Glutathione S-transferase P1 Ile105Val polymorphism and breast cancer risk: convergence and divergence of the two recent meta-analyses

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Dear Editor,

We read with great interest the recent meta-analysis by Lu et al. [1], which has reached important conclusions about the association between glutathione S-transferase P1 (GSTP1) Ile105Val polymorphism and breast cancer risk.

Nevertheless, some methodological issues need to be addressed concerning the meta-analysis by Lu et al. [1]. Importantly, three sizeable eligible studies [2-4] (2,204 cases and 2,530 controls) have not been included in the meta-analysis, even though they satisfied the search criteria.

In addition, close inspection of the data provided by the authors (Table 1) revealed some issues that are worth discussing, so as to provide the scientific audience with an accurate presentation of the underlying data. Specifically, the data reported by Lu et al. [1] for the studies by Maugard et al. [5], Krajinovic et al. [6], Unlu et al. [7] and Torresan et al. [8] do not seem in line with the data provided in the original publications. The genotype frequencies for Ile/Ile, Ile/Val, Val/Val in cases and controls should read: 99-101-20-81-90-*25* for the study by Maugard et al. [5], *69*-55-5-*91*-73-13 for the study by Krajinovic et al. [6], *28*-26-11-51-37-20 for the study by Unlu et al. [7] and *54*-*35*-13-*77*-*22*-3 for the study by Torresan et al. [8] (italics denote the discrepancies between Lu et al. [1] and the original publications). The above may imply that the original odds ratios for the aforementioned studies may significantly differ from those calculated by Lu et al. [1].

It can be also secondarily noted that the selection of controls in the study by Lee et al. [9] is not hospital-based, given that Lee et al. [9] clearly states that "*controls were*

randomly selected from the general population of Shanghai". As a result, the studies by Lee et al. [9] and Egan et al. [10] seem to have been performed on mutually overlapping populations; consequently the smaller study [10] should have been excluded from the analysis.

Despite the above, the results reported by Lu et al. [1] confirm our previous meta-analysis [11] and essentially expand them among the subset of hospital-based studies. Discussing methodological issues of meta-analyses [12, 13] may well elaborate and substantiate their original results.

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Response to the comments raised by Drs. Economopoulos and Sergentanis

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We would like to thank Dr. Economopoulos and Dr. Sergentanis for their thoughtful comments concerning our article [1]. Taking into account the comments, we immediately undertook a thorough check and a full reanalysis of the data. As a result, we found that the correction to the five data points used in the analysis that was originally presented does not change the results or the interpretation of the meta-analysis. Our findings continue to support the existence of a significant association between GSTP1 Ile105Val polymorphism

and increased breast cancer susceptibility in Asian population (for recessive model Val/Val vs. Ile/Ile + Ile/Val: OR = 1.36, 95% CI = 1.13–1.63, Fig.1) and hospital-based studies (for Val/Val vs. Ile/Ile: OR = 1.32, 95% CI = 1.07–1.63; for recessive model Val/Val vs. Ile/Ile + Ile/Val: OR = 1.24, 95% CI = 1.01–1.51; for dominant model: Val/Val + Ile/Val vs. Ile/Ile: OR = 1.14, 95% CI = 1.01– 1.27, Fig.2). The main results and the heterogeneity tests are presented in Table 1.

Dr. Economopoulos pointed out that our meta-analysis missed three sizeable eligible studies [2-4]. Actually, these three articles were not overlooked in our analysis. In the articles by McCarty et al. [3] and Chang et al. [2], authors provided the genotype frequencies of AG+GG instead of the frequency of each single genotype, which failed to meet our inclusion criteria previously described in our article [1]. In Steck et al.'s article [4], we found that the frequencies of genotypes in controls given in the results part of the text seem not in accordance to those listed in this article's Table 1. For the above reasons, we excluded the three articles from our meta-analysis, though they do have a relatively large number of subjects.

