IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2017; 8(2): 266-277. doi: 10.7150/jca.17379

Research Paper

Association of *MTRR* A66G polymorphism with cancer susceptibility: Evidence from 85 studies

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Received: 2016.08.29; Accepted: 2016.11.14; Published: 2017.01.15

Abstract

Methionine synthase reductase (MTRR) is a key regulatory enzyme involved in the folate metabolic pathway. Previous studies investigating the association of *MTRR* A66G polymorphism with cancer susceptibility reported inconclusive results. We performed the current meta-analysis to obtain a more precise estimation of the possible association. Published literatures were identified from PubMed, Embase and CBM databases up to October 2016. The strength of the association between the *MTRR* A66G polymorphism and cancer susceptibility was assessed using odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Eighty five published studies with 32,272 cases and 37,427 controls were included in this meta-analysis. Pooled results indicated that the *MTRR* A66G polymorphism was associated with an increased overall cancer risk (homozygous model: OR = 1.08, 95% CI = 1.02-1.15, $P = 0.009$; recessive model: OR = 1.06, 95% CI = 1.00-1.12, $P < 0.001$ and allele comparison: OR = 1.03, 95% CI = 1.00-1.06, $P < 0.001$). Stratification analysis further indicated significant associations in head and neck cancer, Caucasians, Africans, and high quality studies. However, to avoid the "false-positive report", the significant findings were assessed by the false-positive report probability (FPRP) test. Interestingly, the results of FPRP test revealed that the increased risk for *MTRR* A66G polymorphism among Africans need further validation due to the high probabilities of false-positive results. This meta-analysis suggests that the *MTRR* A66G polymorphism is associated with significantly increased cancer risk, a finding that needs to be confirmed in single large studies.

Key words: Methionine synthase reductase (*MTRR*); polymorphism; susceptibility; meta-analysis.

Introduction

Cancer remains the leading cause of death worldwide, with approximately 14.1 million new cancer cases and 8.2 million deaths occurring in 2012 according to the GLOBOCAN estimates [1]. It has been estimated that about one-third of cancers are attributable to diet and lifestyle [2], and a number of studies have reported a relationship between folate intake and cancer risk [3-5].

Folate plays an important role in one-carbon metabolism, and acts as a coenzyme in DNA methylation and synthesis [6]. Folate can provide the methyl group donor S-adenosylmethionine for many biological reactions. It also plays a critical role in the de novo synthesis of purines and thymidylate, which

are necessary for DNA replication and repair [7]. Abnormal folate metabolism can lead to the aberrant distribution of methyl groups and affect DNA biosynthesis and methylation, which is considered as a mechanism in the development of cancer [8].

Methionine synthase reductase (MTRR) is one of the key regulatory enzymes involved in the folate metabolic pathway. It can catalyze the regeneration of methyl cobalamin, which is a cofactor of methionine synthase (MTR) in the remethylation of homocysteine to methionine [9]. Because MTRR plays a vital role in maintaining the active state of MTR, genetic variation within the *MTRR* gene may be associated with cancer susceptibility. The *MTRR* gene is located on chromosome 5 at 5p15.2-p15.3, and the most common polymorphism is the substitution of isoleucine with methionine at position 22 (A66G; rs1801394). It has been suggested that the 66GG genotype is negatively correlated with plasma homocysteine levels [10]. A large number of studies have investigated the role of the *MTRR* A66G polymorphism and cancer risk [11-82], but the results remain controversial. Therefore, we conducted this updated meta-analysis from all eligible studies to derive a more precise estimation of this association.

Materials and methods

Search strategy

A comprehensive literature search was carried out in PubMed, Embase, and Chinese Biomedical (CBM) databases for all relevant articles using the following search terms: "*MTRR* or methionine synthase reductase or one-carbon metabolism", "polymorphism or variant or variation" and "cancer or tumor or carcinoma or neoplasm" (the last search was updated on October 21, 2016). Review articles and references cited in the searched studies were examined manually to identify additional relevant articles. Only the most recent study or the one with most participants was included in the final meta-analysis if two or more studies overlapped.

Inclusion and exclusion criteria

The included studies met the following criteria: (1) case-control study design; (2) investigating the association between the *MTRR* A66G polymorphism and cancer risk; (3) providing detail information for calculating pooled odds ratios (ORs) and their 95% confidence intervals (CIs). Studies were excluded if one of the following existed: (1) not a case-control study; (2) duplicate publications; (3) without detail genotype frequencies; and (4) genotype frequencies in the controls departed from Hardy-Weinberg equilibrium (HWE).

Data extraction

Information was extracted from all eligible studies independently by two authors (Ping Wang and Meilin Wang) according to the inclusion and exclusion criteria listed above. Disagreement was resolved by discussion until consensus was reached. The following information was collected from each study: first author's surname, year of publication, country of origin, ethnicity, cancer type, control source (hospital-based or population-based), genotyping methods, and numbers of cases and controls with the AA, AG and GG genotypes. Ethnicities were categorized as Asians, Caucasians, Africans or Mixed, which included individuals belonging to more than one ethnic group.

Quality assessment

Quality assessment was performed by two authors independently according to the criteria as described previously [83]. Quality scores of studies ranged from 0 (lowest) to 15 (highest), and the studies were categorized into high quality (scores > 9) and low quality (scores ≤ 9).

