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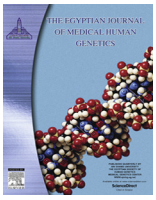

Review

MTHFR C677T polymorphism and risk of esophageal cancer: An updated meta-analysis

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ABSTRACT

Background: Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in folate/homocysteine metabolism. A polymorphism C677T has been reported to be linked with risk of several diseases/disorders like birth defects, metabolic and psychiatric disorders and different cancers. The association between esophageal cancer and MTHFR gene C677T polymorphism has been investigated in several case-control studies, which rendered contradictory results.

Aim: To shed light on association between MTHFR C677T polymorphism and risk of esophageal cancer, a meta-analysis of published case control association studies was conducted.

Methods: Four electronic databases: PubMed, Google Scholars, Elsevier and Springer Link were searched up to August 2016. All statistical analyses were performed using MetaAnalyst and Mix (version 1.7). Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated. Total twenty-nine studies with 6520 cases and 9192 controls were included in the present meta-analysis.

Results: The results of meta-analysis suggested that there were significant association between C677T polymorphism and esophageal cancer risk using overall comparisons in five genetic models (T vs. C: OR = 1.20, 95% CI = 1.1–1.27, p = <0.0001; TT + CT vs. CC: OR = 1.37, 95% CI = 1.14–1.62, p = 0.0004; TT vs. CC: OR = 1.43, 95% CI = 1.1–1.84, p = 0.005; CT vs. CC OR = 1.35, 95% CI = 1.15–1.58, p = 0.0002; TT vs. CT + CC: OR = 1.19, 95% CI = 0.99–1.42, p = 0.05). Publication bias was absent. Subgroup analysis based on ethnicity and source of controls were also performed.

Conclusion: In conclusion, results of present meta-analysis showed significant association between MTHFR C677T polymorphism and esophageal cancer.

Contents

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1. Introduction

Esophageal cancer is the sixth most common cancer worldwide, which is characterized by rapid development [1–3] and survival rates for esophageal cancer are quiet poor [4,5]. Its incidence rates vary globally, and the highest rates found in Southern and Eastern Africa and Eastern Asia [3]. Higher incidence of the cancer in certain geographic regions suggests the role of environmental risk factors such as nutritional deficiency, in its pathogenesis [6–9].

Folate deficiency resulting from low consumption of vegetables and fruits is associated with increased risk of esophageal cancer [9]. The biological function of folate is to provide methyl groups, required for DNA methylation and synthesis [10]. Therefore, folate deficiency is thought to be carcinogenic through disruption of DNA methylation, synthesis, and impaired repair. Besides inadequate folate intake, functional polymorphisms in folate metabolizing genes especilaly methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism may also influence susceptibility to cancer.

MTHFR is a key enzyme of folate metabolism. It catalyzes irreversible reduction of 5, 10-methylene tetrahydrofolate to 5-methyl tetra-hydro folate, which provides the methyl group with the ability to convert homocysteine to methionine, the precursor of S-adenosyl methionine (SAM). SAM is a universal methyl-group donor for methylation of a wide variety of biological substrates. MTHFR is also involved in production of deoxythymidine monophosphate (dTMP) via thymidylate synthase and purine synthesis. Therefore, MTHFR is also thought to play a role in the provision of nucleotides essential for DNA synthesis and repair [11].

MTHFR gene is located at 1p36.3 [12] and Frosst et al. [11] identified a single nucleotide polymorphism (SNP), the C to T transition at nucleotide 677 in exon 4 of the MTHFR gene (rs1801133), which results in an alanine (A) to valine (V) substitution (A222V). Individuals with homozygous variant 677TT and heterozygote 677CT genotypes have only about 30% and 65%, respectively, of in vitro enzyme activity as compared to those with 677CC wild type genotype [11]. The frequency of C677T polymorphism varies greatly in different populations [13–15].

Epidemiologic studies have revealed that MTHFR C677T polymorphism is associated with an increased risk of endometrial cancer [16], cervical intraepithelial neoplasia [17], breast cancer [18], gastric cancer [19] and bladder cancer [20] etc. Several case control studies [21–28] were investigated MTHFR gene C677T polymorphism as risk for esophageal cancer but results were contradictory. Hence, we performed a meta-analysis of case-control studies, to obtain a more precise estimation of the relationship between MTHFR C677T polymorphism and esophageal cancer risk.