There is another issue raised by Dr. Economopoulos that the genotype frequencies for Ile/Ile, Ile/Val, Val/Val in cases and controls

should be 54-35-13-77-22-3 for the study by Torresan et al. [8] However, the HWE in controls calculated based on Dr. Economopoulos' data ($\chi^2 = 0.813$, $P = 0.367$) seems not in line with that in the original publication ($\chi 2 = 1.0$; $P > 0.30$). Meanwhile, the HWE from our analysis confirms the validity of our data ($\chi^2 = 1.043$, $P = 0.307$).

After taking the suggestion of Dr. Economopoulos and Dr. Sergentanis, we reached a more elaborating conclusion which remains to provide strong support for an association between GSTP1 Ile105Val polymorphism and elevated breast cancer risk.

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Table 1 Summary ORs and 95% CIs of GSTP1 Ile105Val polymorphism and breast cancer risk

	Val/Val vs. Ile/Ile		Ile/Val vs. Ile/Ile		Val/Val vs.Ile/Ile+Ile/Val		Val/Val+Ile/Val vs.Ile/Ile	
	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*
Total	0.99(0.79–1.24)	0.00†	0.99(0.88–1.12)	0.00†	0.99(0.83–1.19)	0.00†	1.00(0.88–1.14)	0.00†
Ethnicity								
Asian	1.28(0.92–1.78)	0.03†	1.07(0.94–1.23)	0.08	1.36(1.13–1.63)	0.11	1.10(0.94–1.28)	0.02†
European	0.93(0.68–1.28)	0.00†	0.98(0.81–1.17)	0.00†	0.94(0.73–1.20)	0.00†	0.98(0.80–1.20)	0.00†
Source of control								
Populaiton based	0.85(0.61–1.17)	0.00†	0.92(0.78–1.10)	0.00†	0.89(0.69–1.15)	0.00†	0.92(0.76–1.11)	0.00†
Hospital based	1.32(1.07–1.63)	0.43	1.11(0.98–1.25)	0.42	1.24(1.01–1.51)	0.64	1.14(1.01–1.27)	0.19
Menopausal status								

Premenopausal	0.70(0.37–1.33)	0.00†	0.77(0.54–1.09)	0.00†	0.87(0.54–1.42)	0.00†	0.76(0.53–1.11)	0.00†
postmenopausal	0.87(0.53–1.43)	0.00†	0.89(0.67–1.18)	0.00†	0.92(0.62–1.36)	0.00†	0.89(0.66–1.22)	0.00†

