GSTT1 and GSTP1 polymorphisms and breast cancer risk: a meta-analysis

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Running title: *GSTT1, GSTP1 polymorphisms and breast cancer.*

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Abstract

Cytosolic glutathione S-transferase (GST) comprises multiple isoenzymes; studies have principally examined mu-1 (GSTM1: null/present), theta-1 (GSTT1: null/present) and pi-1 (GSTP1 Ile105Val) gene polymorphisms concerning breast cancer risk. Regarding GSTT1 and GSTP1 polymorphisms, studies remain controversial and no recent meta-analysis has appeared. This meta-analysis aims to examine whether GSTT1 and GSTP1 polymorphisms are associated with breast cancer risk. Separate analyses were performed on Chinese and non-Chinese populations, in an attempt to investigate race-specific effects. Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to August 2009. Regarding GSTT1 null/present genotype, 41 case-control studies were eligible (16,589 breast cancer cases and 19,995 controls); 30 case-control studies were eligible for GSTP1 Ile105Val (16,908 cases and 20,016 controls). Pooled odds ratios (OR) were appropriately derived from fixed-effects or random-effects models. At the overall analysis, the null GSTT1 genotype was associated with elevated breast cancer risk (pooled OR=1.114, 95%CI: 1.035-1.199, random effects). However, the association seemed confined to non-Chinese populations (33 studies, pooled OR=1.128, 95%CI: 1.042-1.221, random effects), given that the association was not significant in the subset of Chinese studies (eight studies, pooled OR=1.061, 95%CI: 0.875-1.286, random effects). Regarding GSTP1 Ile105Val, no statistically significant associations were detected in non-Chinese populations (25 studies). On the other hand, the GG genotype was associated with increased breast cancer risk in Chinese populations (five studies, pooled OR=1.297, 95%CI: 1.023-1.645, fixed effects); accordingly, the recessive model yielded statistically significant results (pooled OR=1.273, 95%CI: 1.006-1.610, fixed effects). In conclusion, polymorphisms of both

GSTT1 and GSTP1 genes seem associated with elevated breast cancer risk in a race-specific manner. Given the small number of Chinese studies, the finding on GSTP1 Ile105Val merits further investigation.

Keywords: GSTT1; GSTP1; glutathione S-transferase; polymorphism; breast cancer.

Introduction

Cytosolic glutathione S-transferase (GST) comprises multiple isoenzymes; studies have principally examined mu-1 (GSTM1), theta-1 (GSTT1) and pi-1 (GSTP1) genes concerning breast cancer risk. GSTs catalyze reactions between glutathione and lipophilic compounds with electrophilic centers, leading to neutralization of toxic compounds [1].

GSTM1, GSTT1 and GSTP1 genes have been found polymorphic in the population, i.e. "present" or "null" genotypes may characterize an individual regarding GSTM1 and GSTT1, whereas a single-nucleotide polymorphism (A-to-G transition) has been identified in the exon 5 of the GSTP1 gene (Ile105Val) [2].

Attention has been drawn at a meta-analytical level upon those polymorphisms; a recent meta-analysis has demonstrated that GSTM1 null genotype is associated with elevated breast cancer risk [3]. Interestingly enough, the latest meta-analyses on the association between GSTT1, GSTP1 genotypes and breast cancer risk appeared in 2004 [4, 5]; the above meta-analyses had been based upon a small number of studies available at that time period (at best 15 case-control studies) and had pointed to null associations. Since then, more than 20 additional case-control studies have been published regarding both GSTT1 [6-28] and GSTP1 [7, 8, 11-15, 17, 20-32] polymorphisms and breast cancer risk, with contradictory findings. Under the light of the substantial improvement in the power of the meta-analysis, the need for an up-to-date meta-analysis has become evident.

This meta-analysis aims to examine whether GSTT1 and GSTP1 polymorphisms status is associated with breast cancer risk. Separate analyses were

performed on Chinese and non-Chinese populations, in an attempt to investigate race-specific effects.

Methods

Trial Identification

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to August 2009 (last search: August 11, 2009) using combinations of the following keywords: “glutathione-S tranferase”, “GSTT1”, “GSTP1”, “polymorphism”, “genotype”, “variant”, “breast cancer”. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used and two investigators (KPE and TNS), working independently, searched the literature and extracted data from each eligible case-control study.

