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

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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],

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]	2003	Asians	China	Hospital	104	104	0.466350
Su [41]	2001	Asians	China	Hospital	162	244	0.848338
Uppal [52]	2000	Asians	India	Unknown	102	100	0.001582
Vogel [42]	2014	Caucasians	Denmark	Population	256	269	0.522834
Wang [43]	2004	Asians	China	Hospital	209	256	0.302192
Yin [44]	2012	Asians	China	Hospital	205	193	0.198358
Yoo [53]	2007	Asians	Korea	Hospital	203 599	580	0.217986
	2015			-	399 104		0.288300
Yu [45] Zhang [46]		Asians Asians	China China	Hospital	104 149	121 157	0.288300 0.853973
Zhang [46]	2005			Hospital			
Zhou [47]	2003	Caucasians	USA	Population	1091	1240	0.661362
Zhu [54] Zianalddinas [48]	2014	Asians	China	Unknown	320	346	0.941896
Zienolddiny [48]	2006	Caucasians	Norway	Population	331	391	0.784938

 Table 1
 Characteristics of selected studies in this meta-analysis

HWE Hardy-Weinberg equilibrium

Table 2 Summery odds	tratios of the relation	on of XRCC1	codon 399 po	Summery odds ratios of the relation of XRCC1 codon 399 polymorphism to lung cancer risk	risk							
Genotype	Cases/controls	Heterogeneity test	leity test	Analysis model	Summery OR (95 % CI)	Hypothesis test	esis test	đf	Begg's test	test	Egger's test	test
		\widetilde{O}	Ρ			Z	Ρ		Z	Ρ	t	Р
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	09.66	<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	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	control											
Population-based control	ol											
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	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	cal type											
Squamous cell carcinoma	na											

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- J /		Cases/controls neterogeneticy test	nerty test		is an analytic (is a contraction of the second seco	Hypoth	esis test	đf	df Begg's test	test	Egger's test	test
		6	Ρ			Z	Ρ		Z P	Ρ	t	Ρ
CM+MM vs. CC 891/2347	//2347	22.13	0.001	Random-effects model 1.06 (0.74–1.54)	1.06 (0.74–1.54)	0.33	0.33 0.74	9	0.00	6 0.00 1.000 0.33 0.751	0.33	0.751
CM+MM vs. CC 1425/3994	5/3994	21.69	0.03	Random-effects model 1.05 (0.87–1.26)	1.05 (0.87–1.26)	0.48	0.48 0.63	11	1.03	11 1.03 0.304	0.23	0.822

Table 2 (continued)

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.