*P value for heterogeneity

† Estimates for Random–effects model

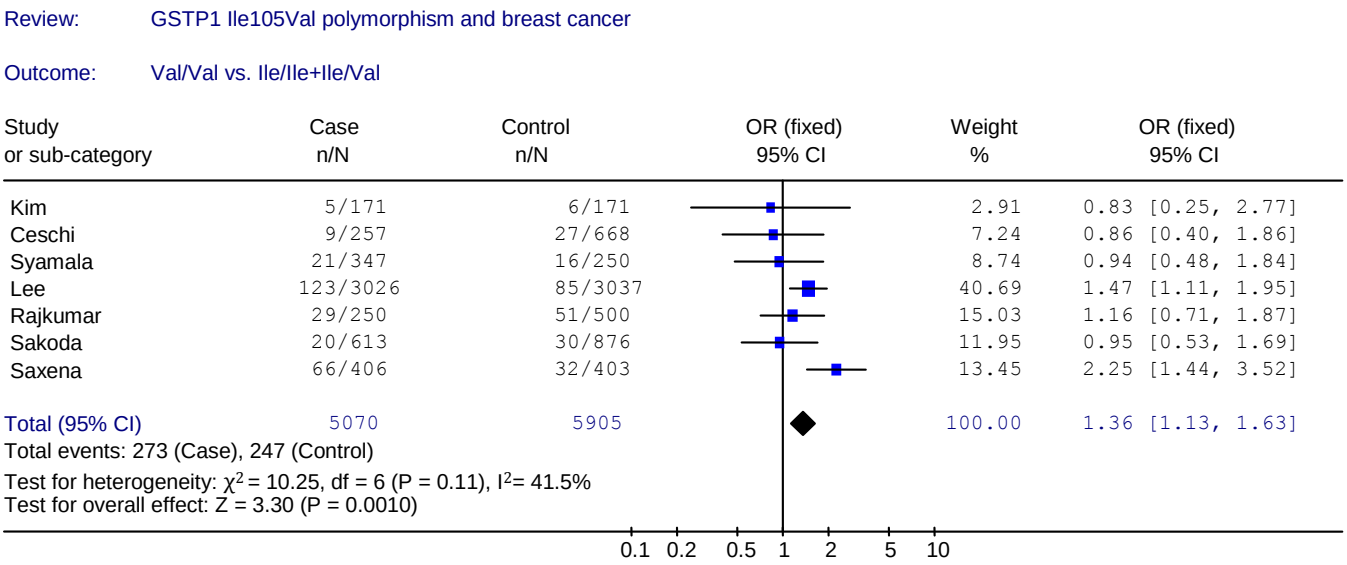

Fig.1 OR of breast cancer associated with GSTP1 Ile105Val polymorphism for the Val/Val genotype compared with the Ile/Ile +Ile/Val genotypes in Asian population.

Review: GSTP1 Ile105Val polymorphism and breast cancer

Outcome: Val/Val vs. Ile/Ile

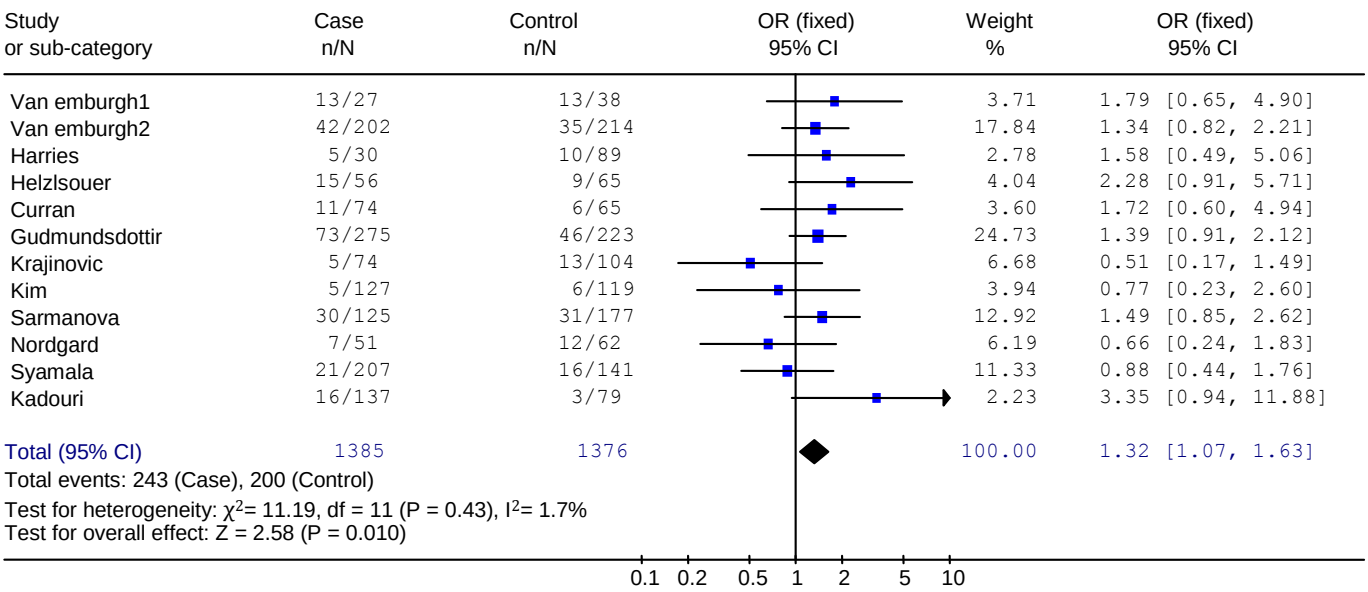

Fig.2 OR of breast cancer associated with GSTP1 Ile105Val polymorphism for the Val/Val genotype compared with the Ile/Ile genotype in hospital–based studies.