and socio-economic problem, which leads to the damage of many organs: some of which are the liver[34,35], pancreas[36,37], heart[38,39] and brain[40,41]. When damage occurs in the pancreas, it is common for acute or chronic pancreatitis to develop. The occurrence of alcohol-induced pancreatitis has no differences in gender and alcohol consumption patterns[42]. It is reported that the genetic differences in alcohol-metabolizing enzymes may result in different metabolizing rates and affect the susceptibility of alcoholic pancreatitis[43,44]. CYP2E1 plays an important role in the initial stage of alcohol metabolism, especially in the microsomal ethanol oxidizing system[34]. Therefore, we performed this meta-analysis to demonstrate the association between genetic polymorphism of *CYP2E1* and the risk of alcoholic pancreatitis. Our results for the overall data suggested that *CYP2E1* RsaI/PstI and DraI polymorphisms were not associated with risk of alcoholic pancreatitis.

CYP2E1 genetic polymorphism varies marked in frequency among different ethnic and racial groups[45]. *CYp2E1* RsaI/PstI polymorphism may modify the susceptibility to head and neck carcinoma and nasopharyngeal carcinoma in Asians, but not among Caucasians and African-Americans[13,46]. Thus, in order to determine the ethnic difference of the association between *CYP2E1* RsaI/PstI polymorphism and alcoholic pancreatitis risk, a subgroup analysis on ethnicity (divided into two groups: Asian and non-Asian populations) was performed. The results showed significantly increased alcoholic pancreatitis risk among the Non-Asians with c2 allele or c2c2+c1c2 genotypes. *CYP2E1* polymorphism in different ethnicities may influence the risk of alcoholic pancreatitis[47]. *CYP2E1* variations were different among ethnicities. Therefore, *CYP2E1* RsaI/PstI polymorphism may influence the risk of alcoholic pancreatitis differently in different races.

Moreover, this study suggested that the interaction of race and *CYP2E1* polymorphism may have a significant influence on the risk of alcoholic pancreatitis. In non-Asians, c2 allele and c2c2+c1c2 genotypes of *CYP2E1* RsaI/PstI may significantly increase the susceptibility of alcoholic pancreatitis. In Asians, c2 allele and c2c2+c1c2 genotypes of *CYP2E1* RsaI/PstI may increase the susceptibility of alcoholic pancreatitis, without significant statistical difference.

There are two forms of pancreatitis: acute and chronic pancreatitis, both of which can progress to pancreatic cancer[48]. About 20 % of acute pancreatitis will progress into chronic pancreatitis[49,50]. Therefore, in order to demonstrate the effect of the type of alcoholic pancreatitis on the association between *CYP2E1* RsaI/PstI polymorphism and alcoholic pancreatitis, we performed subgroup analysis regarding the type of alcoholic pancreatitis. The results showed that *CYP2E1* RsaI/PstI polymorphism significantly increased the risk of CAP, but not AAP, although this may also be due to the small number of studies concerning AAP.

There was no significant degree of linkage disequilibrium between *CYP2E1* RsaI/PstI and DraI in normal controls and alcoholic subjects[51]. In the present meta-analysis, two models, the dominant and allelic contrast models, were analyzed to measure the impact of *CYP2E1* RsaI/PstI and DraI polymorphisms on alcoholic pancreatitis susceptibility. Interaction of race with *CYP2E1* RsaI/PstI polymorphism may significantly influence alcoholic pancreatitis risk in dominant and allelic contrast models, but not in the homozygote comparison model

(c2c2 vs c1c1, data not shown). The results may be due to the rare frequency of c2c2 homozygote in individuals with alcoholic pancreatitis, healthy alcoholics, or healthy controls. Thus, further investigation with large sample sizes is needed to investigate the role of *CYP2E1* polymorphism on the susceptibility of alcoholic pancreatitis.

Some possible limitations of this meta-analysis include race, age, sex, occupation, smoking history, and so on. However, we only performed subgroup analysis on ethnicity and the type of alcoholic pancreatitis; subgroup analyses on other risk factors could not be performed due to the limited information of the included studies. Secondly, this meta-analysis only included in published articles; thus, publication bias may exist. Thirdly, only 11 studies were included in our meta-analysis, ten for RsaI/PstI polymorphism and four for DraI polymorphism. Although subgroup analysis for RsaI/PstI polymorphism was performed, there were only four articles for the Asian group, and six for the non-Asian group. Therefore, large sample, preferable studies were needed to demonstrate the results.

