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EDITORIAL

Note of clarification of data in the paper titled X-ray repair cross-complementing group 1 codon 399 polymorphism and lung cancer risk: an updated meta-analysis

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Abstract We read with great interest the paper titled "X-ray repair cross-complementing group 1 codon 399 polymorphism and lung cancer risk: an updated meta-analysis" published by Wang et al in Tumor Biology, 2014, 35:411–418. Their results suggest that codon 399 polymorphism of XRCC1 gene might contribute to individual's susceptibility to lung cancer in Asian population and especially in nonsmoking Chinese women. The result is encouraging. Nevertheless, several key issues are worth noticing.

Keywords XRCC1 · Polymorphism · Lung cancer · Risk

The X-ray repair cross-complementing group 1 (XRCC1) gene is a major DNA repair gene involved in base excision repair (BER) and single-strand break (SSB) repair. XRCC1 interacts strongly with poly[ADP-ribose] polymerase 1 (PARP1), which recognizes SSBs, and LIGIII that seals SSBs and BER intermediates [1]. Several single nucleotide polymorphisms (SNPs) have been identified in the XRCC1 gene [2], and the potential associations with lung cancer risk have been proposed [3–6]. Among them, a polymorphism of rs25487 (Arg399Gln, G>A) is one the most extensively studied SNPs, which leads to amino acid substitutions (exon 10). This mutation could alter XRCC1 function, diminish repair kinetics, and influence susceptibility to cancers. To date, a considerable number of studies have investigated the association between XRCC1 Arg399Gln polymorphism and lung cancer risk [7–54]. However, the results remained conflicting rather than conclusive.

Recently, we have read with great interest the paper titled "X-ray repair cross-complementing group 1 codon 399 polymorphism and lung cancer risk: an updated meta-analysis" published online in Tumor Biology, 2014, 35:411–418 [3]. The authors performed a meta-analysis of 46 studies on the association between XRCC1 codon 399 polymorphism and lung cancer risk published before June 2013. In general population, the authors found that the M (Gln) allele and MM (Gln/Gln) genotype were associated with an increased risk of lung cancer compared with C (Arg) allele and CC (Arg/Arg) genotype, and the odds ratios (ORs) were 1.06 [95 % confidence interval (95 %CI) 1.01–1.12] and 1.19 (95 % CI 1.05–1.34), respectively. When it was stratified according to Asian population, the association between XRCC1 codon 399 polymorphism and lung cancer risk was further strengthened. It is an extremely interesting study.

However, after carefully examining the data provided by Wang et al. (Table 1 in the original text) [3], we found that there are several overlapping data that were not properly excluded from Wang et al.'s study [3]. Firstly, the data from Zhang et al.'s study [55] overlapped with the data reported by Hao et al. [17]. Secondly, the data from Liu et al.'s study [56] overlapped with Zhou et al.'s data [47]. Thirdly, the data reported by Yin et al. in 2009 [57] overlapped with the data reported by Yin et al. in 2007 [44]. Fourthly, Hung et al.'s paper published in 2008 [58] was a pooled analysis study, which included the data from Hung et al.'s paper published in 2005 [20], Zhou et al.'s paper published in 2003 [47],

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Table 1 Characteristics of selected studies in this meta-analysis

