Note of clarification of data in the paper entitled no association between XRCC1 gene Arg194Trp polymorphism and risk of lung cancer: evidence based on an updated cumulative meta-analysis

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We read with great interest the paper entitled “No association between XRCC1 gene Arg194Trp polymorphism and risk of lung cancer: evidence based on an updated cumulative meta-analysis” published in *Tumor Biol.* 2014, 35: 5629–5635 [1]. Zhang et al. performed a meta-analysis to explore the association between X-ray repair cross-complementing group 1 (XRCC1) Arg194Trp polymorphism and lung cancer risk on the basis of 25 case-control studies with 8876 cases and 11,210 controls. The authors found that XRCC1 Arg194Trp polymorphism was not associated with lung cancer risk [odds ratio (OR)=0.97 with 95 % confidence interval (95 %CI): 0.92–1.03 for Trp vs. Arg; OR=0.92 with 95 %CI: 0.85–0.98 for Arg/Trp vs. Arg/Arg; OR=1.07 with 95 %CI: 0.92–1.23 for Trp/Trp vs. Arg/Arg; OR=0.93 with 95 %CI: 0.87–1.00 for Trp/Trp+Arg/Trp vs. Arg/Arg; and OR=1.08 with 95 %CI: 0.94–1.25 for Trp/Trp vs. Arg/Trp+Arg/Arg]. The cumulative meta-analysis showed that the results maintained the same, while the ORs with 95 % CI were

more stable with the accumulation of case-control studies. It is a valuable study.

Nevertheless, careful examination of the data provided by Zhang et al. [1] (shown in Table 1 in their original text) revealed two key issues that are worth noticing. Firstly, one overlapping paper [2] was not properly excluded from Zhang et al.’s study [1]. Secondly, the data reported by Zhang et al. [1] for the study by Wang et al. [3] do not seem in line with the data provided by Wang et al. [3] in their original publication. The numbers reported by Wang et al. [3] (shown in Table 1 in Wang et al.’s original paper) for Arg/Arg, Arg/Trp, and Trp/Trp, in cases and controls, are 89, 80, and 40 and 138, 90, and 28, respectively. Interestingly enough, after carefully examining the data reported by Zhang et al. [1], the numbers are 105, 83, and 21 in cases and 137, 96, and 23 in controls, respectively (supporting information). Therefore, the conclusions by Zhang et al. [1] are not entirely reliable. It is required to clarify the association between XRCC1 Arg194Trp polymorphism and lung cancer risk. We reassessed this association by performing a meta-analysis on the basis of a total of 30 studies with 9508 cases and 11,845 controls, which may provide comprehensive evidence for the association of XRCC1 Arg194Trp polymorphism with lung cancer risk.

Table 1 listed the general information of selected studies. Table 2 listed the summary odds ratios of the association between XRCC1 Arg194Trp polymorphism and lung cancer risk. Overall, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 194 Trp/Trp genotype (OR=1.26, 95 %CI: 1.10–1.45) compared with Arg/Arg genotype carriers in total population (Fig. 1a). We did not observe any association of Arg/Trp and Trp/Trp+Arg/Trp polymorphisms with lung cancer risk (OR=0.96, 95 %CI: 0.86–1.08 for Arg/Trp

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Table 1 Characteristics of selected papers