2. Methods

Meta-analysis was carried out according to MOOSE guidelines [29].

2.1. Search strategy and identification of studies

A literature search of the PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://scholar.google.com), Science Direct (http://www.sciencedirect.com), and Springer Link (http://link.springer.com) databases (updated to August 2016) was conducted using combinations of the following terms: "polymorphism or variant or mutation" and "Esophageal cancer" and "Methylenetetrahydrofolate reductase or MTHFR".

2.2. Inclusion/exclusion criteria of studies

Studies that were included in the present meta-analysis had to meet the following criteria: (1) study should evaluate MTHFR gene C677T polymorphism in esophageal cancer cases, (2) study should be a case-control, and (3) study should report sufficient genotype/allele numbers for estimation of odds ratio (OR) with a 95% confidence interval (CI). Accordingly, the following exclusion criteria were also used: (1) editorials, abstracts, reviews and linkage or pedigree studies, (2) only cases were reported, and (3) studies that did not report genotype/allele number.

2.3. Data extraction

The following information was extracted from each included study: first author's family name, journal name, year of publication, country name and number of cases and controls. Number of alleles or genotypes in both cases and controls were extracted or calculated from published data to recalculate ORs.

2.4. Statistical analysis

Crude odds ratio with 95% CI were used to assess strength of association between MTHFR C677T genotypes and risk of esophageal cancer in log additive/ allele contrast (T vs C), homozygote (TT vs CC), co-dominant/heterozygote (CT vs CC), dominant (TT + CT vs CC) and recessive (TT vs CT + CC) models. The statistical significance of the pooled OR was determined using a Z test, and $p < 0.05$ was considered statistically significant.

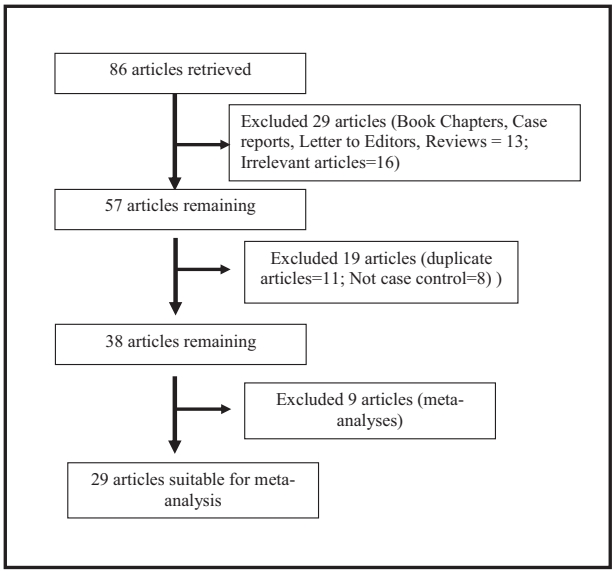

Fig. 1. Flow diagram of study search and selection process.

Table 1
Distribution of different genotypes in included thirty-two studies.