Author	Year	Ethnicity	Country	Source of control	Cases	Controls	*P* value of HWE
Chan [7]	2005	Asians	China	Hospital	75	162	0.879127
Chang [8]	2009	Africans and Latinos	USA	Population	368	578	0.592618
Chen [9]	2002	Asians	China	Population	103	99	0.853812
Cote [10]	2009	Africans and Caucasians	USA	Population	502	527	0.893601
David-Beabes [11]	2001	Africans and Caucasians	USA	Population	334	704	0.465443
De-Ruyck [12]	2007	Caucasians	Belgium	Hospital	109	109	0.916778
Divine [13]	2001	Caucasians	USA	Hospital	172	143	0.579995
Du [14]	2012	Asians	China	Hospital	100	100	0.000006
Du [15]	2014	Asians	China	Hospital	120	120	0.000000
Guo [16]	2013	Asians	China	Hospital	684	602	0.005453
Hao [17]	2006	Asians	China	Population	1024	1118	0.101696
Harms [18]	2004	Caucasians	Germany	Population	110	119	0.256632
Hu [19]	2005	Asians	China	Population	710	710	0.679058
Hung [20]	2005	Caucasians	France	Hospital	2049	2015	0.105562
Improta [21]	2008	Caucasians	Italy	Population	94	121	0.049457
Ito [22]	2004	Asians	Japan	Hospital	178	448	0.749648
Janik [23]	2011	Caucasians	Poland	Hospital	88	79	0.055572
Kim [24]	2010	Asians	Korea	Population	139	217	0.318155
Kiyohara [25]	2012	Asians	Japan	Hospital	462	379	0.858615
Letkova [49]	2013	Caucasians	Slovak	Unknown	382	379	0.097863
Li [26]	2008	Asians	China	Hospital	350	350	0.239615
Li [27]	2011	Asians	China	Hospital	455	443	0.052370
Lopez-Cima [28]	2007	Caucasians	Spain	Hospital	516	533	0.153908
Matullo [29]	2006	Caucasians	Italy	Population	116	1094	0.632227
Misra [30]	2003	Caucasians	Finland	Population	315	313	0.835918
Natukula [50]	2013	Asians	India	Unknown	100	101	0.266487
Osawa [31]	2010	Asians	Japan	Hospital	104	120	Not estimable
Ouyang [32]	2013	Asians	China	Population	82	201	0.148702
Pachouri [33]	2007	Asians	India	Population	103	122	0.055915
Park [34]	2002	Asians	Korea	Population	192	135	0.739912
Popanda [35]	2004	Caucasians	Germany	Hospital	463	460	0.845748
Qian [36]	2011	Asians	China	Population	581	603	0.411222
Ratnasinghe [37]	2001	Asians	China	Population	107	208	0.572907
Saikia [51]	2014	Asians	India	Population	272	544	0.354912
Schneider [38]	2005	Caucasians	Germany	Hospital	446	622	0.778779
Shen [39]	2005	Asians	China	Population	116	109	0.053219
Song [40]	2004	Asians	China	Hospital	104	104	0.466350
Su [41]	2008	Asians	China	Hospital	162	244	0.848338
Uppal [52]	2014	Asians	India	Unknown	100	100	0.001582
Vogel [42]	2004	Caucasians	Denmark	Population	256	269	0.522834
Wang [43]	2012	Asians	China	Hospital	209	256	0.302192
Yin [44]	2007	Asians	China	Hospital	205	193	0.198358
Yoo [53]	2015	Asians	Korea	Hospital	599	580	0.217986
Yu [45]	2006	Asians	China	Hospital	104	121	0.288300
Zhang [46]	2005	Asians	China	Hospital	149	157	0.853973
Zhou [47]	2003	Caucasians	USA	Population	1091	1240	0.661362
Zhu [54]	2014	Asians	China	Unknown	320	346	0.941896
Zienolddiny [48]	2006	Caucasians	Norway	Population	331	391	0.784938

HWE Hardy-Weinberg equilibrium

Table 2 Summery odds ratios of the relation of XRCC1 codon 399 polymorphism to lung cancer risk