Eligible Studies and Data Abstraction

All case-control studies with any sample size examining the association between breast cancer and GSTT1 null genotype or GSTP1 Ile105Val were considered eligible for this meta-analysis. For each one of the eligible case-control studies the following data were collected: journal name, year of publication, inclusion and exclusion criteria, demographic characteristics of the population being studied, menopausal status, frequencies of genotypes in cases and controls for each of the above genotypes/polymorphisms.

Statistics

Based on the genotype frequencies in cases and controls, crude odds ratios (OR) as well as their standard errors (SE) were calculated. Regarding GSTT1, the ORs pertained to null genotype carriers vs. present (positive) genotype carriers.

Concerning GSTP1, four different ORs were calculated: i) AG vs AA (heterozygous carriers), ii) GG vs AA (homozygous carriers), iii) G allele carriers (AG and GG grouped together) vs. AA (dominant model) and iv) GG genotype vs. A allele carriers (AG and AA grouped together) (recessive model). Separate analyses were performed in Chinese and non-Chinese populations.

The fixed-effects model (Mantel-Haenszel method), as well as the random effects (DerSimonian Laird) model, were used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2 respectively [33]. In case no significant heterogeneity was detected, the fixed effects model was chosen. Evidence of publication bias was determined using Egger's formal statistical test [34] and by visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $p<0.1$. Meta-analysis was performed using the STATA "metan" command.

In addition, meta-regression was performed to assess whether Odds Ratio (OR) was associated with publication year. The exponentiated coefficient is provided, since the dependent variable in the meta-regression model is log(OR). Meta-regression was performed with the *"metareg"* STATA command. Analyses were conducted using STATA 10.0 (STATA Corp. College Station, TX, USA).

Results

Figure 1 graphically illustrates the trial flow chart. Out of the 161 abstracts retrieved through the search criteria, 94 were irrelevant, nine articles [35-43] were excluded because they were conducted on overlapping populations with other eligible studies [6, 8, 20, 25, 30, 44, 45] (these excluded articles represent smaller studies performed on subsets of larger eligible studies), five studies [46-50] were excluded given that

they have not included controls in their study design, two articles [4, 51] were reviews/meta-analyses, and three studies [52-54] were excluded due to other reasons (two of them [52, 53] was excluded due to reporting reasons, i.e. no reporting of the relevant genotype frequencies, whereas the other [54] was excluded for examining the association between GSTA1 polymorphism and survival after breast cancer treatment). As a result, 48 case-control articles [5-32, 44, 45, 55-72] were included in this meta-analysis; 41 case-control studies [5-28, 44, 45, 55-59, 61-65, 67-71] were included in the meta-analysis on GSTT1 genotype (16,589 breast cancer cases and 19,995 controls) and 30 case-control studies [7, 8, 11-15, 17, 20-32, 60, 62, 64-68, 70, 72] on GSTP1 polymorphism (16,908 cases and 20,016 controls). Evidently, the sum of studies surpasses the number of eligible articles, as more than one study were presented per article. In addition, 33 case-control studies were included in the meta-analysis on GSTT1 genotype on non-Chinese subjects (14,139 cases and 16,465 controls) [7, 9, 12-15, 17, 19-28, 44, 45, 55-58, 61-65, 67-71] and eight case-control studies on Chinese subjects (2,450 cases and 3,530 controls) [5, 6, 8, 10, 11, 16, 18, 59]. Accordingly, 25 case-control studies [7, 12-15, 17, 20-28, 32, 60, 62, 64-69, 70, 72] were included in the meta-analysis on GSTP1 genotype on non-Chinese subjects (12,652 cases and 14,843 controls) and five case-control studies on Chinese subjects (4,256 cases and 5,173 controls) [8, 11, 29-31].

At the overall analysis, the null GSTT1 genotype was associated with elevated breast cancer risk (pooled OR=1.114, 95%CI: 1.035-1.199, random effects). Interestingly enough, stratification by race pointed to discrepancy between non-Chinese and Chinese studies. The association seemed confined to non-Chinese populations (pooled OR= 1.128, 95%CI: 1.042-1.221, random effects, Figure 2a),

given that the association was not significant in the subset of Chinese studies (pooled OR= 1.061, 95%CI: 0.875-1.286, random effects, Figure 2b).

Regarding GSTP1 Ile105Val, the results of the meta-analysis are presented in detail in the Table 1. No statistically significant associations were detected in non-Chinese populations. On the other hand, the GG genotype was associated with increased breast cancer risk in Chinese populations; accordingly, the recessive model yielded statistically significant results (Figure 3a and 3b).