In conclusion, though the overall data failed to suggest the relationship of *CYP2E1* RsaI/PstI and DraI polymorphisms with the risk of alcoholic pancreatitis, the variant c2 allele and c2c2+c1c2 genotypes of *CYP2E1* RsaI/PstI polymorphism may play a role in the susceptibility of alcoholic pancreatitis within the non-Asian population, as shown by the subgroup analysis. The variant c2 allele and c2c2+c1c2 genotypes of *CYP2E1* RsaI/PstI polymorphism may also increase the risk of CAP. Studies with large samples and more specified designs were needed to demonstrate the results of this study more clearly and definitively.

Conflict of Interest

All authors declared that there were no potential conflicts of interest.

Acknowledgement

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References

1. Greenfield TK, Midanik LT, Rogers JD. A 10-year national trend study of alcohol consumption, 1984-1995: is the period of declining drinking over? Am J Public Health. 2000; 90: 47-52.
2. Dzieniszewski J, Gabryelewicz A. Pancreas; pancreatitis--Polish accomplishments. J Physiol Pharmacol. 2003; 54 Suppl 3: 155-166.
3. Singh M, Simsek H. Ethanol and the pancreas. Current status. Gastroenterology. 1990; 98: 1051-1062.
4. Ciocan D, Rebours V, Voican CS, Wrzosek L, Puchois V, Cassard AM1, et al. Characterization of intestinal microbiota in alcoholic patients with and without alcoholic hepatitis or chronic alcoholic pancreatitis. Sci Rep. 2018; 8: 4822.
5. Rosendahl J, Kirsten H, Hegyi E, Kovacs P, Weiss FU, Laumen H, et al. Genome-wide association study identifies inversion in the *CTRB1-CTRB2* locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis. Gut. 2018: 67: 1855-1863.
6. Singh D, Negi TS, Upadhyay G, Choudhuri G. Polymorphism of Alcohol Metabolizing Gene ADH3 Predisposes to Development of Alcoholic Pancreatitis in North Indian Population. Front Mol Biosci. 2015; 2: 67.
7. Porubsky PR, Meneely KM, Scott EE. Structures of human cytochrome P-450 2E1. Insights into the binding of inhibitors and both small molecular weight and fatty acid substrates. J Biol Chem. 2008; 283: 33698-33707.
8. Zhong Y, Dong G, Luo H, Cao J, Wang C, Wu J, et al. Induction of brain CYP2E1 by chronic ethanol treatment and related oxidative stress in hippocampus, cerebellum, and brainstem. Toxicology. 2012; 302: 275-284.
9. Wacke R, Kirchner A, Prall F, Nizze H, Schmidt W, Fischer U, et al. Up-regulation of cytochrome P450 1A2, 2C9, and 2E1 in chronic pancreatitis. Pancreas. 1998; 16: 521-528.
10. Hayashi S, Watanabe J, Kawajiri K. Genetic polymorphisms in the 5'-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J Biochem. 1991; 110: 559-565.
