The association between methylenetetrahydrofolate reductase gene C677T polymorphisms and breast cancer risk in Chinese population

Yadong Wang¹ · Haiyan Yang² · Huiyan Gao¹ · Haiyu Wang¹

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Abstract With great interest, we read the recent article entitled “Methylenetetrahydrofolate reductase polymorphisms and breast cancer risk in Chinese population: a meta-analysis of 22 case-control studies” published online in *Tumor Biology*, 2014, 35: 1695–1701. This article suggests that methylenetetrahydrofolate reductase (*MTHFR*) C677T polymorphism was significantly associated with breast cancer risk in Chinese population. The result is encouraging. Nevertheless, three key issues in this meta-analysis are worth noticing.

Keywords *MTHFR* · Polymorphism · Breast cancer · Risk · Meta-analysis · Chinese

We read with great interest the recent paper entitled “Methylenetetrahydrofolate reductase polymorphisms and breast cancer risk in Chinese population: a meta-analysis of 22 case-control studies” published online in *Tumor Biology*, 2014, 35: 1695–1701 [1]. Liang et al. conducted a meta-analysis to investigate the association between methylenetetrahydrofolate reductase (*MTHFR*) gene C677T polymorphisms and breast cancer risk in the Chinese population on the basis of 13 case-control studies with 3272 cases and 4419 controls. The authors found that *MTHFR* C677T

polymorphism was significantly associated with breast cancer risk in the Chinese population under three genetic models [T vs. C: odds ratio (OR)=1.12, 95 % confidence interval (95 % CI)=1.02–1.23, $P=0.015$; TT vs. CC: OR=1.35, 95 % CI=1.10–1.67, $P=0.005$; TT vs. CC+CT: OR=1.37, 95 % CI=1.11–1.70, $P=0.004$]. It is an extremely valuable study.

Nevertheless, after carefully examining the data provided by Liang et al. (shown in Table 1 in their original text) [1], we found that three key issues should be worth noticing. Firstly, one overlapping paper [2] was not properly excluded from the study of Liang et al. [1]. Secondly, the meta-analysis of Liang et al. failed in including two eligible articles [3, 4] that were available at the time their meta-analysis was performed. Thirdly, the data reported by Liang et al. [1] for the study of Gao et al. [5] did not seem in line with the data provided by Gao et al. [5] in their original publication. The numbers reported by Gao et al. [5] (shown in Table 2 of the original paper of Gao et al.) for CC, CT, and TT, in cases and controls, are 202-305-117 and 235-301-88, respectively. Interestingly enough, after carefully examining the data reported by Liang et al. [1], the numbers are 217-327-125 in cases and 257-329-96 in controls, respectively. Therefore, the conclusions by Liang et al. are not entirely reliable. It is required to clarify the association between *MTHFR* C677T polymorphisms and the risk of breast cancer in Chinese population comprehensively and objectively. We reassessed this association by performing an updated meta-analysis on the basis of a total of 18 studies with 6808 cases and 7872 controls. Further subgroup analysis was conducted in this study stratified by source of control and Hardy-Weinberg equilibrium (HWE) in controls. In addition, cumulative meta-analysis was carried out to examine the tendency of results by accumulating single study year by year, which could be used to determine whether new relevant studies are needed or

✉ Yadong Wang
wangyd76@yahoo.com; wangyd76@126.com;
wangyd76@163.com

¹ Department of Toxicology, Henan Center for Disease Control and Prevention, No. 105 of South Nongye Road, Zhengzhou 450016, China

² Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou 450052, China

Table 1 Main characteristics of selected studies in this meta-analysis

Author	Year	Region	Source of control	Number of case	Number of control	<i>P</i> value of HWE
Cheng C [6]	2008	Taiwan	HB	349	530	0.623636
Gao C [5]	2009	Nanjing	PB	624	624	0.592439
Han H [3]	2011	Shandong	HB	47	52	0.073532
He J [7]	2014	Henan	HB	310	381	0.000019
Hua Z [8]	2011	Yunnan	PB	95	90	0.021217
Huang C [9]	2014	Taiwan	HB	1232	1232	0.288652
Inoue M [10]	2008	Singapore	PB	380	608	0.527225
Kan X [11]	2007	Yunnan	PB	125	103	0.041775
Li W [12]	2009	Guangdong	PB	65	143	0.187377
Liu Y [13]	2013	Guangdong	HB	435	435	0.222884
Qi J [14]	2004	Beijing	PB	217	218	0.593105
Qiao J [15]	2014	Henan	HB	535	673	0.000002
Shrubsole M [16]	2004	Shanghai	PB	1112	1160	0.442466
Wu X [17]	2012	Yunnan	HB	75	75	0.800632
Wu Y [4]	2012	Shandong	HB	200	200	0.023998
Xi J [18]	2014	Guangdong	HB	818	848	0.355550
Yu C [19]	2007	Taiwan	PB	109	420	0.336255
Yuan H [20]	2009	Heilongjiang	HB	80	80	0.515565

HB hospital-based control, PB population-based control, HWE Hardy-Weinberg equilibrium

Table 2 The summary odds ratio for the association of *MTHFR* C677T polymorphisms with breast cancer risk in Chinese population

Genetic model	Cases/controls	Heterogeneity test		Summary OR (95 % CI)	Hypothesis test		df	Begg's test		Egger's test		
		<i>Q</i>	<i>P</i>		<i>Z</i>	<i>P</i>		<i>Z</i>	<i>P</i>	<i>t</i>	<i>P</i>	
Total												
CT vs. CC	5810/7045	18.88	0.34	1.03 (0.95–1.10)	0.69	0.49	17	0.08	0.940	0.06	0.954	
TT vs. CC	4069/4635	56.68	<0.00001	1.57 (1.26–1.97)	3.95	<0.0001	17	1.59	0.112	1.53	0.145	
CT+TT vs. CC	6808/7872	36.45	0.004	1.12 (1.00–1.25)	2.05	0.04	17	0.68	0.495	0.91	0.377	
T vs. C	13,616/15,744	64.46	<0.00001	1.20 (1.08–1.34)	3.30	0.001	17	1.36	0.173	1.31	0.208	
Stratification by HWE												
Yes												
CT vs. CC	4785/5765	13.15	0.36	1.01 (0.93–1.09)	0.27	0.79	12	0.43	0.669	0.62	0.545	
TT vs. CC	3229/3696	44.10	<0.0001	1.51 (1.15–1.98)	2.95	0.003	12	1.65	0.100	1.71	0.115	
CT+TT vs. CC	5543/6425	25.56	0.01	1.09 (0.96–1.23)	1.36	0.17	12	1.40	0.161	1.39	0.192	
T vs. C	11,086/12,850	45.40	<0.00001	1.16 (1.03–1.31)	2.44	0.01	12	1.65	0.100	1.58	0.143	
Stratification by source of control												
Population-based control												
CT vs. CC	2285/2937	9.97	0.19	0.98 (0.88–1.10)	0.32	0.75	7	1.11	0.266	0.55	0.601	
TT vs. CC	1532/1881	22.71	0.002	1.34 (0.94–1.92)	1.62	0.11	7	0.62	0.536	1.14	0.298	
CT+TT vs. CC	2727/3366	15.30	0.03	1.04 (0.87–1.25)	0.41	0.68	7	0.12	1.000	0.27	0.796	
T vs. C	5454/6732	23.60	0.001	1.09 (0.93–1.29)	1.06	0.29	7	0.12	0.902	0.58	0.584	
Hospital-based control												
CT vs. CC	3525/4108	8.00	0.53	1.05 (0.96–1.16)	1.14	0.25	9	0.36	0.721	0.70	0.506	
TT vs. CC	2537/2754	24.98	0.003	1.75 (1.33–2.29)	4.03	<0.0001	9	1.07	0.283	0.97	0.359	
CT+TT vs. CC	4081/4506	18.08	0.03	1.18 (1.03–1.36)	2.40	0.02	9	1.07	0.283	1.24	0.250	
T vs. C	8162/9012	32.80	0.0001	1.29 (1.12–1.48)	3.50	0.0005	9	1.43	0.152	1.36	0.211	