Fig. 1 Forest plots for the association between XRCC1

and lung cancer risk

codon 399 MM genotype variant

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

	Case		Cont			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
Chan 2005	4	44	11	101	1.0%	0.82 [0.25, 2.73]	
hang 2009	16	252	22	386	2.2%	1.12 [0.58, 2.18]	- - -
Chen 2002	5	60	7	59	1.0%	0.68 [0.20, 2.26]	
Cote 2009	62	320	51	299	3.3%	1.17 [0.78, 1.76]	+-
David-Beabes 2001	20	212	67	417	2.8%	0.54 [0.32, 0.92]	
De-Ruyck 2007	18	56	13	59	1.7%	1.68 [0.73, 3.85]	+
Divine 2001	29	111	14	79	2.0%	1.64 [0.80, 3.36]	+
Du 2012	15	89	8	86	1.5%	1.98 [0.79, 4.94]	+
)u 2014	23	104	10	105	1.8%	2.70 [1.21, 6.00]	—
Guo 2013	56	431	21	361	2.8%	2.42 [1.43, 4.08]	
lao 2006	82	648	101	686	3.8%	0.84 [0.61, 1.15]	-+
larms 2004	9	68	8	64	1.3%	1.07 [0.38, 2.96]	_
łu 2005	48	426	58	428	3.4%	0.81 [0.54, 1.22]	-+
lung 2005	254	1098	260	1134	4.4%	1.01 [0.83, 1.23]	+
mprota 2008	11	53	7	60	1.3%	1.98 [0.71, 5.56]	+
o 2004	14	112	26	279	2.1%	1.39 [0.70, 2.77]	+
anik 2011	0	64	0	51		Not estimable	
(im 2010	7	88	10	155	1.3%	1.25 [0.46, 3.42]	
iyohara 2012	48	291	16	258	2.5%	2.99 [1.65, 5.41]	
etkova 2014	42	180	37	194	2.9%	1.29 [0.79, 2.12]	+
i 2008	43	211	26	227	2.8%	1.98 [1.17, 3.36]	
i 2011	26	262	27	247	2.6%	0.90 [0.51, 1.59]	-+-
opez-Cima 2007.	75	297	82	299	3.6%	0.89 [0.62, 1.29]	-+
1atullo 2006	7	58	128	612	1.7%	0.52 [0.23, 1.17]	
lisra 2003	24	175	29	183	2.5%	0.84 [0.47, 1.52]	
latukula 2013	19	59	10	65	1.6%	2.61 [1.10, 6.22]	
)sawa 2010	0	0	0	0		Not estimable	
Duyang 2013	8	60	10	115	1.3%	1.62 [0.60, 4.34]	+
achouri 2007	12	65	17	52	1.6%	0.47 [0.20, 1.09]	
ark 2002	17	117	6	87	1.4%	2.29 [0.87, 6.09]	+
opanda 2004	63	249	67	238	3.4%	0.86 [0.58, 1.29]	-+
Qian 2011	39	360	35	367	3.0%	1.15 [0.71, 1.87]	
Ratnasinghe 2001	8	67	11	128	1.4%	1.44 [0.55, 3.78]	-
aikia 2014	23	169	34	356	2.6%	1.49 [0.85, 2.62]	+
chneider 2005	49	248	78	342	3.4%	0.83 [0.56, 1.25]	-+
hen 2005	4	76	4	58	0.7%	0.75 [0.18, 3.13]	
ong 2004	9	51	9	66	1.3%	1.36 [0.50, 3.71]	-
u 2008	27	93	24	141	2.4%	1.99 [1.07, 3.73]	- - -
lppal 2014	50	68	23	35	1.6%	1.45 [0.60, 3.50]	+
ogel 2004	35	152	40	148	2.8%	0.81 [0.48, 1.36]	-+
Vang 2012	21	126	23	160	2.3%	1.19 [0.63, 2.27]	+
′in 2007	2	140	9	141	0.7%	0.21 [0.05, 1.00]	
′oo 2015	5	511	5	453	0.9%	0.89 [0.25, 3.08]	
′u 2006	14	64	4	75	1.0%	4.97 [1.54, 15.99]	
hang 2005	19	94	13	91	1.9%	1.52 [0.70, 3.29]	
hou 2003	156	623	143	694	4.1%	1.29 [0.99, 1.67]	
hu 2014	19	240	5	274	1.3%	4.63 [1.70, 12.59]	
ienolddiny 2006	31	160	54	205	2.9%	0.67 [0.41, 1.11]	
otal (95% CI)		9502		11120	100.0%	1.19 [1.04, 1.37]	•
Fotal events	1568	==	1663	,			['
orean original	1000		1003				