Genotype	Cases/controls	Heterogeneity test		Analysis model	Summery OR (95 % CI)	Hypothesis test		*df*	Begg's test		Egger's test	
		Q	*P*			*Z*	*P*		*Z*	*P*	*t*	*P*
Total												
CM vs. CC	14126/16966	86.96	0.0002	Random-effects model	0.98 (0.92–1.05)	0.49	0.62	46	0.26	0.797	0.78	0.440
MM vs. CC	9502/11120	99.60	<0.00001	Random-effects model	1.19 (1.04–1.37)	2.59	0.01	45	1.06	0.289	1.76	0.085
CM+MM vs. CC	15751/18688	101.06	<0.00001	Random-effects model	1.02 (0.95–1.10)	0.66	0.51	47	0.76	0.450	0.31	0.756
Stratification by HWE in control												
Yes												
CM vs. CC	13136/15931	79.39	0.0003	Random-effects model	0.99 (0.92–1.07)	0.22	0.82	41	0.24	0.812	0.36	0.723
MM vs. CC	8757/10473	82.70	<0.0001	Random-effects model	1.12 (0.98–1.29)	1.72	0.09	40	0.89	0.375	1.26	0.217
CC	14549/17525	94.41	<0.00001	Random-effects model	1.02 (0.94–1.10)	0.40	0.69	41	0.69	0.488	0.14	0.891
Stratification by ethnicity												
Asians												
CM vs. CC	7285/8370	66.07	<0.0001	Random-effects model	1.01 (0.90–1.13)	0.16	0.87	28	0.39	0.694	0.03	0.975
MM vs. CC	5126/5656	64.88	<0.0001	Random-effects model	1.43 (1.16–1.76)	3.32	0.0009	28	0.66	0.511	1.13	0.269
CM+MM vs. CC	8009/8992	78.81	<0.00001	Random-effects model	1.09 (0.97–1.22)	1.44	0.15	29	0.32	0.748	0.82	0.420
Caucasians												
CM vs. CC	6229/7690	19.78	0.23	Fixed-effects model	0.99 (0.92–1.06)	0.32	0.75	16	0.70	0.484	2.23	0.041
MM vs. CC	3924/4812	19.92	0.17	Fixed-effects model	1.00 (0.90–1.11)	0.04	0.97	15	0.14	0.893	0.35	0.728
CM+MM vs. CC	7105/8754	17.61	0.35	Fixed-effects model	0.99 (0.93–1.06)	0.27	0.79	16	1.03	0.303	2.08	0.055
Stratification by source of control												
Population-based control												
CM vs. CC	6322/8580	35.11	0.02	Random-effects model	0.92 (0.84–1.02)	1.59	0.11	20	1.24	0.216	1.11	0.283
MM vs. CC	4209/5559	29.53	0.08	Fixed-effects model	0.98 (0.87–1.10)	0.34	0.73	20	0.33	0.740	0.20	0.845
CM+MM vs. CC	6946/9422	35.23	0.02	Random-effects model	0.93 (0.85–1.02)	1.46	0.14	20	1.12	0.264	0.98	0.340
Hospital-based control												
CM vs. CC	7032/7535	34.23	0.03	Random-effects model	1.02 (0.93–1.13)	0.43	0.67	21	0.34	0.735	0.01	0.990
MM vs. CC	4746/4993	52.20	0.0001	Random-effects model	1.37 (1.11–1.70)	2.91	0.004	20	0.45	0.651	1.85	0.080
CM+MM vs. CC	7903/8340	45.24	0.002	Random-effects model	1.09 (0.98–1.20)	1.56	0.12	22	1.21	0.224	0.89	0.382
Stratification by smoking status												
Smokers												
CM+MM vs. CC	2893/2856	10.97	0.61	Fixed-effects model	1.02 (0.92–1.13)	0.36	0.72	13	0.00	1.000	0.36	0.726
Nonsmokers												
CM+MM vs. CC	656/1814	18.49	0.02	Random-effects model	1.19 (0.87–1.65)	1.08	0.28	8	0.52	0.602	0.65	0.537
Stratification by histological type												
Squamous cell carcinoma												

Table 2 (continued)

Genotype	Cases/controls	Heterogeneity test		Analysis model	Summery OR (95 % CI)	Hypothesis test		*df*	Begg's test		Egger's test	
		Q	*P*			*Z*	*P*		*Z*	*P*	*t*	*P*
CM+MM vs. CC	891/2347	22.13	0.001	Random-effects model	1.06 (0.74–1.54)	0.33	0.74	6	0.00	1.000	0.33	0.751
Adenocarcinoma												
CM+MM vs. CC	1425/3994	21.69	0.03	Random-effects model	1.05 (0.87–1.26)	0.48	0.63	11	1.03	0.304	0.23	0.822

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

Popanda et al.'s paper published in 2004 [35], and Shen et al.'s paper published in 2005 [39]. Fifthly, the data from two papers reported by Li et al. in 2005 [59, 60] overlapped with Li et al.'s paper published in 2008 [26]. Sixthly, the data from Li et al.'s published in 2005 [61] overlapped with the data reported by Su et al. [41]. As a consequence, 5986 cases and 6495 controls were calculated two times in Wang et al.'s paper [3]. In addition, two eligible papers [7, 23] published before 2013 was not included in Wang et al.'s paper [3]. Therefore, it is required to verify the conclusions by Wang et al. [3]. In order to clarify the association between XRCC1 Arg399Gln polymorphism and lung cancer risk, a meta-analysis including the updated data was reconducted, which may provide comprehensive evidence for this association. We also presented the stratified results by mainly confounding factors such as source of control, ethnicity, smoking status, histological subtypes, and Hardy-Weinberg equilibrium (HWE) in control besides giving overall estimates.

A comprehensive search was performed through the database of Medline/PubMed, Science Direct, Elsevier, China National Knowledge Infrastructure (CNKI), and Wanfang Medical Online with a combination of the following terms: "lung cancer," "lung neoplasm" or "lung carcinoma" and "*XRCC1*" or "rs25487" and "polymorphism" or "variant." Last search was updated on March 20, 2015. The references cited in the publications and review articles were also manually searched.