Author	Year	Country	Ethnicity	Source of control	Number of case	Number of control	HWE
Buch Shama [6]	2012	USA	Caucasian	HB	720	928	0.015858
Chan Eunice [7]	2005	China	Asian	HB	75	162	0.745951
Chang Jeffrey-A [8]	2009	USA	African	PB	255	280	0.976205
Chang Jeffrey-C [8]	2009	USA	Caucasian	PB	113	299	0.073084
Chen Senqing [9]	2002	China	Asian	PB	103	102	0.546278
David-Beabes-A [10]	2001	USA	African	PB	154	243	0.736731
David-Beabes-C [10]	2001	USA	Caucasian	PB	180	461	0.181632
De Ruyck Kim [11]	2007	Belgium	Caucasian	HB	110	110	0.379774
Du Yong [12]	2012	China	Asian	HB	100	100	0.000012
Du Yong [5]	2014	China	Asian	HB	120	120	0.000009
Guo Shujie [13]	2013	China	Asian	HB	684	602	0.526784
Hao B. [14]	2006	China	Asian	PB	1024	1118	0.701669
Hu Zhibin [15]	2005	China	Asian	HB	710	710	0.556829
Hung Rayjean [16]	2005	Mixed	Caucasian	HB	2147	2132	0.926867
Improta Giuseppina [17]	2008	Italy	Caucasian	HB	94	121	0.405911
Janik Justyna [18]	2011	Poland	Caucasian	HB	88	79	0.548137
Li Mingchuan [19]	2008	China	Asian	HB	350	350	0.803017
Matullo G. [20]	2006	Mixed	Caucasian	PB	116	1094	0.170586
Pachouri Suparna [21]	2007	India	Asian	PB	103	122	0.042833
Ratnasinghe Duminda [22]	2001	China	Asian	PB	108	210	0.182984
Schneider Joachim [23]	2005	German	Caucasian	HB	446	622	0.811054
Shen Min [24]	2005	China	Asian	HB	118	112	0.614295
Song Yahui [4]	2004	China	Asian	HB	100	65	0.797994
Su Jia [25]	2008	China	Asian	PB	396	465	0.126621
Tanaka Yugo [26]	2010	Japan	Asian	PB	50	50	0.237879
Wang Na [3]	2012	China	Asian	HB	209	256	0.027626
Yin Jiaoyong [27]	2007	China	Asian	HB	241	249	0.570251
Yu Hongping [28]	2006	China	Asian	HB	104	121	0.043211
Zhang Wenjuan [29]	2005	China	Asian	HB	149	157	0.356342
Zienolddiny Shanbeh [30]	2006	Norway	Caucasian	PB	336	405	0.249941

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

vs. Arg/Arg and OR=1.01, 95 %CI: 0.90–1.14 for Trp/Trp+Arg/Trp vs. Arg/Arg, respectively) (Fig. 1b, c). The cumulative meta-analysis accumulated the studies in the light of publication year and showed that there was still a significant association between XRCC1 codon 194 Trp/Trp polymorphism and lung cancer risk, the cumulative odds ratio was 1.26 with 95 %CI: 1.09–1.45 (Fig. 2). Limiting the analysis to the studies with controls in agreement with Hardy-Weinberg equilibrium (HWE), we observed an increased risk of lung cancer among subjects carrying Trp/Trp genotype, compared with Arg/Arg genotype (OR=1.17, 95 %CI: 1.01–1.36)

(Table 2). When the subgroup analysis was performed by ethnicity, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 194 Trp/Trp genotype, compared with Arg/Arg genotype carries in Asians (OR=1.28, 95 %CI: 1.11–1.47), but we observed a decreased lung cancer risk among subjects carrying XRCC1 codon 194 Arg/Trp and Arg/Trp+Trp/Trp genotypes compared with Arg/Arg genotype carries in Caucasians (OR=0.85, 95 %CI: 0.73–0.99 for Arg/Trp vs. Arg/Arg and OR=0.86, 95 %CI: 0.76–0.97 for Arg/Trp+Trp/Trp vs. Arg/Arg, respectively) (Table 2). In subgroup analysis by source of control, we observed an increased risk of XRCC1

Table 2 Summary of odds ratios for the relationship of XRCC1 Arg194Trp polymorphism with lung cancer risk