Statistical analysis

The strength of association between the *MTRR* A66G polymorphism and cancer risk was assessed by calculating the ORs with the corresponding 95% CIs. The pooled ORs of 5 comparison models were calculated: homozygous model (GG *vs.* AA), heterozygous model (AG *vs.* AA), recessive model [GG *vs.* (AA + AG)], dominant model [(GG +AG) *vs.* AA] as well as an allele comparison (G *vs.* A). The Chi square-based Q-test was used to check heterogeneity between studies. A *P* value greater than 0.1 for the Q-test indicated the homogeneity among studies, in which case the fixed-effects model (the Mantel-Haenszel method) [84] was adopted. Otherwise, the random-effects model (the DerSimonian and Laird method) [85] was applied. Data were stratified by cancer type (if one cancer type was represented by fewer than two studies, it was merged into the "other cancers" group), ethnicity (Asians, Caucasians, Africans or Mixed), source of control (hospital-based studies and population-based studies), and quality scores (≤ 9 and > 9). Potential publication bias was estimated using Begg's funnel plot [86] and Egger's linear regression test [87]. Sensitivity analysis was carried out to evaluate the effect of each individual study on the pooled ORs by excluding studies one-by-one and recalculating the ORs and 95% CIs.

For significant results found in the present meta-analysis, the false-positive report probability (FPRP) was used to evaluate positive associations. We

calculated FPRP with 0.2 as a threshold and assigned a prior probability of 0.1 to detect an OR of 0.67/1.50 (protective/risk effects) for an association with genotypes under investigation. FPRP values < 0.2 were considered as noteworthy associations [88]. All the statistical tests were performed with STATA version 12.0 (Stata Corporation, College Station, TX). All the *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study characteristics

As shown in **Figure 1**, a total of 381 published records were identified from PubMed, Embase and CBM by using the search terms described above. By checking the reference lists, we identified 29 additional publications. After screening the abstracts and texts, only 96 publications met the crude inclusion criteria and were selected for further assessment. Among them, five were excluded for containing survival data only [89-93], seven lacked detailed data for further analysis [94-100], eleven deviated from HWE [101-111] and one was a case-only study [112]. Ultimately, 72 publications [11-82] were included in the final meta-analysis (**Table 1**).

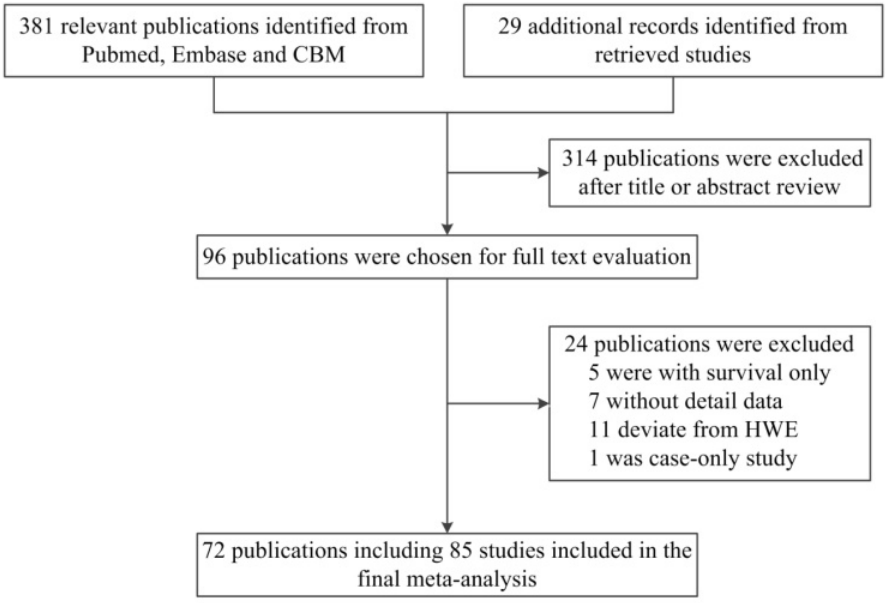

Figure 1. Flow diagram of the study selection process.

Table 1. Characteristics of studies included in the meta-analysis.

Surname [ref]	Year	Country	Ethnicity	Cancer type	Control source	Genotype method	Case			Control			MAF	HWE	Score
							AA	AG	GG	AA	AG	GG			
Le Marchand [11]	2002	USA	Asian	Colorectal	PB	PCR-RFLP	148	140	26	193	170	30	0.29	0.374	11
Le Marchand [11]	2002	USA	Caucasian	Colorectal	PB	PCR-RFLP	26	81	40	45	86	39	0.48	0.865	10
Le Marchand [11]	2002	USA	Mixed	Colorectal	PB	PCR-RFLP	30	34	12	40	38	9	0.32	0.995	9
Stolzenberg-Solomon [12]	2003	China	Asian	Esophagus	PB	Real-time PCR	50	63	16	186	179	33	0.31	0.268	14
Stolzenberg-Solomon [12]	2003	China	Asian	Gastric	PB	Real-time PCR	43	37	10	186	179	33	0.31	0.268	13
Gemmati [13]	2004	Italy	Caucasian	ALL	PB	PCR-RFLP	28	58	23	59	122	76	0.47	0.457	10
Gemmati [13]	2004	Italy	Caucasian	NHL	PB	PCR-RFLP	51	106	43	59	122	76	0.47	0.457	10
Otani [14]	2005	Japan	Asian	Colorectal	HB	Taqman	58	44	5	128	82	14	0.25	0.858	8
Shi [15]	2005	USA	Caucasian	Lung	HB	PCR-RFLP	162	503	370	231	542	375	0.44	0.168	11
Zhang [16]	2005	USA	Caucasian	Head and neck	HB	PCR-RFLP	114	376	231	276	589	369	0.46	0.161	11
Chen [17] [a]	2006	China	Asian	Colorectal	PB	PCR-RFLP	32	107 (AG+GG)		89	253 (AG+GG)		NA	NA	9
Koushik [18]	2006	USA	Mixed	Colorectal	PB	Taqman	82	159	116	163	399	245	0.45	0.981	14