Study	Country	Case/Control	Case genotype			Control Genotype			HWE P- value
			CC	CT	TT	CC	CT	TT	
Song et al. (2001)	China	240/360	29	118	93	126	172	62	0.82
Miao et al. (2002)	China	217/468	47	107	63	151	217	100	0.18
Wu et al. (2002)	China	93/200	31	47	15	63	99	38	0.93
Stolzenberg et al. (2003)	China	129/398	23	58	48	65	209	124	0.14
Zhang et al. (2003)	China	198/141	16	93	89	25	54	62	0.05
Kureshi et al. (2004)	Pakistan	34/54	22	12	0	32	18	4	0.51
Zhang et al. (2004), China	China	189/141	16	93	80	25	54	62	0.03*
Zhang et al. (2004), Germany	Germany	241/256	94	116	31	107	115	34	0.74
Wang et al. (2005)	China	275/315	51	105	119	74	143	98	0.12
Yang et al. (2005)	China	165/493	63	82	20	186	227	80	0.44
Feng et al. (2006)	China	275/315	51	105	119	74	143	98	0.12
Zhang et al. (2006), Kazakh	China	94/98	53	34	7	57	29	12	0.01*
Zhang et al. (2006), Han	China	84/57	27	34	23	13	30	14	0.68
He et al. (2007)	China	584/540	73	263	248	119	234	187	0.005*
Li et al. (2008)	China	126/169	22	52	52	41	62	66	0.001*
Qin et al. (2008)	China	120/240	60	53	7	170	59	11	0.06
Chen et al. (2009)	China	103/181	11	49	43	45	85	51	0.42
Langevin et al. (2009)	Mixed	725/1531	209	328	188	486	731	314	0.19
Wang et al. (2009)	China	102/110	39	47	16	58	36	16	0.01*
Umar et al. (2010)	India	208/223	155	48	5	155	63	5	0.63
Cai et al. (2011)	China	125/250	32	66	27	114	95	41	0.007*
Li et al. (2011)	China	270/262	112	113	45	95	82	85	000*
Zhao et al. (2011)	China	155/310	68	74	13	179	120	11	0.09
Ekiz et al. (2012)	Turkey	26/30	17	9	0	16	12	2	0.9
Jing et al.,2012	China	168/92	75	74	19	37	41	14	0.05
Yang et al. (2012)	China	100/97	37	45	18	40	41	16	0.32
Huang et al. (2013), EPL	China	109/167	52	37	20	90	60	17	0.14
Hunag et al. (2013), ESCC	China	126/167	44	65	17	90	60	17	0.14
Qu et al. (2013)	China	378/425	69	181	128	47	185	193	0.78
Chang et al. (2014)	USA	202/391	65	105	32	135	199	57	0.23
Keld et al. (2014)	UK	44/58	19	20	5	27	27	4	0.42
Tang et al. (2014)	China	615/653	188	288	139	188	348	117	0.06

* Control population of these studies was not in Hardy Weinberg Equilibrium.

Table 2
Summary estimates for the odds ratio (OR) of MTHFR C677T in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric and publication bias p-value (Egger Test).

Genetic models	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p-value (Q test)	I^2 (%)	Publication bias (p of egger's test)