Meta-regression with publication year did not point to any modifying effect of publication year in the case of GSTT1 polymorphism (exponentiated coefficient= 0.994, 95%CI: 0.970-1.019, p=0.630). Accordingly, no modifying effects of publication year were observed at any approach regarding GSTP1 status (for heterozygous carriers: exponentiated coefficient= 0.993, 95%CI: 0.953-1.035, p=0.738; for homozygous carriers: exponentiated coefficient= 0.993, 95%CI: 0.916-1.076, p=0.864; for the dominant model: exponentiated coefficient= 0.995, 95%CI: 0.954-1.038, p=0.809; for the recessive model: exponentiated coefficient= 0.999, 95%CI: 0.939-1.063, p=0.970).

Concerning GSTT1 polymorphism, publication bias was significant in the overall meta-analysis (p=0.048), mainly due to the publication bias in non-Chinese studies (p=0.045); no significant publication bias was detected in Chinese studies (p=0.742). On the contrary, no significant publication bias was detected in any meta-analysis performed on GSTP1 polymorphism status (p=0.607 for heterozygous carriers, p=0.557 for homozygous carriers, p=0.787 for the dominant model, p=0.393 for the recessive model).

Discussion

The principal message of this meta-analysis is that polymorphisms of both GSTT1 and GSTP1 genes seem associated with elevated breast cancer risk in a race-specific manner. Specifically, GSTT1 null phenotype seems able to confer additional breast cancer risk in non-Chinese populations, whereas GSTP1 Ile105Val G allele seems associated with increased breast cancer risk in Chinese subjects following a recessive model.

Concerning GSTT1 null phenotype, it is worth mentioning that the present meta-analysis makes one step beyond the existing meta-analysis by Egan et al [5], which had been published five years ago and had pointed to marginal associations, characterized by the authors as "*null results*". In the present meta-analysis, under the light of a nearly 3-fold increase in the number of eligible studies, a clear association between GSTT1 null genotype and increased breast cancer risk became evident and seemed indeed confined to non-Chinese populations. Race-specific effects of GSTT1 polymorphism status may not seem surprising at a meta-analytical level, as race-specific associations have been described in meta-analyses examining lung [73] and gastric [74] cancer.

Similarly, the results concerning GSTP1 Ile105Val exhibited a race-specific pattern, but opposite to that demonstrated in GSTT1. The association between the G allele seemed confined in Chinese studies; nevertheless, given that the sample size of the study by Lee at al [30] is considerably larger than that of the remaining studies, the latter emerges as particularly influential. As a result, the need for additional studies on Chinese populations seems warranted, so as to establish the present findings.

An issue that has been raised in previous meta-analyses examining GSTT1 and GSTP1 status vis-à-vis breast cancer risk is the putative interaction with menopausal status. In the present meta-analysis, such subanalyses have not been presented after

carefully taking into account that solely ten [6, 9, 15, 28, 44, 58, 65, 67, 69, 70] out of 41 studies on GSTT1 and nine [15, 28-32, 65, 67, 70] out of 30 studies on GSTP1 status have presented subanalyses on pre- and postmenopausal women. Indeed, the power of the above subsets of studies was so limited that the main associations were blurred (data not shown); as a result, proceeding to subanalyses on pre- and postmenopausal subjects did not seem of particular value.

In conclusion, this meta-analysis points to a positive association between GSTT1 null genotype and breast cancer risk in non-Chinese subjects; the positive association between GSTP1 G allele and elevated breast cancer risk in Chinese subjects is worth investigating further.

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Figure Legends

Figure 1: Study flow chart explaining the selection of the 48 eligible case-control studies.

Figure 2: Forest plot for the overall association between null GSTT1 genotype and breast cancer risk for **a.** non-Chinese and **b.** Chinese subjects. Each study is shown by the point estimate of the Odds Ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence interval for the OR (extending lines); the pooled OR and 95% confidence interval have been appropriately derived from random effects model.

Figure 3: Forest plot for the overall association between the GSTP1 GG *(Val/Val)* genotype and breast cancer risk for **a.** non-Chinese (random effects) and **b.** Chinese subjects (fixed effects).

Table 1. Pooled ORs by race for heterozygous, homozygous carriers, dominant and recessive model. All pooled ORs were derived from random-effects models except for cells marked with [F] (fixed-effects model). Bold letters denote statistically significant results.