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

2 Forest plots for the		Case		Cont			Odds Ratio	Odds Ratio
ociation between XRCC1	Study or Subgroup	Events		Events		Weight	M-H, Random, 95% C	
lon 399 CM genotype variant l lung cancer risk	Chan 2005	31	71	61	151	1.2%	1.14 [0.65, 2.02]	
i lung cancer lisk	Chang 2009	116	352	192	556	2.9%	0.93 [0.70, 1.24]	
	Chen 2002	43	98	40	92	1.2%	1.02 [0.57, 1.80]	
	Cote 2009	182	440	228	476	3.1%	0.77 [0.59, 1.00]	
	David-Beabes 2001	122	314	287	637	2.9%	0.77 [0.59, 1.02]	
	De-Ruyck 2007	53	91	50	96	1.2%	1.28 [0.72, 2.29]	
	Divine 2001	61	143	64	129	1.5%	0.76 [0.47, 1.22]	
	Du 2012	11	85	14	92	0.6%	0.83 [0.35, 1.94]	
	Du 2014	16	97	15	110	0.7%	1.25 [0.58, 2.69]	
	Guo 2013	253	628	241	581	3.4%	0.95 [0.76, 1.20]	
	Hao 2006	376	942	432	1017	4.0%	0.90 [0.75, 1.08]	
	Harms 2004	42	101	55	111	1.3%	0.72 [0.42, 1.25]	
	Hu 2005	284	662	282	652	3.5%	0.99 [0.79, 1.23]	T
	Hung 2005	951	1795	881	1755	4.5%	1.12 [0.98, 1.28]	T
	Improta 2008	41	83	61	114	1.2%	0.85 [0.48, 1.49]	
	Ito 2004	66	164	169	422	2.2%	1.01 [0.70, 1.46]	Ť
	Janik 2011	24	88	28	79	0.9%	0.68 [0.35, 1.32]	
	Kim 2010	51	132	62	207	1.6%	1.47 [0.93, 2.33]	<u> </u>
	Kiyohara 2012	171	414	121	363	2.8%	1.41 [1.05, 1.89]	-
	Letkova 2014	202	340	185	342	2.7%	1.24 [0.92, 1.68]	<u>t</u> -
	Li 2008	139	307	123	324	2.6%	1.35 [0.98, 1.86]	
	Li 2011	193	429	196	416	3.0%	0.92 [0.70, 1.20]	
	Lopez-Cima 2007	219	441	234	451	3.1%	0.91 [0.70, 1.19]	-
	Matullo 2006	58	109	482	966	2.0%	1.14 [0.77, 1.70]	+-
	Misra 2003	140	291	130	284	2.5%	1.10 [0.79, 1.52]	+
	Natukula 2013	41	81	36	91	1.1%	1.57 [0.85, 2.87]	+
	Osawa 2010	0	47	0	61		Not estimable	
	Ouyang 2013	22	74	86	191	1.2%	0.52 [0.29, 0.92]	
	Pachouri 2007	38	91	70	105	1.2%	0.36 [0.20, 0.64]	
	Park 2002	75	175	48	129	1.6%	1.27 [0.79, 2.02]	
	Popanda 2004	214	400	222	393	2.9%	0.89 [0.67, 1.17]	-
	Qian 2011	221	542	236	568	3.3%	0.97 [0.76, 1.23]	+
	Ratnasinghe 2001	40	99	80	197	1.5%	0.99 [0.61, 1.62]	+
	Saikia 2014	103	249	188	510	2.6%	1.21 [0.89, 1.65]	+-
	Schneider 2005	198	397	280	544	3.1%	0.94 [0.72, 1.22]	
	Shen 2005	40	112	51	105	1.3%	0.59 [0.34, 1.01]	
	Song 2004	53	95	38	95	1.2%	1.89 [1.06, 3.37]	
	Su 2008	69	135	103	220	1.8%	1.19 [0.77, 1.82]	
	Uppal 2014	32	50	65	77	0.6%	0.33 [0.14, 0.76]	
	Vogel 2004	104	221	121	229	2.2%	0.79 [0.55, 1.15]	
	Wang 2012	83	188	96	233	2.0%	1.13 [0.76, 1.66]	
	Yin 2007	65	203	52	184	1.8%	1.20 [0.77, 1.85]	
	Yoo 2015	88	594	127	575	2.7%	0.61 [0.45, 0.83]	
	Yu 2006	40	90	46	117	1.2%	1.23 [0.71, 2.16]	
	Zhang 2005	55	130	66	144	1.5%	0.87 [0.54, 1.40]	
	Zhou 2003	468	935	546	1097	4.0%	1.01 [0.85, 1.20]	
	Zhu 2014	80	301	72	341	2.2%	1.35 [0.94, 1.95]	
	Zienolddiny 2006	171	300	186	337	2.2 %	1.08 [0.79, 1.47]	
	Total (95% CI)		14126		16966	100.0%	0.98 [0.92, 1.05]	
				7440			0.00 [0.02, 1.00]	1
	Total events	6145	- 00 00	7448	(D - ^ ^	000). 12	70/	
	Heterogeneity: Tau ² =	0.02; Chi2	- 86.96	, at = 46	(P = 0.0	∪∪∠); I = 4	1 70	0.01 0.1 1 10 10