Shrubsole [19]	2006	China	Asian	Breast	PB	Taqman	621	393	70	687	422	76	0.24	0.304	14
Hazra [20]	2007	USA	Mixed	Colorectal	PB	Taqman	113	258	162	111	264	158	0.46	0.970	14
Kim [21]	2007	Korea	Asian	Multiple myeloma	PB	Pyrosequencing	91	69	14	857	718	125	0.28	0.127	11
Lissowska [22]	2007	Poland	Caucasian	Breast	PB	PCR-RFLP	358	970	663	430	1110	753	0.43	0.558	13
Moore [23]	2007	Spain	Caucasian	Bladder	HB	Illumina	267	531	291	232	510	274	0.48	0.857	10
Petra [24]	2007	Slovenia	Caucasian	ALL	HB	PCR-RFLP	15	36	17	47	136	75	0.45	0.283	7
Suzuki [25]	2007	Japan	Asian	Head and neck	HB	PCR-RFLP	108	100	29	332	315	64	0.31	0.382	9
Suzuki [26]	2007	Japan	Asian	Lung	HB	Taqman	235	256	54	484	446	100	0.31	0.852	9
Zhang [27]	2007	Poland	Caucasian	Gastric	PB	Taqman	56	133	106	78	188	147	0.42	0.197	13
Bethke [28]	2008	Multi-center	Caucasian	Brain	PB	Illumina	534	795	307	579	783	286	0.41	0.447	14
Gra [29] [b]	2008	Russia	Caucasian	ALL	PB	PCR-based biochip	109 (AA+AG)		31	151 (AA+AG)		95	NA	NA	7
Gra [29] [b]	2008	Russia	Caucasian	AML	PB	PCR-based biochip	26 (AA+AG)		11	151 (AA+AG)		95	NA	NA	7
Gra [30]	2008	Russia	Caucasian	NHL	PB	PCR-based biochip	16	40	20	33	92	52	0.45	0.492	9
Gra [30]	2008	Russia	Caucasian	CLL	PB	PCR-based biochip	20	32	31	33	92	52	0.45	0.492	9
Ikeda [31]	2008	Japan	Asian	Colorectal	HB	MassARRAY	51	47	8	132	78	12	0.23	0.914	8
Ikeda [31]	2008	Japan	Asian	Gastric	HB	MassARRAY	83	55	5	134	120	24	0.30	0.694	8
Kim [32]	2008	Korea	Asian	NHL	PB	Pyrosequencing	292	235	57	857	718	125	0.28	0.127	10
Kwak [33]	2008	Korea	Asian	Liver	PB	PCR-RFLP	40	45	9	111	78	12	0.25	0.726	7
Lima [34]	2008	Brazil	Mixed	Multiple myeloma	HB	PCR-RFLP	32	63	28	53	102	33	0.45	0.181	6
Marchal [35]	2008	Spain	Caucasian	Prostate	HB	Real-time PCR	38	105	39	46	111	47	0.50	0.207	8
Mir [36] [c]	2008	India	Asian	Breast	HB	PCR-RFLP	1	27	7	0	9	24	0.14	0.364	4
Steck [37]	2008	USA	African	Colorectal	PB	Taqman	116	99	24	169	127	26	0.28	0.755	13
Steck [37]	2008	USA	Caucasian	Colorectal	PB	Taqman	53	155	99	109	256	168	0.44	0.526	13
Suzuki [38]	2008	Japan	Asian	Breast	HB	Taqman	205	205	42	456	366	90	0.30	0.191	10
Suzuki [39]	2008	Japan	Asian	Pancreatic	HB	Taqman	78	67	12	374	330	81	0.31	0.517	10
Theodoratou [40]	2008	Scotland	Caucasian	Colorectal	PB	Illumina	200	456	339	198	482	329	0.44	0.370	12
de Jonge [41]	2009	Netherlands	Caucasian	ALL	PB	Real-time PCR	59	117	66	101	245	153	0.45	0.871	7
Kim [42]	2009	Korea	Asian	ALL	PB	Pyrosequencing	58	34	15	857	718	125	0.28	0.127	9
Kim [42]	2009	Korea	Asian	AML	PB	Pyrosequencing	195	162	42	857	718	125	0.28	0.127	10
Kim [42]	2009	Korea	Asian	CML	PB	Pyrosequencing	73	68	11	857	718	125	0.28	0.127	9
Rouissi [43]	2009	Tunisia	African	Bladder	PB	PCR-RFLP	59	88	38	77	85	29	0.37	0.490	5
Burcos [44] [c]	2010	Romania	Caucasian	Breast	HB	PCR-RFLP	0	37	23	3	32	25	0.32	0.072	6
Burcos [44]	2010	Romania	Caucasian	Colorectal	HB	PCR-RFLP	11	64	45	7	35	18	0.41	0.108	6
Cai [45]	2010	China	Asian	Prostate	HB	PCR-RFLP	111	92	14	118	89	13	0.26	0.479	8
Eussen [46]	2010	Multi-center	Caucasian	Gastric	PB	MALDI-TOF MS	58	100	81	156	286	165	0.49	0.157	12
Sangrajrang [47]	2010	Thailand	Asian	Breast	HB	Taqman	295	218	46	229	210	46	0.31	0.830	11
Tong [48] [b]	2010	Korea	Asian	Cervical	HB	Multiplexed PCR	137 (AA+AG)		11	407 (AA+AG)		23	NA	NA	9
Wettergren [49]	2010	Sweden	Caucasian	Colorectal	PB	Real-time PCR	22	94	61	50	152	97	0.42	0.463	7
Curtin [50]	2011	USA	Mixed	Colorectal	PB	Illumina	193	363	187	211	464	278	0.46	0.509	12
Guimaraes [51]	2011	Brazil	Mixed	Colorectal	HB	PCR-RFLP	26	55	32	53	102	33	0.45	0.181	6
Jokic [52]	2011	Croatia	Caucasian	Colorectal	PB	Taqman	53	159	88	74	143	83	0.49	0.428	10
Metayer [53]	2011	USA	Mixed	ALL	PB	Illumina	133	178	66	145	220	82	0.43	0.928	11
Mostowska [54]	2011	Poland	Caucasian	Cervical	PB	HRM	44	54	26	61	78	29	0.40	0.636	12
Pardini [55]	2011	Czech	Caucasian	Colorectal	HB	Taqman	113	330	218	291	671	410	0.46	0.592	11
te Winkel [56]	2011	Netherlands	Caucasian	ALL	PB	Real-time PCR	17	42	21	15	26	17	0.48	0.436	9
Webb [57]	2011	Australia	Mixed	Ovarian	PB	MassARRAY	584	888	405	447	730	292	0.44	0.846	12
Weiner [58]	2011	Russia	Caucasian	NHL	PB	Real-time PCR	26	64	35	97	259	162	0.44	0.716	8
Yang [59]	2011	China	Asian	ALL	PB	Real-time PCR	180	154	27	198	146	23	0.26	0.568	12
Amigou [60]	2012	France	Caucasian	ALL	PB	Illumina	112	187	110	95	226	120	0.47	0.553	13
Galbiatti [61] [a]	2012	Brazil	Mixed	Head and neck	PB	Real-time PCR	69	196 (AG+GG)		149	317 (AG+GG)		NA	NA	10
Lajin [62]	2012	Syria	Caucasian	Breast	PB	ARMS-PCR	40	59	20	43	58	25	0.43	0.499	4
Pawlik [63]	2012	Poland	Caucasian	Ovarian	PB	HRM	47	68	19	63	68	29	0.39	0.165	12
Weiner [64]	2012	Russia	Caucasian	Breast	PB	Real-time PCR	162	387	285	158	394	216	0.46	0.376	12
Yoo [65]	2012	Korea	Asian	Gastric	HB	MassARRAY	655	513	81	212	135	22	0.24	0.934	7
Yoshimitsu [66]	2012	Japan	Asian	Colorectal	HB	PCR-RFLP	281	198	39	490	454	107	0.32	0.903	10
Yuan [67]	2012	China	Asian	Gastric	HB	MassARRAY	27	112	140	17	114	165	0.25	0.642	7
Chen [68]	2013	China	Asian	Cervical	HB	PCR-RFLP	50	46	11	54	44	9	0.29	0.993	7
Jackson [69] [a]	2013	Jamaica	African	Prostate	HB	Taqman	111	84 (AG+GG)		120	83 (AG+GG)		NA	NA	7
Liu [70]	2013	USA	Mixed	Colorectal	PB	Illumina	264	717	439	356	869	550	0.45	0.704	12
Morita [71]	2013	Japan	Asian	Colorectal	PB	PCR-RFLP	342	278	65	361	343	74	0.32	0.565	11
Tomita [72]	2013	Brazil	Mixed	Cervical	HB	Allele-specific	70	90	40	38	43	19	0.41	0.281	8