Race	Heterozygous[§] (AG vs. AA)		Homozygous[§] (GG vs. AA)		Dominant model (GG and AG vs. AA)		Recessive model[§] (GG vs. AA and AG)	
	OR (95%CI)	Test for heterogeneity	OR (95%CI)	Test for heterogeneity	OR (95%CI)	Test for heterogeneity	OR (95%CI)	Test for heterogeneity
Overall (n=30)	1.004 (0.886-1.137)	p<0.001	0.991 (0.788-1.246)	p<0.001	1.013 (0.899-1.142)	p<0.001	0.992 (0.826-1.192)	p<0.001
Non-Chinese (n=25)	1.001 (0.858-1.169)	p<0.001	0.980 (0.754-1.273)	p<0.001	1.007 (0.869-1.167)	p<0.001	0.979 (0.795-1.204)	p<0.001
Chinese (n=5)	1.057[F] (0.965-1.159)	p=0.370	**1.297[F] (1.023-1.645)**	p=0.374	1.083[F] (0.994-1.180)	p=0.611	**1.273[F] (1.006-1.610)**	p=0.323

[§]the calculations were based on 23 non-Chinese and four Chinese studies, as the studies by Chang et al. [11], Steck et al. [15] and McCarty et al. [26] did not provide the necessary data.

Figure
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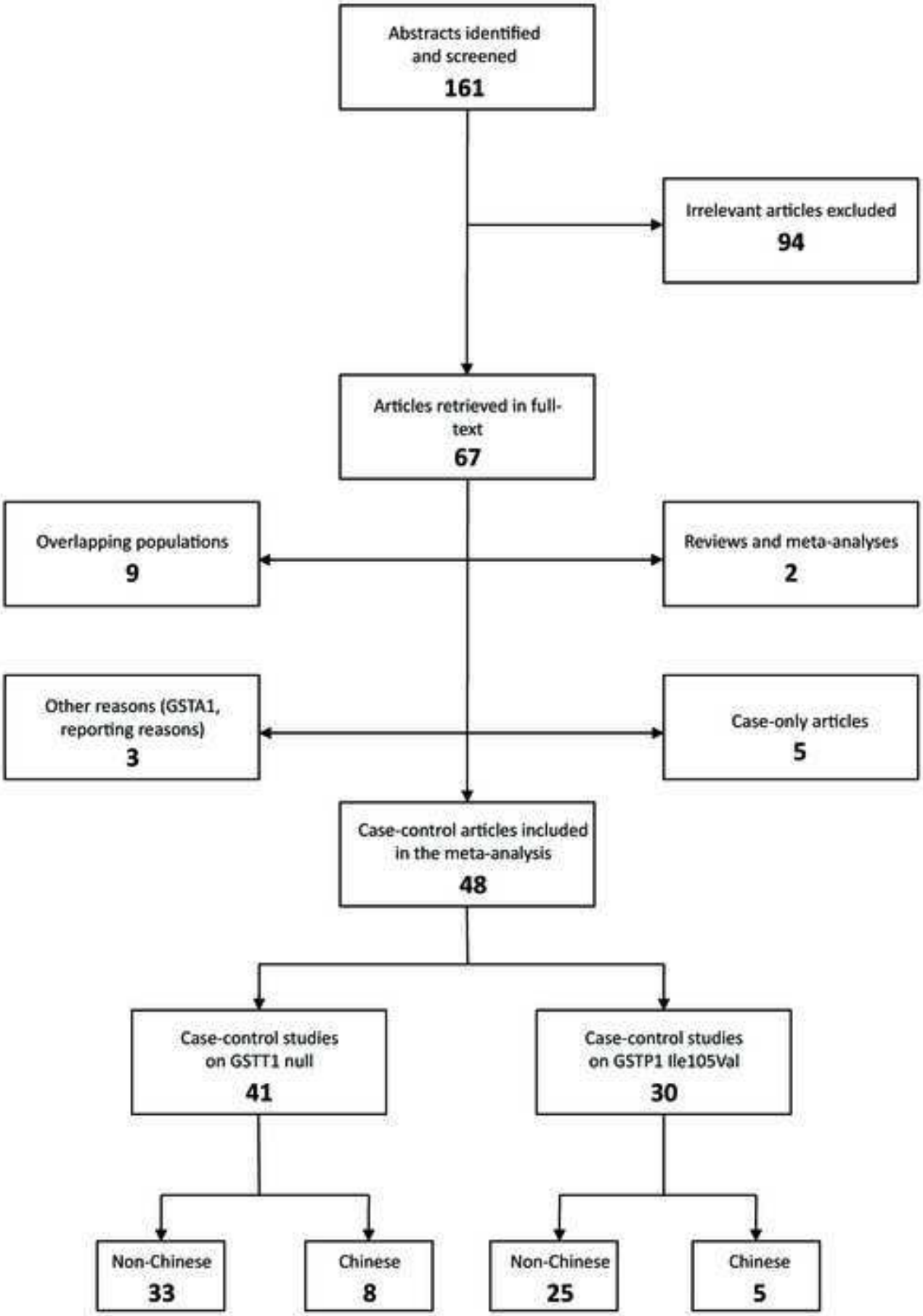