Data inclusion criteria were as follows: (a) the papers reporting lung cancer risk and *XRCC1* codon 399 polymorphism; (b) case-control studies or cohort studies; and (c) sufficient data to estimate the OR and 95 % CI. For overlapping or repeated studies, the results including more information were included. Accordingly, papers lacking essential information were excluded; review papers were also excluded. In total, 69 published papers were identified with the association between XRCC1 Arg399Gln polymorphism and lung cancer risk. We reviewed all papers in the light of the criteria defined above and excluded 12 reviews and 9 overlapping articles. Therefore, 48 studies were determined to enter our study.

The Cochrane *Q* statistics test was used to assess the heterogeneity among studies. A fixed-effects model or a random-effects model was applied to estimate the combined effects according to the results of heterogeneity test [62]. A fixed-effects model is used while the effects are assumed to be homogenous; otherwise, a random-effects model is used. The funnel plot was drawn to evaluate publication bias visually. In addition, Begg's test and Egger's test were used to assess the publication bias [63, 64]. The χ^2 test was used to check whether the genotype frequencies of the controls were in agreement with HWE.

All of the statistical analyses were conducted by using Review Manager (version 4.2.10, the Cochrane Collaboration) and STATA10.0 software package (Stata Corporation, College Station, TX). Statistical significance was determined as a two-sided *P* value less than 0.05 for any test or model.

Table 1 lists the characteristics of included studies. Table 2 lists the summary effects of the association