						PCR									
Zhang [73]	2013	China	Asian	Brain	PB	PCR-RFLP	209	269	122	225	282	93	0.39	0.765	12
Chang [74]	2014	China	Asian	Gastric	PB	Taqman	119	63	9	204	149	25	0.26	0.752	12
Chang [74]	2014	China	Asian	Liver	PB	Taqman	114	64	13	204	149	25	0.26	0.752	11
Chang [74]	2014	China	Asian	Esophagus	PB	Taqman	117	74	10	204	149	25	0.26	0.752	12
Xu [75]	2014	China	Asian	Liver	HB	SNaPshot	103	86	16	112	73	15	0.26	0.520	6
Gong [76]	2015	USA	Caucasian	Breast	PB	Illumina	158	318	140	165	321	138	0.48	0.442	14
Greenop [77]	2015	Australia	Mixed	Brain	PB	MassARRAY	80	148	90	102	264	175	0.43	0.890	11
Suthandiram [78]	2015	Multi-center	Asian	NHL	HB	MassARRAY	178	153	41	353	306	63	0.30	0.774	10
Kim [79]	2016	Korea	Asian	Gastric	HB	Affymetrix Array	136	111	23	295	211	35	0.26	0.739	10
Nakao [80]	2016	Japan	Asian	Pancreatic	HB	Dynamic Array	167	157	36	206	158	36	0.29	0.473	11
Peres [81]	2016	Brazil	Mixed	Liver	HB	Real-time PCR	12	50	9	105	179	72	0.45	0.787	8
Tao [82]	2016	China	Asian	Breast	HB	MassARRAY	175	85	38	162	115	21	0.26	0.924	9

MAF, minor allele frequency; HB: hospital based; PB: population based; NA, not applicable; PCR-RFLP: polymorphism chain reaction restriction fragment length polymorphism; MALDI-TOF MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; HRM: high resolution melt; ARMS-PCR: amplification refractory mutation system-PCR; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin's lymphoma; AML: acute myelogenous leukemia; CML: chronic myelogenous leukemia; CLL: chronic lymphocytic leukemia.

[a] Chen [17], Galbiatti [61] and Jackson [69] were only calculated for the dominant model.

[b] Gra [29] and Tong [48] were only calculated for the recessive model.

[c] Mir [36] and Burcos [44] (breast cancer) were only calculated for the recessive model and allele comparison, and the number of AA genotype was zero.