All studies (32)					
Allele Contrast (T vs C)	1.19(1.13–1.24), <0.0001	1.19(1.05–1.32),0.003	<0.0001	79.66	0.82
Co-dominant (Ct vs CC)	1.23(1.13–1.33),<0.0001	1.29(1.11–1.49),0.0007	<0.0001	67.52	0.18
Homozygote (TT vs CC)	1.38(1.25–1.52),<0.0001	1.38(1.10–1.72),0.004	<0.0001	76.69	0.80
Dominant (TT + CT vs CC)	1.27(1.18–1.36),<0.0001	1.3(1.12–1.53),0.0007	<0.0001	74.62	0.39
Recessive (TT vs CT + CC)	1.21(1.12–1.31),<0.0001	1.18(1.0–1.38),0.04	<0.0001	70.65	0.37
Asian studies (28)					
Allele Contrast (T vs C)	1.2(1.13–1.26),<0.0001	1.2(1.04–1.35),0.01	<0.0001	82.1	0.76
Co-dominant (Ct vs CC)	1.28(1.17–1.40), <0.0001	1.33(1.11–1.58),0.001	<0.0001	70.57	0.34
Homozygote (TT vs CC)	1.40(1.25–1.56), <0.0001	1.38(1.07–1.82),0.01	<0.0001	79.44	0.75
Dominant (TT + CT vs CC)	1.31(1.2–1.42), <0.0001	1.34(1.11–1.61),0.002	<0.0001	77.47	0.52
Recessive (TT vs CT + CC)	1.2(1.10–1.30), <0.0001	1.17(0.97–1.66), 0.0.09	<0.0001	73.88	0.45
Caucasian studies (4)					
Allele Contrast (T vs C)	1.14(1.03–1.23), 0.009	1.14(1.03–1.26), 0.009	0.82	0	0.49
Co-dominant (Ct vs CC)	1.07(0.91–1.25),0.4	1.07(0.91–1.25),0.4	0.97	0	0.5
Homozygote (TT vs CC)	1.31(1.07–1.60),0.009	1.31(1.07–1.60),0.009	0.73	0	0.68
Dominant (TT + CT vs CC)	1.14(0.98–1.320),0.09	1.14(0.98–1.320),0.09	0.96	0	0.49
Recessive (TT vs CT + CC)	1.27(1.06–1.51),0.007	1.27(1.06–1.51),0.007	0.57	0	0.6
Hospital based controls (17)					
Allele Contrast (T vs C)	1.12(1.03–1.20),0.003	1.15(0.98–1.35),0.08	<0.0001	75.43	0.58
Co-dominant (Ct vs CC)	1.2(1.07–1.35),0.001	1.27(1.02–1.57),0.02	<0.0001	67.96	0.35
Homozygote (TT vs CC)	1.15(0.98–1.35),0.07	1.26(0.98–1.71),0.14	<0.0001	66.76	0.77
Dominant (TT + CT vs CC)	1.19(1.07–1.32),0.001	1.25(1.01–1.55),0.03	<0.0001	71.27	0.36
Recessive (TT vs CT + CC)	1.08(0.94–1.24),0.27	1.11(0.85–1.44),0.43	0.0004	61.98	0.99
Population based studies (16)					
Allele Contrast (T vs C)	1.22(1.15–1.29),<0.0001	1.21(1.03–1.39),0.01	<0.0001	82.36	0.71
Co-dominant (Ct vs CC)	1.24(1.11–1.37),<0.0001	1.29(1.05–1.57),0.01	<0.0001	67.22	0.33
Homozygote (TT vs CC)	1.51(1.34–1.70),<0.0001	1.48(1.10–2.00),0.009	<0.0001	80.95	0.74
Dominant (TT + CT vs CC)	1.33(1.20–1.46),<0.0001	1.35(1.08–1.68),0.007	<0.0001	76.65	0.61
Recessive (TT vs CT + CC)	1.27(1.15–1.39),<0.0001	1.26(1.01–1.51),0.03	<0.0001	75.27	0.43