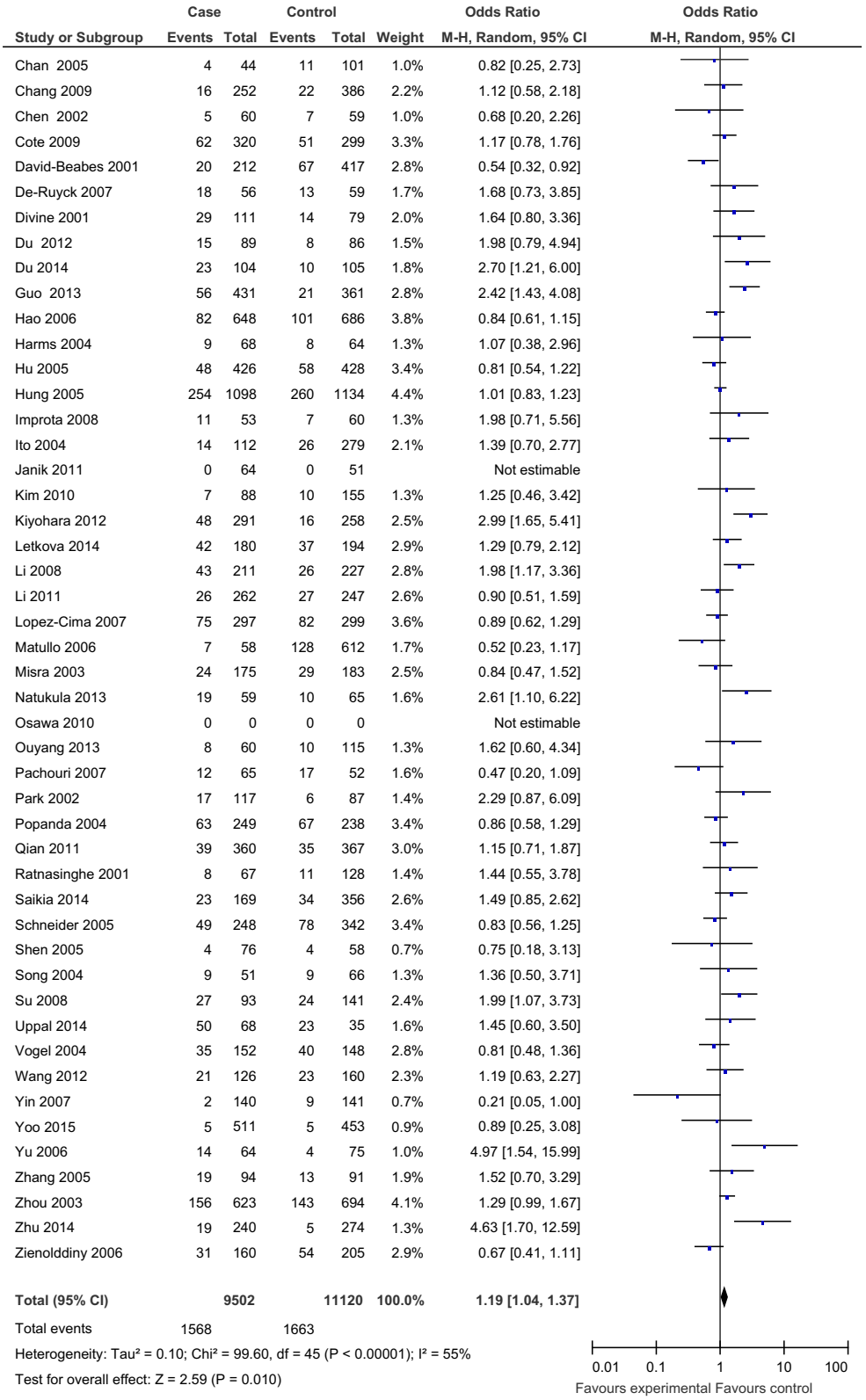

Fig. 1 Forest plots for the association between XRCC1 codon 399 MM genotype variant and lung cancer risk

between XRCC1 codon 399 polymorphism and lung cancer risk on the basis of 48 published studies including 15,751 cases and 18,688 controls. Overall, we observed a significant association between XRCC1 codon 399 MM genotype variant and lung cancer risk, and the summary OR was 1.19 (95 %CI 1.04–1.37) (Fig. 1); we did not observe any association between XRCC1 codon 399 CM and CM+MM genotype variants and lung