Of the 72 publications, two publications [11, 37] with different ethnic groups were separated as five independent studies and eight publications [12, 13, 29-31, 42, 44, 74] with different cancer types were also treated as 18 independent studies. For those studies [12, 13, 21, 25, 26, 29, 30, 32, 38, 39, 42, 50, 54, 63, 70, 74] with the same control group, the control numbers were calculated once in the total number. Overall, 72 publications including 85 studies of 32,272 cases and 37,427 controls were included in the final meta-analysis. Of the 85 studies, 20 studies focused on colorectal cancer [11, 14, 17, 18, 20, 31, 37, 40, 44, 49-52, 55, 66, 70, 71], ten on breast cancer [19, 22, 36, 38, 44, 47, 62, 64, 76, 82], nine on acute lymphoblastic leukemia (ALL) [13, 24, 29, 41, 42, 53, 56, 59, 60], eight on gastric cancer [12, 27, 31, 46, 65, 67, 74, 79], five on non-Hodgkin lymphoma (NHL) [13, 30, 32, 58, 78], four each on cervical cancer [48, 54, 68, 72] and liver cancer [33, 74, 75, 81], three each on prostate cancer [35, 45, 69], head and neck cancer [16, 25, 61] and brain cancer [28, 73, 77], and "other cancers" with no more than two studies. There were 37 studies on Asians, 32 studies on Caucasians, 13 studies on mixed ethnicities and three on Africans. Of all the studies, 52 were population-based and 33 were hospital-based. Furthermore, 37 studies were considered as low quality (quality score ≤ 9), and 48 studies (56.5%) were considered as high quality (quality score > 9). Controls were matched for age, sex and ethnicity in most studies.

Meta-analysis results

The main results of the meta-analysis are shown in **Table 2** and **Figure 2**. Pooled analysis indicated a significant association between the *MTRR* A66G polymorphism and cancer risk (homozygous: OR = 1.08, 95% CI = 1.02-1.15, P = 0.009; recessive: OR = 1.06, 95% CI = 1.00-1.12, P < 0.001 and allele comparison: OR = 1.03, 95% CI = 1.00-1.06, P < 0.001). In the subgroup analysis, statistically significant associations were found for head and neck cancer (homozygous: OR = 1.49, 95% CI = 1.17-1.89, P = 0.768; dominant: OR = 1.30, 95% CI = 1.03-1.64, P = 0.143 and allele comparison: OR = 1.17, 95% CI = 1.04-1.31, P = 0.560), Caucasians (homozygous: OR = 1.09, 95% CI = 1.00-1.19, P = 0.077; dominant: OR = 1.08, 95% CI = 1.00-1.17, P = 0.045 and allele comparison: OR = 1.05, 95% CI = 1.01-1.09, P = 0.193), Africans (homozygous: OR = 1.52, 95% CI = 1.00-2.32, P = 0.577 and allele comparison: OR = 1.23, 95% CI = 1.01-1.49, P = 0.474) and high quality studies (homozygous: OR = 1.07, 95% CI = 1.00-1.15, P = 0.005 and recessive: OR = 1.06, 95% CI = 1.01-1.11, P = 0.262).

Heterogeneity and sensitivity analysis

Substantial heterogeneity was detected among all studies of the *MTRR* A66G polymorphism and overall cancer risk (homozygous: P = 0.009; heterozygous: P = 0.007; dominant: P = 0.001; recessive: P < 0.001 and allele comparison: P < 0.001). Therefore, the random-effects model was applied to generate wider CIs. Leave-one-out sensitivity analysis was performed and the results suggested the pooled ORs were not influenced by omitting any single study (data not shown).

Publication bias

As shown by the relative symmetric funnel plot (**Figure 3**) and Egger's test, no evidence of publication bias was found in the current analysis under any of the models (homozygous: P = 0.913; heterozygous: P = 0.551; dominant: P = 0.510; recessive: P = 0.666 and allele comparison: P = 0.560).

FPRP test results

The significant associations were investigated using the FPRP test and the results were shown in **Table 3**. For a prior probability of 0.1, the FPRP value was 0.128 for the *MTRR* A66G polymorphism with an increased cancer risk under the homozygous model, and positive associations were also found in head and neck cancer (homozygous: FPRP = 0.017 and allele comparison: FPRP = 0.055), Caucasians (allele comparison: FPRP = 0.087) and high score studies (recessive: FPRP = 0.106). However, no positive association was found between the *MTRR* A66G polymorphism and cancer risk in Africans.

Table 2. Meta-analysis of the association between *MTRR* A66G polymorphism and cancer risk.