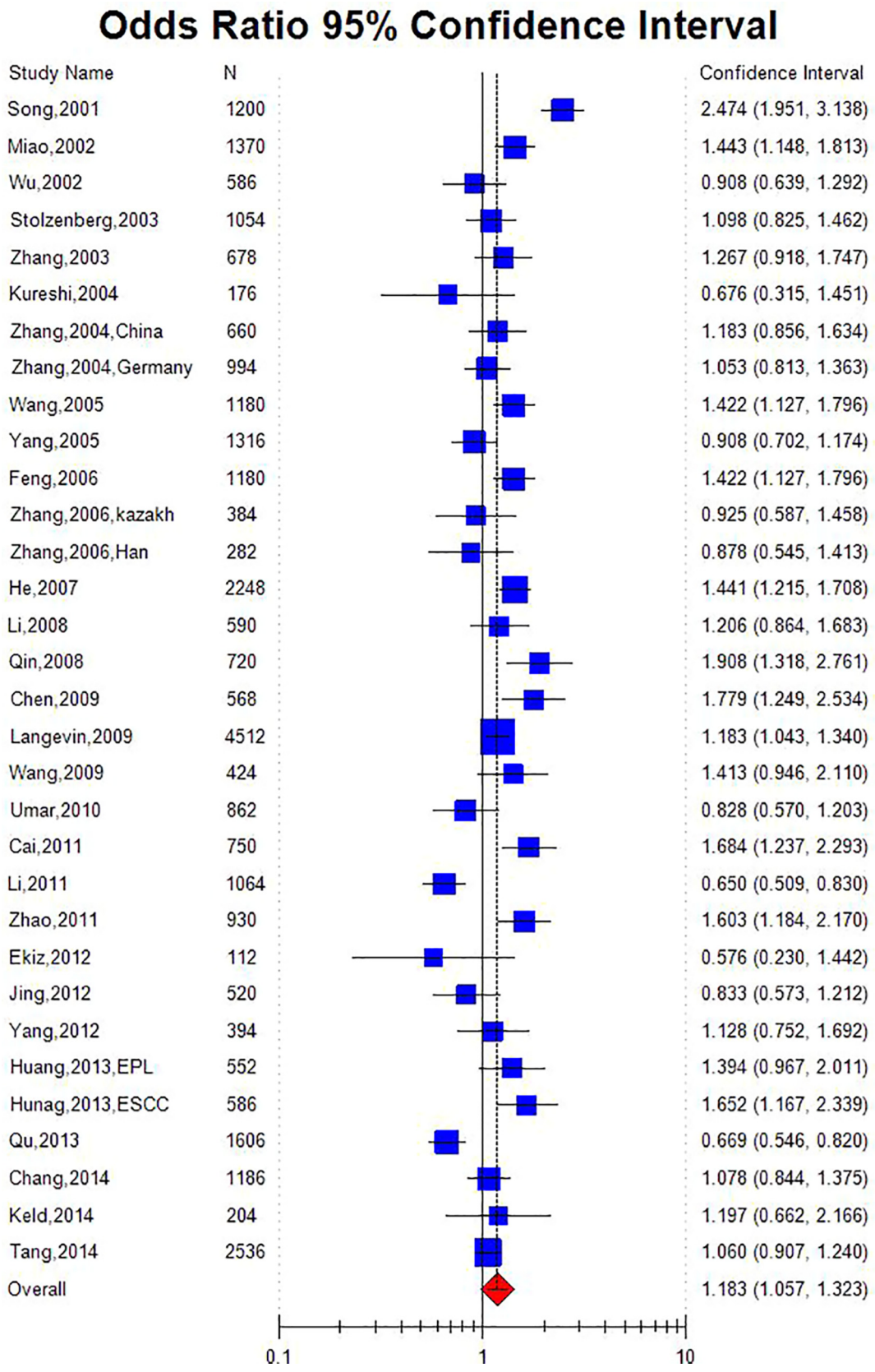

Fig. 2. Random effect forest plot of allele contrast model (T vs. C) of *MTHFR* C677T polymorphism.