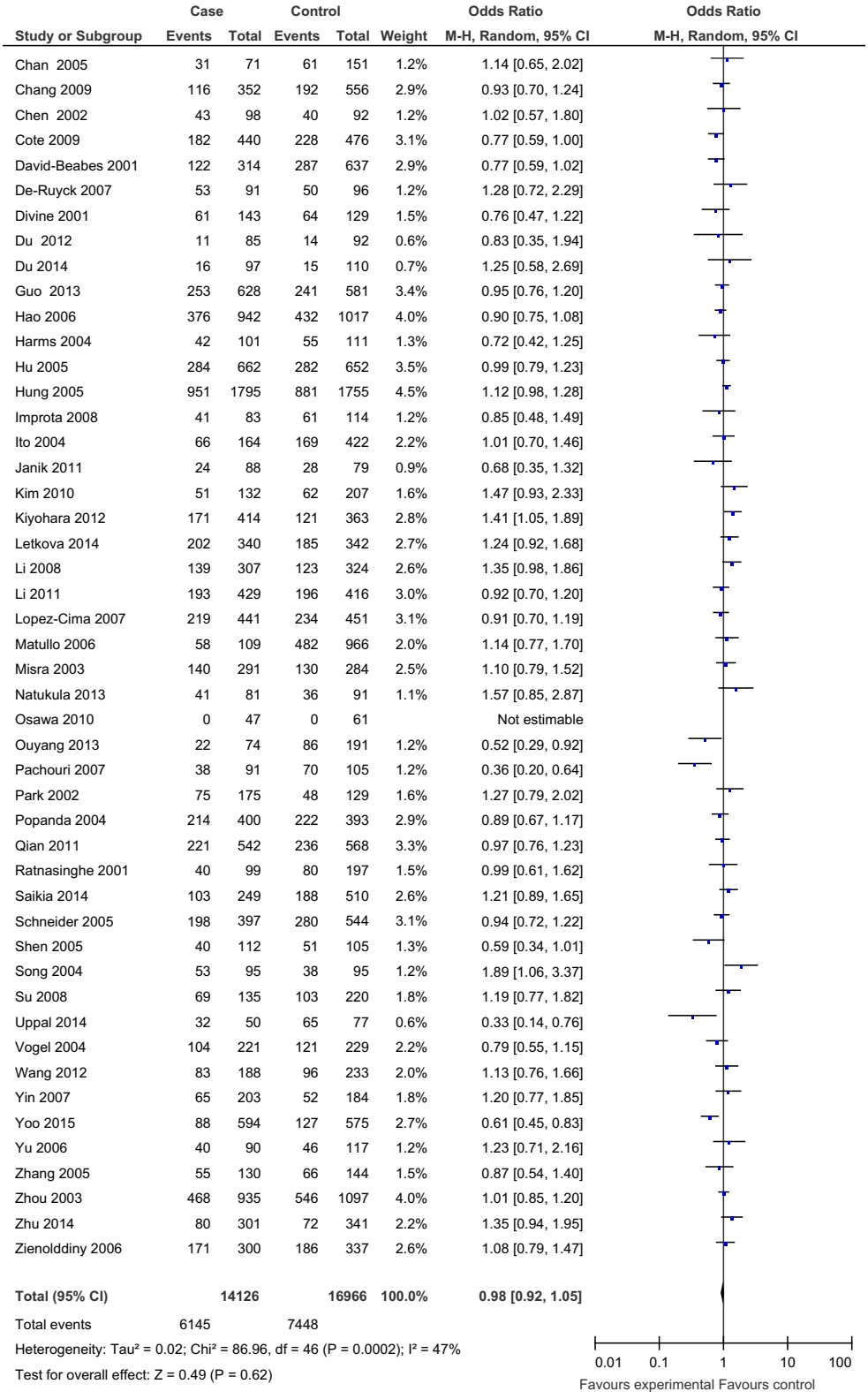

Fig. 2 Forest plots for the association between XRCC1 codon 399 CM genotype variant and lung cancer risk

cancer risk, and the summary ORs were 0.98 (95 % CI 0.92–1.05) for CM vs. CC (Fig. 2) and 1.02 (95 % CI 0.95–1.10) for CM+MM vs. CC (Fig. 3), respectively. Our results are consistent with Wang et al.'s study [3]. They also found that the MM genotype was associated with increased risk of lung cancer compared with CC genotype in total population. Limiting the analysis to studies of control in agreement with HWE, we did not

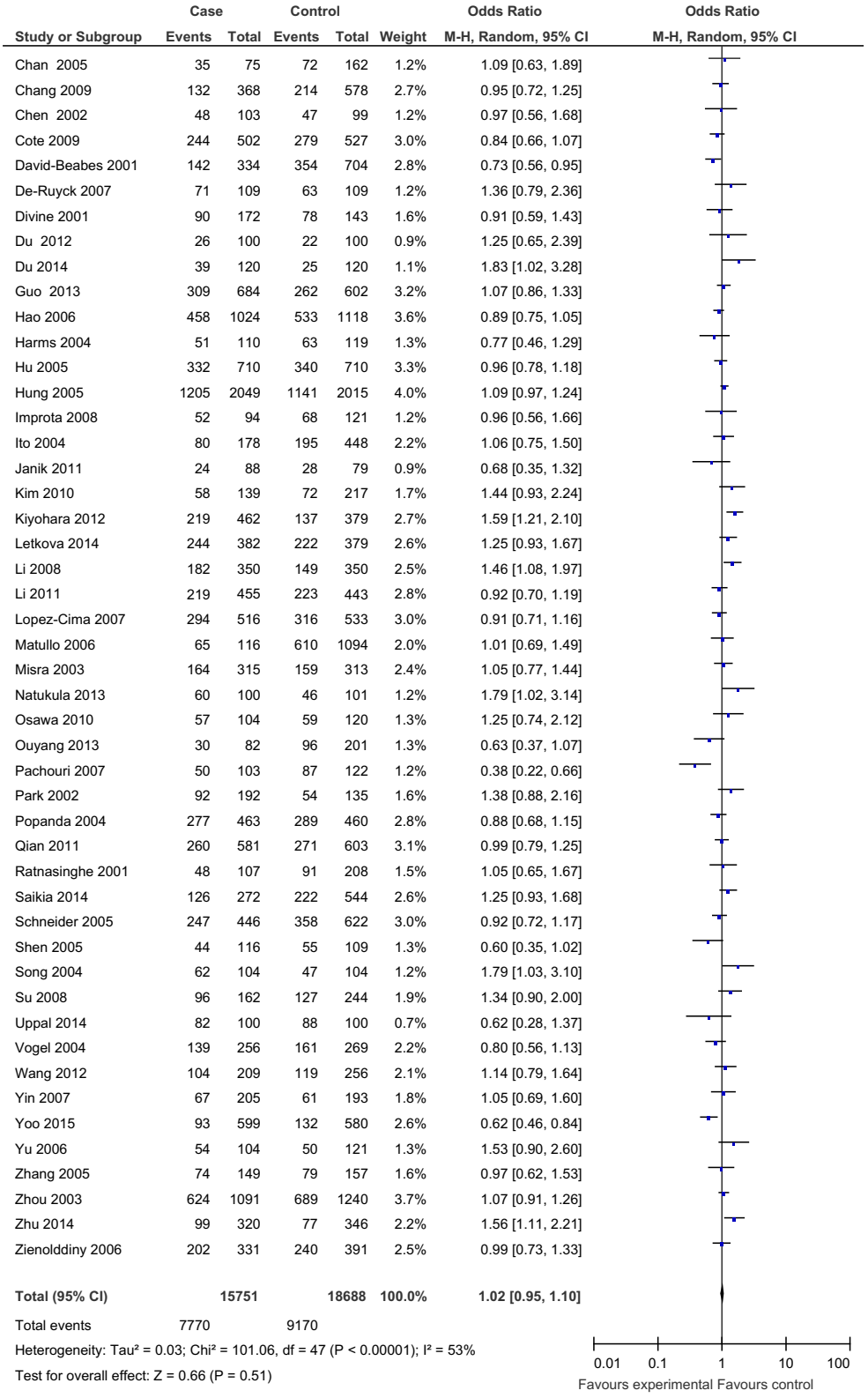

Fig. 3 Forest plots for the association between XRCC1 codon 399 CM+MM genotype variant and lung cancer risk