11. Lu Y, Zhu X, Zhang C, Jiang K, Huang C, Qin X. Role of CYP2E1 polymorphisms in breast cancer: a systematic review and meta-analysis. Cancer Cell Int. 2017; 17: 11.
12. Zhang MX, Liu K, Wang FG, Wen XW, Song XL. Association between CYP2E1 polymorphisms and risk of gastric cancer: An updated meta-analysis of 32 case-control studies. Mol Clin Oncol. 2016; 4: 1031-1038.
13. Zhuo X, Song J, Liao J, Zhou W, Ye H, Li Q, Xiang Z, et al. Does CYP2E1 RsaI/PstI polymorphism confer head and neck carcinoma susceptibility?: A meta-analysis based on 43 studies. Medicine (Baltimore). 2016; 95: e5156.
14. Shen ZT, Wu XH, Li B, Shen JS, Wang Z, Li J, et al. CYP2E1 Rsa Iota/Pst Iota polymorphism and lung cancer susceptibility: a meta-analysis involving 10,947 subjects. J Cell Mol Med. 2015; 19: 2136-2142.
15. Chrostek L, Cylwik B, Szmitkowski M. [Ethanol metabolism in pancreas and its role in alcoholic pancreatitis]. Pol Arch Med Wewn. 2005; 114: 989-996.
16. Apte MV, Pirola RC, Wilson JS. Molecular mechanisms of alcoholic pancreatitis. Dig Dis. 2005; 23: 232-240.
17. Cavestro GM, Comparato G, Nouvenne A, Sereni G, Bertolini S, Frulloni L, et al. Genetics of chronic pancreatitis. JOP. 2005; 6: 53-59.
18. Wilson JS, Apte MV. Role of alcohol metabolism in alcoholic pancreatitis. Pancreas. 2003; 27: 311-315.
19. Kessova IG, DeCarli LM, Lieber CS. Inducibility of cytochromes P-4502E1 and P-4501A1 in the rat pancreas. Alcohol Clin Exp Res. 1998; 22: 501-504.
20. Norton ID, Apte MV, Haber PS, McCaughan GW, Pirola RC, Wilson JS. Cytochrome P4502E1 is present in rat pancreas and is induced by chronic ethanol administration. Gut. 1998; 42: 426-430.
21. Chao YC, Wang LS, Hsieh TY, Chu CW, Chang FY, Chu HC. Chinese alcoholic patients with esophageal cancer are genetically different from alcoholics with acute pancreatitis and liver cirrhosis. Am J Gastroenterol. 2000; 95: 2958-2964.
22. Cichoz-Lach H, Celiński K, Słomka M. Alcohol-metabolizing enzyme gene polymorphisms and alcohol chronic pancreatitis among Polish individuals. HPB (Oxford). 2008; 10: 138-143.
23. Cichoz-Lach H, Partycka J, Nesina I, Wojcierowski J, Słomka M, Celiński K. Genetic polymorphism of CYP2E1 and digestive tract alcohol damage among Polish individuals. Alcohol Clin Exp Res. 2006; 30: 878-882.
24. Chao YC, Young TH, Chang WK, Tang HS, Hsu CT. An investigation of whether polymorphisms of cytochrome P4502E1 are genetic markers of susceptibility to alcoholic end-stage organ damage in a Chinese population. Hepatology. 1995; 22: 1409-1414.
25. Chao YC, Young TH, Tang HS, Hsu CT. Alcoholism and alcoholic organ damage and genetic polymorphisms of alcohol metabolizing enzymes in Chinese patients. Hepatology. 1997; 25: 112-117.
26. Frenzer A, Butler WJ, Norton ID, Wilson JS, Apte MV, Pirola