Variables	No. of studies	Sample size (case/controls)	Homozygous		Heterozygous		Recessive		Dominant		Allele comparison	
			GG *vs.* AA		AG *vs.* AA		GG *vs.* (AA + AG)		(GG + AG) vs. AA		G vs. A	
			OR (95% CI)	*P*het	OR (95% CI)	*P*het	OR (95% CI)	*P*het	OR (95% CI)	*P*het	OR (95% CI)	*P*het
All [a]	85	32,272/37,427	**1.08 (1.02-1.15)**	0.009	1.01 (0.97-1.06)	0.007	**1.06 (1.00-1.12)**	<0.001	1.04 (0.99-1.08)	0.001	**1.03 (1.00-1.06)**	<0.001
Cancer type												
Colorectal	20	8,057/10,465	1.09 (0.96-1.25)	0.031	1.05 (0.95-1.16)	0.030	1.04 (0.97-1.11)	0.462	1.07 (0.97-1.19)	0.006	1.05 (0.98-1.12)	0.007
Breast	10	6,048/5,872	1.08 (0.96-1.21)	0.488	0.99 (0.89-1.11)	0.131	0.99 (0.81-1.22)	0.001	1.02 (0.94-1.11)	0.362	1.01 (0.92-1.11)	0.018
ALL	9	1,893/3,770	0.90 (0.72-1.13)	0.228	0.88 (0.76-1.03)	0.367	0.89 (0.70-1.14)	0.013	0.89 (0.78-1.02)	0.472	0.93 (0.85-1.02)	0.547
Gastric	8	2,756/2,504	0.96 (0.72-1.29)	0.054	0.95 (0.80-1.12)	0.159	1.02 (0.82-1.27)	0.109	0.94 (0.78-1.14)	0.041	0.97 (0.84-1.12)	0.010
NHL	5	1,357/1,674	1.00 (0.74-1.35)	0.126	0.97 (0.84-1.11)	0.998	0.99 (0.74-1.33)	0.053	0.99 (0.87-1.13)	0.911	0.99 (0.89-1.11)	0.295
Cervical	4	579/805	1.22 (0.80-1.86)	0.968	1.07 (0.78-1.46)	0.882	1.77 (0.98-3.20)	0.029	1.11 (0.83-1.48)	0.945	1.10 (0.90-1.36)	0.982
Liver	4	561/757	1.19 (0.79-1.78)	0.600	1.33 (0.84-2.10)	0.011	0.97 (0.65-1.45)	0.335	1.29 (0.86-1.94)	0.022	1.11 (0.89-1.38)	0.151
Brain	3	2,554/2,789	1.05 (0.72-1.52)	0.009	0.98 (0.79-1.21)	0.091	1.08 (0.84-1.40)	0.054	0.99 (0.77-1.27)	0.029	1.02 (0.85-1.22)	0.014
Head and neck	3	1,223/1,700	**1.49 (1.17-1.89)**	0.768	1.24 (0.79-1.94)	0.025	1.15 (0.96-1.38)	0.346	**1.30 (1.03-1.64)**	0.143	**1.17 (1.04-1.31)**	0.560
Prostate	3	594/627	1.05 (0.65-1.71)	0.798	1.12 (0.82-1.52)	0.899	0.96 (0.64-1.44)	0.689	1.10 (0.87-1.40)	0.999	1.04 (0.84-1.27)	0.718
Other cancers	16	6,650/6,464	1.14 (1.01-1.28)	0.282	1.01 (0.94-1.10)	0.335	1.10 (1.01-1.20)	0.533	1.06 (0.97-1.15)	0.211	1.06 (1.00-1.11)	0.340
Ethnicity												
Asian	37	11,829/13,248	1.11 (0.99-1.24)	0.080	0.98 (0.92-1.05)	0.063	1.09 (0.97-1.22)	0.006	1.01 (0.95-1.08)	0.019	1.02 (0.97-1.08)	0.001
Caucasian	32	13,351/16,506	**1.09 (1.00-1.19)**	0.077	1.08 (0.99-1.16)	0.078	1.03 (0.96-1.09)	0.144	**1.08 (1.00-1.17)**	0.045	**1.05 (1.01-1.09)**	0.193
African	3	619/716	**1.52 (1.00-2.32)**	0.577	1.21 (0.92-1.60)	0.553	1.36 (0.92-2.02)	0.751	1.21 (0.97-1.51)	0.624	**1.23 (1.01-1.49)**	0.474
Mixed	13	6,473/6,957	1.01 (0.88-1.15)	0.084	0.96 (0.86-1.06)	0.184	1.12 (0.96-1.32)	<0.001	1.00 (0.90-1.11)	0.075	1.01 (0.94-1.07)	0.088
Source of control												
PB	52	21,300/24,134	1.06 (0.99-1.14)	0.087	0.99 (0.94-1.04)	0.304	1.05 (0.99-1.11)	0.037	1.01 (0.97-1.06)	0.135	1.02 (0.99-1.06)	0.075
HB	33	10,972/13,293	1.12 (0.99-1.26)	0.019	1.06 (0.97-1.16)	0.002	1.07 (0.94-1.21)	<0.001	1.08 (0.99-1.18)	0.001	1.04 (0.98-1.11)	<0.001
Score												
Low	37	6,610/9,768	1.13 (0.99-1.29)	0.265	1.05 (0.96-1.16)	0.144	1.06 (0.90-1.24)	0.000	1.08 (0.99-1.17)	0.299	1.05 (0.98-1.12)	0.042
High	48	25,662/27,659	**1.07 (1.00-1.15)**	0.005	1.00 (0.95-1.05)	0.010	**1.06 (1.01-1.11)**	0.262	1.02 (0.97-1.08)	<0.001	1.02 (0.99-1.06)	0.001

Het, heterogeneity; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin's lymphoma; PB: population based; HB: hospital based.

[a] The number of controls was only calculated once if the same controls were used.