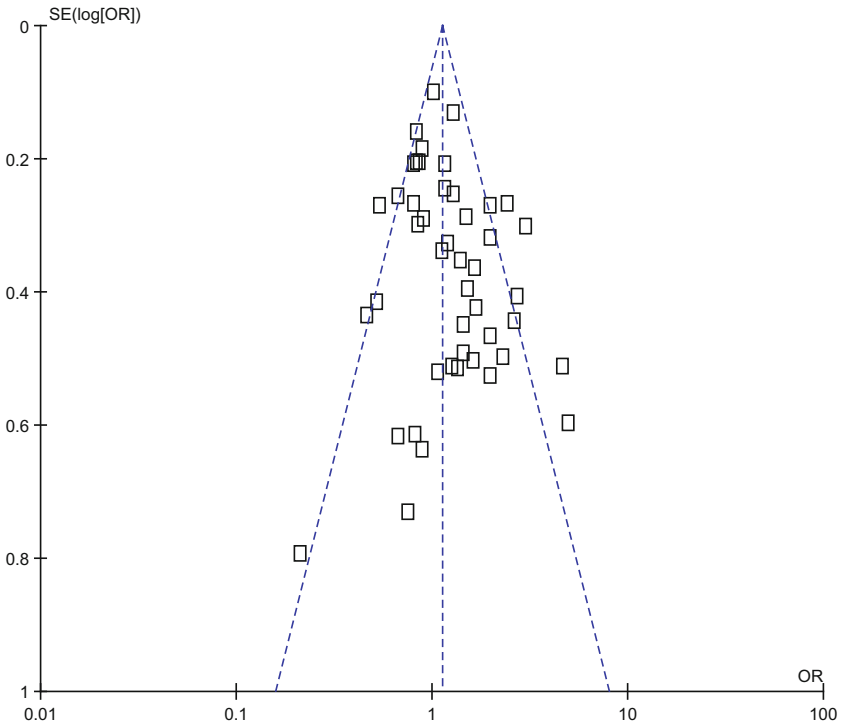

Fig. 4 Funnel plots for the association between XRCC1 codon 399 MM genotype variant and lung cancer risk

observe the association between XRCC1 codon 399 polymorphism and lung cancer risk, the summary ORs were 0.99 (95 % CI 0.92–1.07) for CM vs. CC, 1.12 (95 % CI 0.98–1.29) for MM vs. CC, and 1.02 (95 % CI 0.94–1.10) for CM+MM vs. CC, respectively (Table 2). In subgroup analysis by ethnicity, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 MM genotype compared with CC genotype carriers (OR=1.43, 95 % CI 1.16–1.76) among Asians, which is consistent with Wang et al.'s results [3]. We did not observe the association of XRCC1 codon 399 polymorphism with lung cancer