RC, et al. Polymorphism in alcohol-metabolizing enzymes, glutathione S-transferases and apolipoprotein E and susceptibility to alcohol-induced cirrhosis and chronic pancreatitis. J Gastroenterol Hepatol. 2002; 17: 177-182.
27. Kim MS, Lee DH, Kang HS, Park HS, Jung S, Lee JW, et al. [Genetic polymorphisms of alcohol-metabolizing enzymes and cytokines in patients with alcohol induced pancreatitis and alcoholic liver cirrhosis]. Korean J Gastroenterol. 2004; 43: 355-363.
28. Matsumoto M, Takahashi H, Maruyama K, Higuchi S, Matsushita S, Muramatsu T, et al. Genotypes of alcohol-metabolizing enzymes and the risk for alcoholic chronic pancreatitis in Japanese alcoholics. Alcohol Clin Exp Res. 1996; 20: 289A-292A.
29. Verlaan M, Te Morsche RH, Roelofs HM, Laheij RJ, Jansen JB, Peters WH, et al. Genetic polymorphisms in alcohol-metabolizing enzymes and chronic pancreatitis. Alcohol Alcohol. 2004; 39: 20-24.
30. Burim RV, Canalle R, Martinelli Ade L, Takahashi CS. Polymorphisms in glutathione S-transferases GSTM1, GSTT1 and GSTP1 and cytochromes P450 CYP2E1 and CYP1A1 and susceptibility to cirrhosis or pancreatitis in alcoholics. Mutagenesis. 2004; 19: 291-298.
31. Yang B, O'Reilly DA, Demaine AG, Kingsnorth AN. Study of polymorphisms in the CYP2E1 gene in patients with alcoholic pancreatitis. Alcohol. 2001; 23: 91-97.
32. Gubergrits NB, Kishenya MS, Golubova OA. [Polymorphism of ethanol metabolism genes in alcoholic chronic pancreatitis]. Ter Arkh. 2014; 86: 49-55.
33. Maruyama K, Takahashi H, Matsushita S, Nakano M, Harada H, Otsuki M, et al. Genotypes of alcohol-metabolizing enzymes in relation to alcoholic chronic pancreatitis in Japan. Alcohol Clin Exp Res. 1999; 23: 85S-91S.
34. Lu Y, Cederbaum AI. Cytochrome P450s And Alcoholic Liver Disease. Curr Pharm Des. 2018; 24: 1502-1517.
35. Xu J, Ma HY, Liang S, Sun M, Karin G, Koyama Y, et al. The role of human cytochrome P450 2E1 in liver inflammation and fibrosis. Hepatol Commun. 2017; 1: 1043-1057.
36. Garber A, Frakes C, Arora Z, Chahal P. Mechanisms and Management of Acute Pancreatitis. Gastroenterol Res Pract. 2018; 2018: 6218798.
37. Barry K. Chronic Pancreatitis: Diagnosis and Treatment. Am Fam Physician. 2018; 97: 385-393.
38. Goel S, Sharma A, Garg A. Effect of Alcohol Consumption on Cardiovascular Health. Curr Cardiol Rep. 2018; 20: 19.
39. Dguzeh U, Haddad NC, Smith KTS, Johnson JO, Doye AA, Gwathmey JK, et al. Alcoholism: A Multi-Systemic Cellular Insult to Organs. Int J Environ Res Public Health. 2018; 15: pii: E1083.
40. Godino A, Renard GM. Effects of alcohol and psychostimulants on the vasopressin system: behavioral implications. J Neuroendocrinol. 2018: e12611.
41. Obad A, Peeran A, Little JI, Haddad GE, Tarzami ST. Alcohol-Mediated Organ Damages: Heart and Brain. Front Pharmacol. 2018; 9: 81.
42. Juliusson SJ, Nielsen JK, Runarsdottir V, Hansdottir I, Sigurdardottir R, Björnsson ES. Lifetime alcohol intake and pattern of alcohol consumption in patients with alcohol-induced pancreatitis in comparison with patients with alcohol use disorder. Scand J Gastroenterol. 2018; 53: 748-754.
43. Zhong Y, Cao J, Zou R, Peng M. Genetic polymorphisms in alcohol dehydrogenase, aldehyde dehydrogenase and alcoholic chronic pancreatitis susceptibility: a meta-analysis. Gastroenterol Hepatol. 2015; 38: 417-425.
44. Zhong Y, Zou R, Cao J, Peng M. Glutathione S-transferase M1 and glutathione S-transferase T1 genotype in chronic pancreatitis: a meta-analysis. J Int Med Res. 2015; 43: 9-16.
45. Wang L, Ren G, Li J, Zhu L, Niu F, Yan M, et al. Genetic polymorphism analysis of cytochrome P4502E1 (CYP2E1) in a Chinese Tibetan population. Medicine (Baltimore). 2017; 96: e8855.
46. Yao K, Qin H, Gong L, Zhang R, Li L. CYP2E1 polymorphisms and nasopharyngeal carcinoma risk: a meta-analysis. Eur Arch Otorhinolaryngol. 2017; 274: 253-259.
47. Kandasami P, Harunarashid H, Kaur H. Acute pancreatitis in a multi-ethnic population. Singapore Med J. 2002; 43: 284-288.
48. Kirkegård J, Mortensen MR, Johannsen IR, Mortensen FV, Cronin-Fenton D. Positive predictive value of acute and chronic pancreatitis diagnoses in the Danish National Patient Registry: A validation study. Scand J Public Health. 2018: 1403494818773535.
49. Ren Z, Yang F, Wang X, Wang Y, Xu M, Frank JA, et al. Chronic plus binge ethanol exposure causes more severe pancreatic injury and inflammation. Toxicol Appl Pharmacol. 2016; 308: 11-19.
50. Kalaria R, Abraham P, Desai DC, Joshi A, Gupta T. Rate of recurrence in Indian patients presenting with acute pancreatitis and identification of chronicity on follow up: Possible risk factors for progression. Indian J Gastroenterol. 2018; 37: 92-97.
51. Parsian A, Cloninger CR, Zhang ZH. Association studies of polymorphisms of CYP2E1 gene in alcoholics with cirrhosis, antisocial personality, and normal controls. Alcohol Clin Exp Res. 1998; 22: 888-891.