cancer risk, and the summary ORs were 0.98 (95 $\%~{\rm CI}$ 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

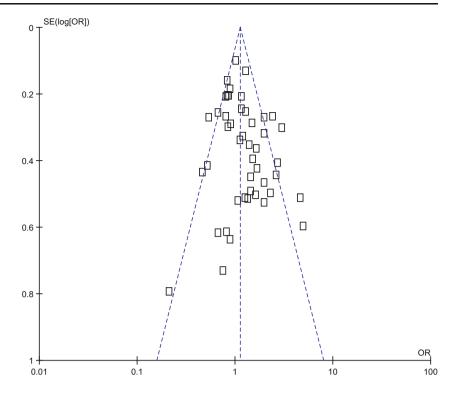
	Case	e	Conti	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Chan 2005	35	75	72	162	1.2%	1.09 [0.63, 1.89]	
Chang 2009	132	368	214	578	2.7%	0.95 [0.72, 1.25]	+
Chen 2002	48	103	47	99	1.2%	0.97 [0.56, 1.68]	
Cote 2009	244	502	279	527	3.0%	0.84 [0.66, 1.07]	-
David-Beabes 2001	142	334	354	704	2.8%	0.73 [0.56, 0.95]	-
De-Ruyck 2007	71	109	63	109	1.2%	1.36 [0.79, 2.36]	+
Divine 2001	90	172	78	143	1.6%	0.91 [0.59, 1.43]	
Du 2012	26	100	22	100	0.9%	1.25 [0.65, 2.39]	- .
Du 2012	39	120	25	120	1.1%	1.83 [1.02, 3.28]	
Guo 2013	309	684	262	602	3.2%	1.07 [0.86, 1.33]	+
Hao 2006	458	1024	533	1118	3.6%	0.89 [0.75, 1.05]	-
Harms 2004	51	110	63	119	1.3%	0.77 [0.46, 1.29]	1
Hu 2005	332	710	340	710	3.3%	0.96 [0.78, 1.18]	Ļ
Hung 2005	1205	2049	1141	2015	4.0%	1.09 [0.97, 1.24]	
Improta 2008	52	94	68 105	121	1.2%	0.96 [0.56, 1.66]	1
lto 2004	80	178	195	448	2.2%	1.06 [0.75, 1.50]	
Janik 2011	24	88	28	79	0.9%	0.68 [0.35, 1.32]	<u> </u>
Kim 2010	58	139	72	217	1.7%	1.44 [0.93, 2.24]	
Kiyohara 2012	219	462	137	379	2.7%	1.59 [1.21, 2.10]	
Letkova 2014	244	382	222	379	2.6%	1.25 [0.93, 1.67]	· · ·
Li 2008	182	350	149	350	2.5%	1.46 [1.08, 1.97]	
Li 2011	219	455	223	443	2.8%	0.92 [0.70, 1.19]	1
Lopez-Cima 2007	294	516	316	533	3.0%	0.91 [0.71, 1.16]	1
Matullo 2006	65	116	610	1094	2.0%	1.01 [0.69, 1.49]	L
Misra 2003	164	315	159	313	2.4%	1.05 [0.77, 1.44]	T
Natukula 2013	60	100	46	101	1.2%	1.79 [1.02, 3.14]	
Osawa 2010	57	104	59	120	1.3%	1.25 [0.74, 2.12]	
Ouyang 2013	30	82	96	201	1.3%	0.63 [0.37, 1.07]	
Pachouri 2007	50	103	87	122	1.2%	0.38 [0.22, 0.66]	
Park 2002	92	192	54	135	1.6%	1.38 [0.88, 2.16]	1-
Popanda 2004	277	463	289	460	2.8%	0.88 [0.68, 1.15]	
Qian 2011	260	581	271	603	3.1%	0.99 [0.79, 1.25]	Ť
Ratnasinghe 2001	48	107	91	208	1.5%	1.05 [0.65, 1.67]	
Saikia 2014	126	272	222	544	2.6%	1.25 [0.93, 1.68]	
Schneider 2005	247	446	358	622	3.0%	0.92 [0.72, 1.17]	*
Shen 2005	44	116	55	109	1.3%	0.60 [0.35, 1.02]	
Song 2004	62	104	47	104	1.2%	1.79 [1.03, 3.10]	
Su 2008	96	162	127	244	1.9%	1.34 [0.90, 2.00]	<u>†</u>
Uppal 2014	82	100	88	100	0.7%	0.62 [0.28, 1.37]	
Vogel 2004	139	256	161	269	2.2%	0.80 [0.56, 1.13]	
Wang 2012	104	209	119	256	2.1%	1.14 [0.79, 1.64]	<u>+</u> -
Yin 2007	67	205	61	193	1.8%	1.05 [0.69, 1.60]	+-
Yoo 2015	93	599	132	580	2.6%	0.62 [0.46, 0.84]	
Yu 2006	54	104	50	121	1.3%	1.53 [0.90, 2.60]	<u>+</u>
Zhang 2005	74	149	79	157	1.6%	0.97 [0.62, 1.53]	+
Zhou 2003	624	1091	689	1240	3.7%	1.07 [0.91, 1.26]	t
Zhu 2014	99	320	77	346	2.2%	1.56 [1.11, 2.21]	- -
Zienolddiny 2006	202	331	240	391	2.5%	0.99 [0.73, 1.33]	+
Total (95% CI)		15751		18688	100.0%	1.02 [0.95, 1.10]	
Total events	7770		9170				
					00001); l²		