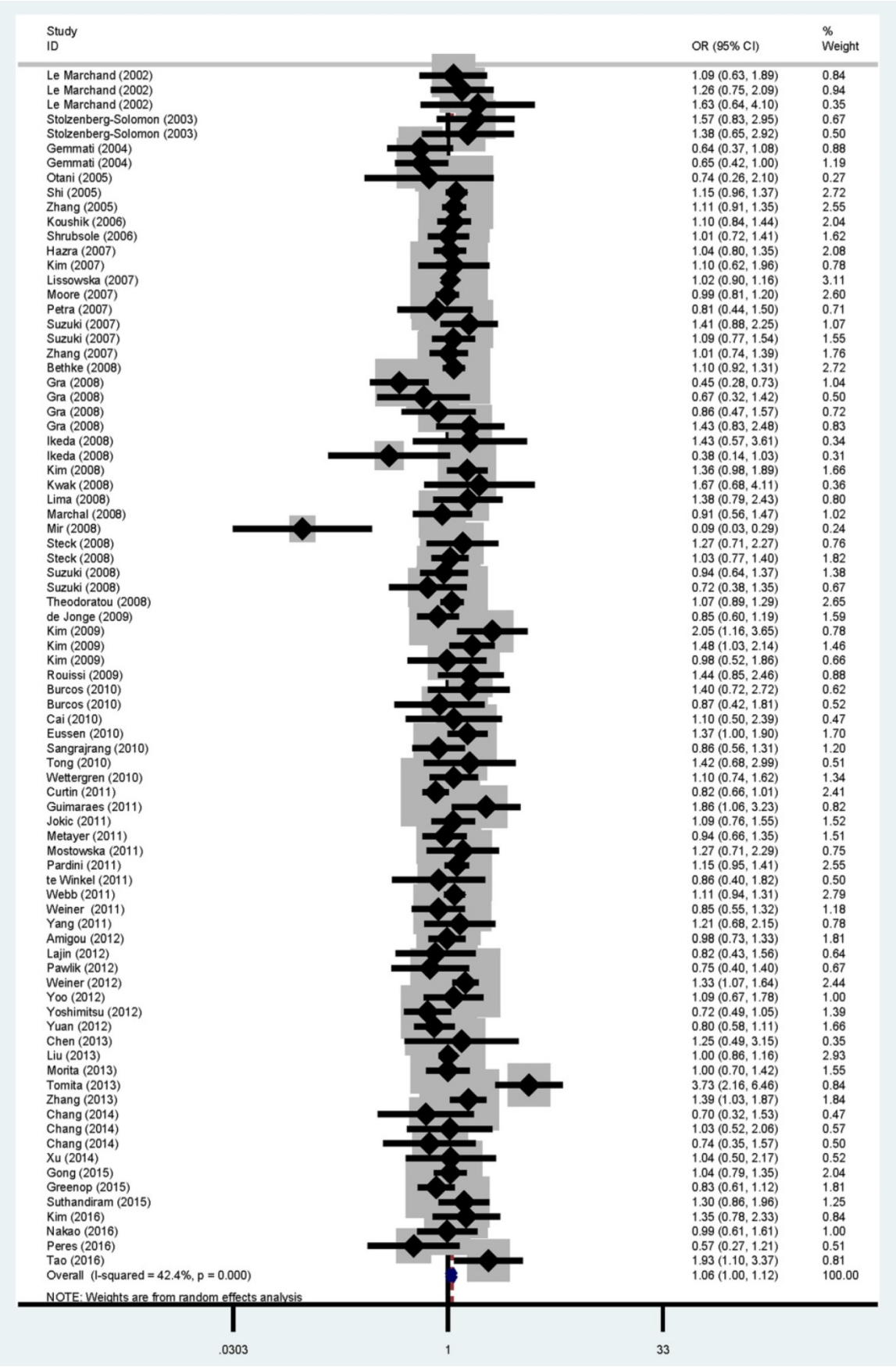

Figure 2. Forest plot for overall cancer risk associated with the *MTRR* A66G polymorphism by a recessive model. For each study, the estimated OR and its 95% CI are plotted with a box and a horizontal line. ◇, pooled ORs and its 95% CIs.

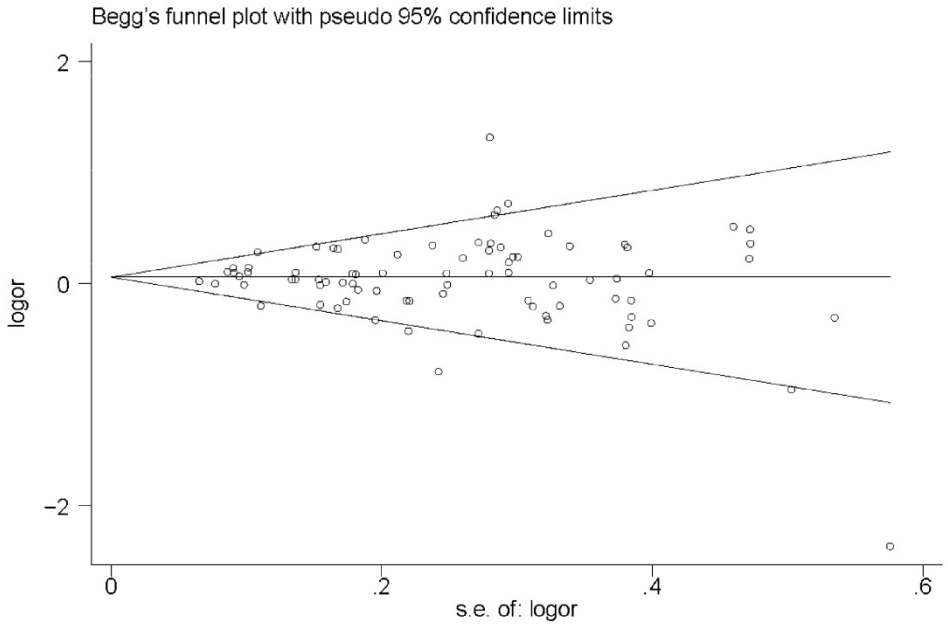

Figure 3. Funnel plot for the *MTRR* A66G polymorphism and cancer risk by a recessive model.

Table 3. False-positive report probability values for associations between cancer risk and genotypes of *MTRR* A66G polymorphism.