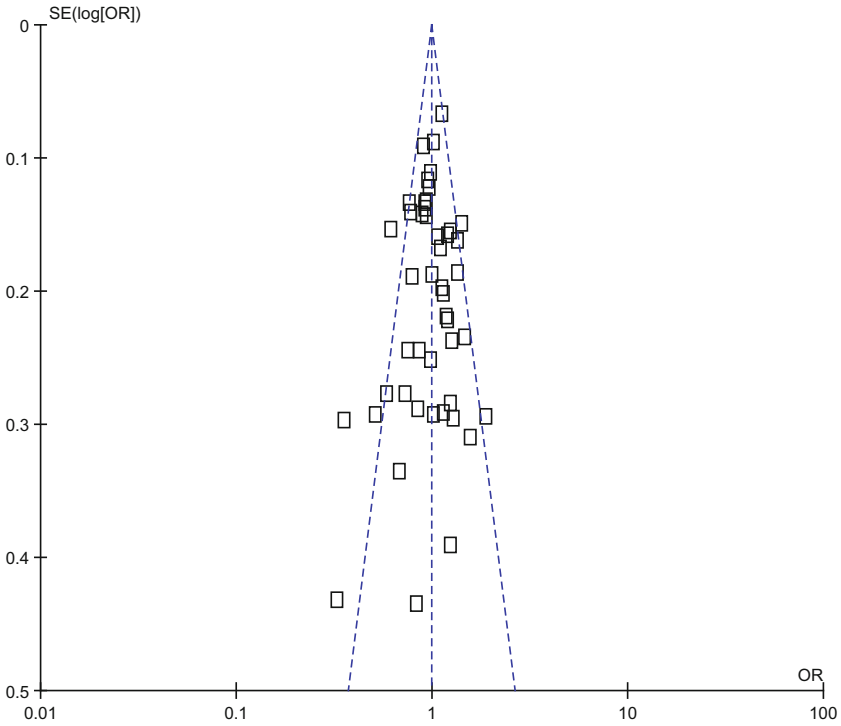

Fig. 5 Funnel plots for the association between XRCC1 codon 399 CM genotype variant and lung cancer risk

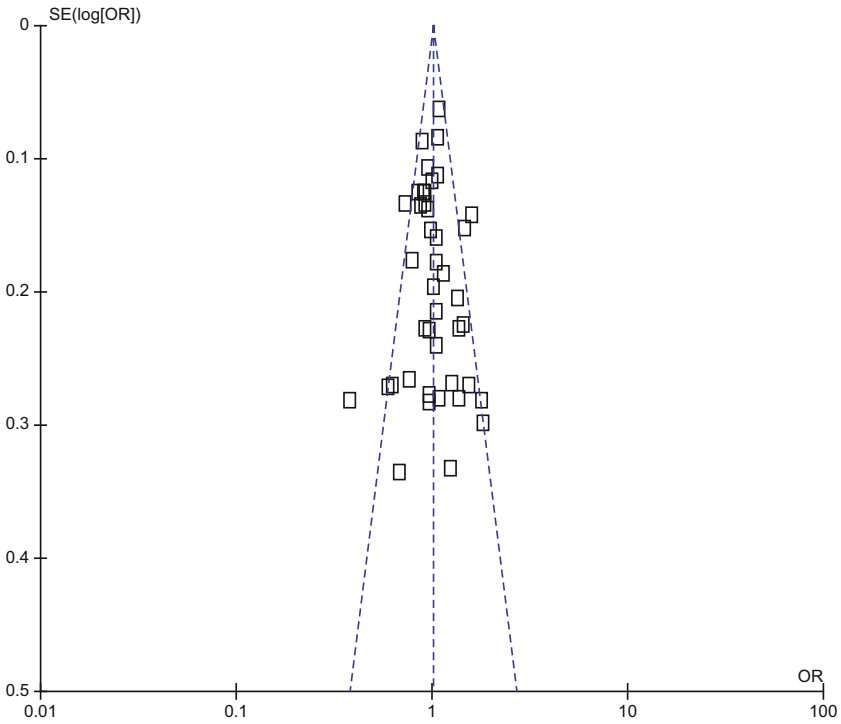

Fig. 6 Funnel plots for the association between XRCC1 codon 399 CM+MM genotype variant and lung cancer risk

risk among Caucasians (Table 2), which is consistent with Wang et al.'s results [3]. When stratified by source of control, we observed an increased lung cancer risk among subjects carrying MM genotype compared with those carrying CC genotype on the basis of hospital-based control (OR=1.37, 95 % CI 1.11–1.70); we did not observe the association of XRCC1 codon 399 polymorphism with lung cancer risk on the basis of population-based control (Table 2). We did not observe the association between XRCC1 codon 399 polymorphism and lung cancer risk in additional subgroup analyses by smoking status and histological subtypes (Table 2).

The shape of funnel plots did not reveal any evidence of obvious asymmetry (Figs. 4, 5, and 6) among total studies, which suggested that there was not any potential publication bias. Begg's test and Egger's test suggested that there was no obvious publication bias in this study, except for the analysis under the genetic model of CM vs. MM among Caucasians, since the *P* value was less than 0.05 in Egger's test (Table 2).

In summary, our results suggest that XRCC1 codon 399 MM genotype variant was associated with an increased lung cancer risk, especially among Asians. To reach a definitive conclusion, further well-designed studies with large sample size are needed to verify the association of XRCC1 codon 399 polymorphism and lung cancer risk. We hope that this remark will contribute to a more accurate elaboration and substantiation of the results presented by Wang et al. [3].

Conflicts of interest None

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