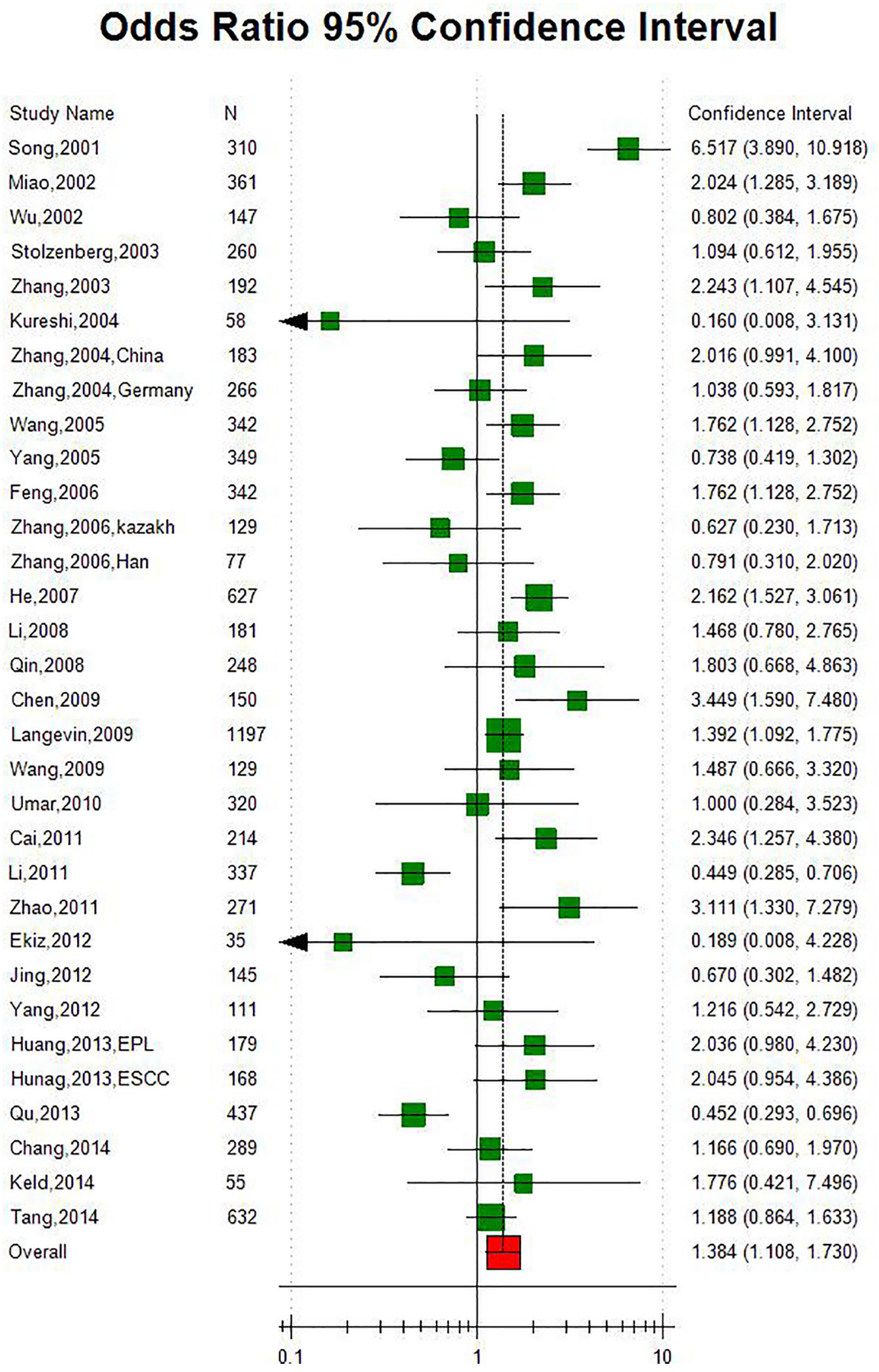

Fig. 3. Random effect forest plot of homozygote model (TT vs. CC) of *MTHFR* C677T polymorphism.