codon 399 CM+MM genotype variant and lung cancer risk

Fig. 3 Forest plots for the association between XRCC1



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

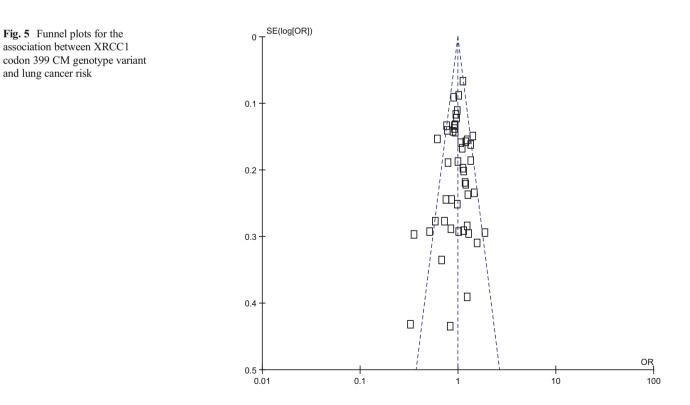
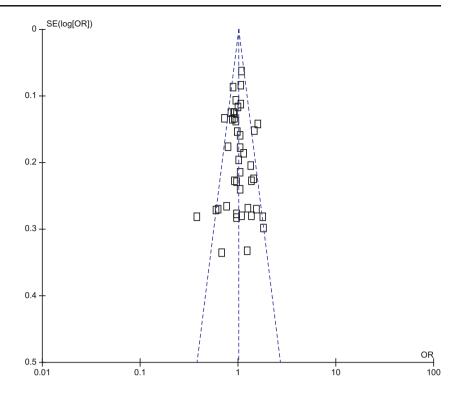


Fig. 6 Funnel plots for the association between XRCC1 codon 399 CM+MM genotype variant and lung cancer risk



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 hospitalbased 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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