HWE Hardy-Weinberg equilibrium, OR odds ratio, 95 % CI 95 % confidence interval

Fig. 1 Forest plots of the odds ratio for *MTHFR* C677T polymorphisms associated with breast cancer risk (**a** TT vs. CC, **b** CT+TT vs. CC, **c** T-allele vs. C-allele, and **d** CT vs. CC)

Fig. 2 Forest plots for cumulative meta-analysis of odds ratio for *MTHFR* C677T polymorphisms associated with breast cancer risk (**a** TT vs. CC, **b** CT+TT vs. CC, **c** T-allele vs. C-allele, and **d** CT vs. CC)

Fig. 3 Funnel plot analysis to detect publication bias for *MTHFR* C677T polymorphisms associated with breast cancer risk (**a** TT vs. CC, **b** CT+TT vs. CC, **c** T-allele vs. C-allele, and **d** CT vs. CC)

Fig. 4 Sensitivity analysis on the association between *MTHFR* C677T polymorphisms and breast cancer risk (T-allele vs. C-allele)

not. We hope that our results are able to provide comprehensive and objective evidence for the association of *MTHFR* C677T polymorphisms with breast cancer risk in Chinese population.

Table 1 listed the main characteristics of selected studies in this meta-analysis. Table 2 listed the summary odds ratios of the association between *MTHFR* C677T polymorphisms and the risk of breast cancer in Chinese population. Overall, we observed an increased risk of breast cancer among the subjects carrying *MTHFR* C677T TT and CT+TT genotypes (OR=1.57, 95 % CI 1.26–1.97 and OR=1.12, 95 % CI 1.00–1.25, respectively) compared with those carrying CC genotype in total Chinese population (Fig. 1a, b). We also observed an increased risk of breast cancer among the subjects carrying *MTHFR* C677T T-allele (OR=1.20, 95 % CI 1.08–1.34) compared with those carrying C-allele in total Chinese population (Fig. 1c). We did not observe the association of *MTHFR* C677T polymorphism with breast cancer risk under the genetic model of CT vs. CC (OR=1.03, 95 % CI 0.95–1.10) (Fig. 1d). The cumulative meta-analysis accumulated the studies in the light of the year of publications, and the results showed that there were still significant associations between *MTHFR* C677T polymorphisms and breast cancer risk under the genetic models of TT vs. CC, CT+TT vs. CC, and T-allele vs. C-allele; the cumulative ORs were 1.57 with 95 % CI 1.26–1.97, 1.12 with 95 % CI 1.00–1.25, and 1.20 with 95 % CI 1.08–1.34, respectively (Fig. 2a–c). When limiting the analysis to the studies with controls in agreement with HWE, we observed an increased risk of breast cancer among the subjects carrying TT genotype compared with those carrying CC genotype (OR=1.51, 95 % CI 1.15–1.98) and among the subjects carrying T-allele compared with those

carrying C-allele (OR=1.16, 95 % CI 1.03–1.31) (Table 2). In a subgroup analysis by source of control, we observed an increased risk of *MTHFR* C677T polymorphisms for breast cancer under the genetic models of TT vs. CC, CT+TT vs. CC and T-allele vs. C-allele on the basis of hospital-based controls (OR=1.75 with 95 % CI 1.33–2.29, OR=1.18 with 95 % CI 1.03–1.36 and OR=1.29 with 95 % CI 1.12–1.48, respectively) (Table 2). We did not observe any association between *MTHFR* C677T polymorphisms and breast cancer risk on the basis of population-based controls (Table 2).

The shape of funnel plots seemed to be approximately symmetrical among total population (Fig. 3a–d). Both Egger's test and Begg's test results suggested that no evidence of publication bias existed in this meta-analysis (Table 2). To evaluate the stability of the results of the meta-analysis, we performed a sensitivity analysis through sequentially removing each individual study. The sensitivity analysis showed that the results were robust and were not influenced by any single study (Fig. 4).

In summary, the results of the study by Liang et al. [1] should be expounded with caution. To reach a definitive conclusion, further well-designed and larger sample size studies are still needed to evaluate the association between *MTHFR* C677T polymorphisms and breast cancer risk in Chinese population. We hope that our remarks will contribute to more accurate elaboration and substantiation of the results provided by Liang et al. [1].

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Conflicts of interest None

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