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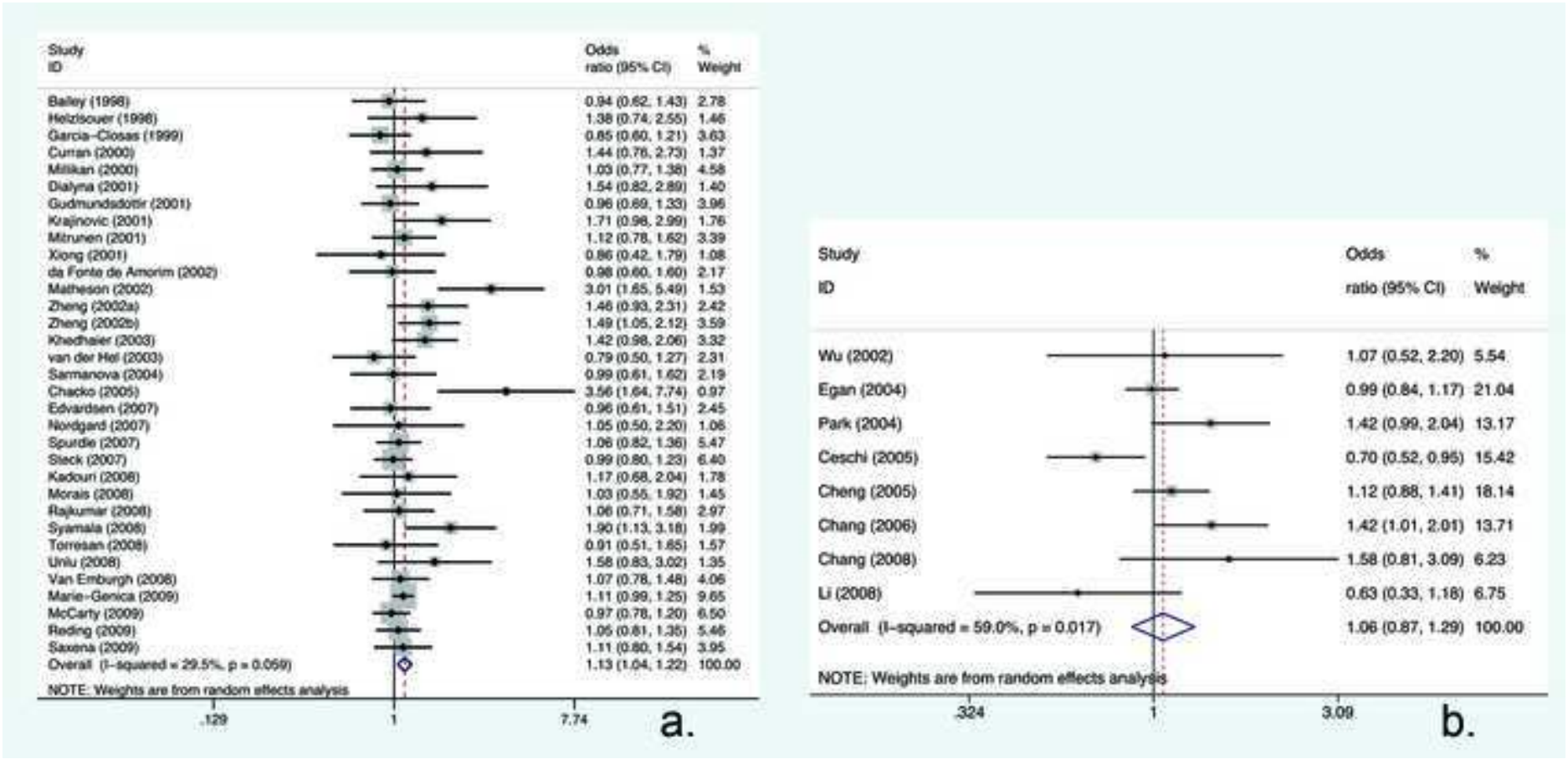

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