Genotype	Case/control	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											
Trp/Trp vs. Arg/Arg	7124/8969	39.17	0.05	1.26 (1.10–1.45)	3.34	0.0008	26	0.57	0.568	0.51	0.613
Arg/Trp vs. Arg/Arg	8981/11,378	59.95	0.0006	0.96 (0.86–1.08)	0.70	0.49	29	0.21	0.830	0.43	0.672
Trp/Trp+Arg/Trp vs. Arg/Arg	9503/11,845	72.47	<0.0001	1.01 (0.90–1.14)	0.22	0.82	29	0.75	0.454	0.80	0.430
Stratification by HWE											
Yes											
Trp/Trp vs. Arg/Arg	6018/7630	29.09	0.09	1.17 (1.01–1.36)	2.09	0.04	20	0.00	1.000	0.51	0.614
Arg/Trp vs. Arg/Arg	7731/9812	40.00	0.02	0.94 (0.84–1.05)	1.08	0.28	23	0.62	0.535	0.07	0.945
Trp/Trp+Arg/Trp vs. Arg/Arg	8147/10,198	43.74	0.0006	0.98 (0.87–1.10)	0.38	0.71	23	0.07	0.941	0.39	0.700
Stratification by ethnicity											
Caucasian											
Trp/Trp vs. Arg/Arg	3884/5461	13.56	0.06	1.13 (0.69–1.87)	0.49	0.63	7	0.00	1.000	0.20	0.851
Arg/Trp vs. Arg/Arg	4322/6216	10.55	0.31	0.85 (0.73–0.99)	2.10	0.04	9	0.18	0.858	0.17	0.872
Trp/Trp+Arg/Trp vs. Arg/Arg	4350/6251	12.78	0.07	0.86 (0.76–0.97)	2.41	0.02	9	0.72	0.474	0.35	0.736
Asian											
Trp/Trp vs. Arg/Arg	2875/3052	24.76	0.07	1.28 (1.11–1.47)	3.35	0.0008	16	0.04	0.967	1.18	0.258
Arg/Trp vs. Arg/Arg	4252/4642	38.29	0.002	1.04 (0.90–1.20)	0.47	0.64	17	0.76	0.449	1.11	0.282
Trp/Trp+Arg/Trp vs. Arg/Arg	4744/5071	46.91	0.0001	1.11 (0.95–1.29)	1.31	0.19	17	1.14	0.256	1.35	0.196
Stratification by source of control											
Population-based study											
Trp/Trp vs. Arg/Arg	2116/3648	14.23	0.16	1.28 (1.03–1.59)	2.22	0.03	10	0.36	0.721	0.43	0.678
Arg/Trp vs. Arg/Arg	2739/4657	10.98	0.45	0.96 (0.86–1.08)	0.61	0.54	11	0.75	0.451	0.94	0.367
Trp/Trp+Arg/Trp vs. Arg/Arg	2938/4849	12.70	0.31	1.00 (0.90–1.12)	0.08	0.94	11	0.07	0.945	0.76	0.465
Hospital-based study											
Trp/Trp vs. Arg/Arg	5008/5321	24.85	0.05	1.25 (1.05–1.49)	2.50	0.01	15	0.77	0.443	0.29	0.776
Arg/Trp vs. Arg/Arg	6242/6721	48.95	<0.0001	0.98 (0.83–1.16)	0.24	0.81	17	0.45	0.649	0.90	0.381
Trp/Trp+Arg/Trp vs. Arg/Arg	6565/6996	56.67	<0.00001	1.04 (0.88–1.25)	0.49	0.63	17	1.21	0.225	1.26	0.226
Stratified by smoking status											
Smoker											
Trp/Trp+Arg/Trp vs. Arg/Arg	2869/2427	5.43	0.37	0.83 (0.71–0.98)	2.25	0.02	5	0.75	0.452	0.34	0.751

HWE Hardy-Weinberg equilibrium

codon Arg194Trp polymorphism for lung cancer in the genetic model of Trp/Trp vs. Arg/Arg based on population-based control and hospital-based control (OR=1.28, 95%CI: 1.03–1.59 and OR=1.25, 95 %CI: 1.05–1.49) (Table 2). A decreased lung cancer risk was observed among smokers carrying XRCC1 codon 194 Arg/Trp+Trp/Trp genotype compared with Arg/Arg genotype carriers (OR=0.83, 95 %CI: 0.71–0.98) when stratified by smoking status (Table 2). We did not observe any association between XRCC1 Arg194Trp polymorphism and lung cancer risk in additional subgroup analyses (Table 2).

The shape of funnel plots seemed to be approximately symmetrical (Fig. 3a–c). Both Egger's test and Begg's test results suggested no evidence of publication biases existed in this meta-analysis (Table 2).

Sensitivity analysis was performed to evaluate the root of heterogeneity. The combined estimates were not altered when the studies were lack of heterogeneity for Arg/Trp vs. Arg/Arg and Trp/Trp+Arg/Trp vs. Arg/Arg polymorphisms among total population by deleting Song et al.'s study [4], Du et al.'s study [5], and Buch et al.'s study [6] (data not shown).

Fig. 1 Forest plots for the association of XRCC1 Arg194Trp polymorphism with lung cancer risk (a Trp/Trp vs. Arg/Arg, b Arg/Trp vs. Arg/Arg, and c: Arg/Trp+Trp/Trp vs. Arg/Arg)

In conclusion, the findings of Zhang et al.'s study [1] should be interpreted with caution. To draw a definitive conclusion, further well-designed studies with large

sample size are still required to assess the association of XRCC1 Arg194Trp polymorphism with lung cancer risk. We hope that our remarks will contribute to a more

Fig. 2 Forest plot for cumulative meta-analysis based on Trp/Trp vs. Arg/Arg

Fig. 3 Funnel plots for the association of XRCC1 Arg194Trp polymorphism with lung cancer risk (**a** Trp/Trp vs. Arg/Arg, **b** Arg/Trp vs. Arg/Arg, and **c** Arg/Trp+Trp/Trp vs. Arg/Arg)

accurate elaboration and substantiation of the results provided by Zhang et al. [1].

Conflicts of interest None

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