Genotype	Crude OR (95% CI)	*P*-value [a]	Statistical Power [b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
All patients								
Homozygous	1.08 (1.02-1.15)	0.016	1.000	**0.047**	**0.128**	0.618	0.942	0.994
Recessive	1.06 (1.00-1.12)	0.038	1.000	**0.102**	0.255	0.790	0.974	0.997
Allele comparison	1.03 (1.00-1.06)	0.044	1.000	**0.116**	0.282	0.812	0.978	0.998
Cancer type-head and neck cancer								
Homozygous	1.49 (1.17-1.89)	0.001	0.522	**0.006**	**0.017**	**0.161**	0.660	0.951
Dominant	1.30 (1.03-1.64)	0.027	0.886	**0.083**	0.214	0.750	0.968	0.997
Allele comparison	1.17 (1.04-1.31)	0.006	1.000	**0.019**	**0.055**	0.391	0.886	0.985
Ethnicity-Caucasian								
Homozygous	1.09 (1.00-1.19)	0.054	1.000	**0.140**	0.328	0.843	0.982	0.998
Dominant	1.08 (1.00-1.17)	0.059	1.000	**0.151**	0.349	0.885	0.983	0.998
Allele comparison	1.05 (1.01-1.09)	0.010	1.000	**0.031**	**0.087**	0.511	0.913	0.991
Ethnicity-African								
Homozygous	1.52 (1.00-2.32)	0.052	0.476	0.248	0.497	0.916	0.991	0.999
Allele comparison	1.23 (1.01-1.49)	0.034	0.979	**0.095**	0.240	0.777	0.972	0.997
Score-high								
Homozygous	1.07 (1.00-1.15)	0.066	1.000	**0.165**	0.372	0.867	0.985	0.998
Recessive	1.06 (1.01-1.11)	0.013	1.000	**0.038**	**0.106**	0.567	0.930	0.992

[a]Chi-square test was used to calculate the genotype frequency distributions.
[b]Statistical power was calculated using the number of observations in the subgroup and the OR and *P* values in this table.

Discussion

Folate is a critical coenzyme in DNA synthesis, and the maintenance of methylation, and folate deficiency has been reported to be associated with various human malignancies [113, 114]. MTRR plays a key role in folate-dependent homocysteine remethylation and is required in the regulation of MTR activity. The A66G polymorphism is one of the most common polymorphisms in the *MTRR* gene, which was first reported in 1998 [115], and the variant enzyme has reduced affinity for MTR [116]. The reported associations between the *MTRR* A66G polymorphism and cancer susceptibility are inconsistent due to the small sample sizes in individual studies, ethnic differences and research methodology.

Our present study represents an updated comprehensive meta-analysis of the association between the *MTRR* A66G polymorphism and cancer risk and included 85 studies with 32,272 cases and 37,427 controls. The results revealed that the *MTRR* A66G polymorphism was significantly associated

with an increased overall cancer risk. In the subgroup analysis, the association was more evident for head and neck cancer, Caucasians, Africans and high quality studies. However, the results for Africans need further validation due to the high probability of false-positive reports. Furthermore, no potential publication bias was detected by the funnel plot and Egger's regression test, indicating the robustness of the results in this study.

One previous meta-analysis focused on the *MTRR* A66G polymorphism and overall cancer risk. In the meta-analysis by Han *et al.* [117], which included 35 studies with 18,661 cases and 27,678 controls, an increased overall cancer risk was observed only under the allele comparison and homozygous model. In the subgroup analysis, significantly increased risks were found in Asians. We found this polymorphism to be associated with an increased overall risk also under the recessive model and increased cancer risks in head and neck cancer, Caucasians and Africans, but not in Asians, which were different from the previous meta-analysis; this result presumably occurred because our analysis was based on a much larger sample size, thereby increasing the statistical power. In the subgroup analysis by cancer type, we did not find any significant association between the *MTRR* A66G polymorphism and colorectal cancer in any comparison models, a finding that was inconsistent with previous meta-analyses [6, 118]. The discrepancy occurred because, in the current study, we added many recently published studies and even included several Chinese publications, allowing the more precise detection of an association.

Large and well-designed studies with "statistically significant" results for genetic variants turned out to be false-positive findings [119, 120]. Thus, we used the FPRP test to investigate positive associations in the current meta-analysis. Interestingly, the FPRP test results showed that the *MTRR* A66G polymorphism could actually increase cancer susceptibility. In the subgroup analysis, the FPRP test indicated that the *MTRR* A66G polymorphism increased cancer susceptibility in head and neck cancer, Caucasians and high score studies. The significant association with Africans in the present meta-analysis was false positive, which may due to the limited sample size.

Although we conducted a comprehensive literature search and included the latest studies on the *MTRR* A66G polymorphism and cancer risk, some possible limitations in this meta-analysis should be addressed. First, the number of cases in the individual studies was small (<1000) in all but eight studies [15, 19, 22, 23, 28, 57, 65, 70]; this limitation may affect the investigation of the real association. Second, our results were based on unadjusted estimates, so the estimates were relatively imprecise. Third, the effects of gene-gene, and gene-environment interactions were not evaluated due to the lack of original data, which may affect cancer risk. Fourth, in the subgroup analysis, only three studies were carried out in Africans, which may lead to relatively weak power to detect the real association. Finally, only studies published in English and Chinese were included, so we may have missed publications in other languages.

In conclusion, we performed this updated meta-analysis with the latest published studies and obtained a more precise estimation of the association between the *MTRR* A66G polymorphism and cancer risk. However, it is necessary to conduct well-designed prospective studies with larger sample sizes to verify our findings.

Acknowledgements

This work was supported by the Key Scientific and Technological Project of Henan province (Grant No. 162102310413) and the Special Financial Grant from the China Postdoctoral Science Fundation (Grant No. 2014T70836).

Competing Interests

The authors have declared that no competing interest exists.

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