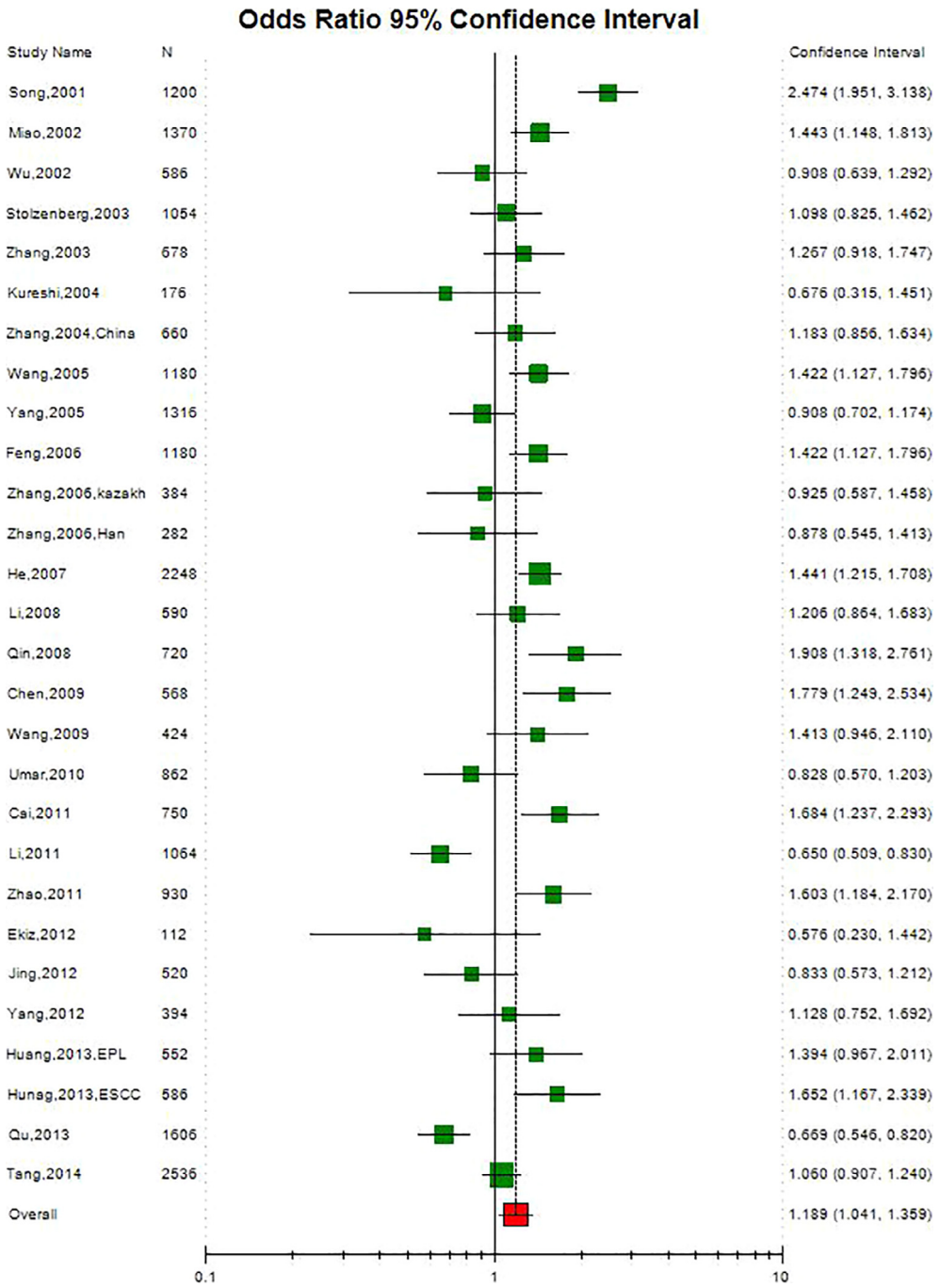

Fig. 4. Random effect forest plot of allele contrast model (T vs. C) of Asian studies.

The heterogeneity of these studies was tested by the Q statistic and was considered statistically significant when $p < 0.05$ [30]. The pooled OR was estimated using the fixed effects model when there was less heterogeneity [31] or random effects model when there was higher heterogeneity [32]. All included studies were tested for genotypic distribution of the MTHFR C677T polymorphism in the control group with the HWE principle using the x^2-test, and considered $p < 0.05$ as statistically significant. Sensitivity analysis was carried out by excluding studies not in HWE [33]. Subgroup analysis was also performed on the basis of ethnicity of subjects and source of controls.

2.5. Publication bias

Funnel plots were used to detect publication bias. However, due to the limitations of funnel plotting, which require a range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test [34], which measures funnel plot asymmetry using a natural logarithm scale of OR. Begg's correlation test also was performed [35]. All p-values are two tailed with a significance level at 0.05. All statistical analyses were undertaken by MetaAnalyst [36] and MIX version 1.7 [37].

3. Results

3.1. Characteristics of included studies

Eighty-six studies were retrieved by literature search strategy. Out of these, 29 articles were excluded. The excluded papers included book chapters, reviews, letter to editor and irrelevant articles. After reviewing the abstract and papers of remaining 57 articles, 19 articles were also excluded (11 articles were duplicates and 8 articles were not case control). Further nine studies were excluded from the analysis as they were meta-analyses (Fig. 1). Only 29 articles, qualifying our strict selection criteria, were included in the present meta-analysis [5,21–28,38–57]. Out of 29 studies, 23 studies were carried out on Chinese subjects and remaining studies were carried out in six other countries- Pakistan [22], Germany [42], India [23], Turkey [5], Britain [28], America [56]. Three authors [42,46,55] studied two different population samples, in present meta-analysis we considered each population as individual study/sample. So finally we have thirty-two studies to include in the present meta-analysis. Number of cases, controls and different genotypes data for all these thirty-two studies were tabulated (Table 1).

Overall, thirty-two studies provided 6,520/9192 cases/controls for MTHFR C677T polymorphism. The percentage frequency of TT genotype among cases and controls was 26.52% and 22%, respectively whereas prevalence of CT heterozygotes among cases was 44.8% and 44.1% in controls. The prevalence of CC homozygote among patients and controls was 28.7% and 34.05%, respectively. The prevalence of T allele was 48.9% and 43.9% for the case and control groups, respectively. In all the studies except seven [24,25,42,46–48,52] the distribution of genotypes in the control group was in Hardy Weinberg equilibrium.

3.2. Meta-analysis

A summary of meta-analyses findings regarding associations between the MTHFR C677T polymorphism and esophageal cancer is given in Table 2. Meta-analysis revealed a significant association between esophageal cancer and MTHFR T allele (T vs C) with both fixed effects (OR = 1.19, 95% CI = 1.13–1.24, p < 0.0001) and random effects model (OR = 1.18, 95% CI = 1.05–1.32, p = 0.003) (Fig. 2; Table 2). Results showed an increased risk of oesophageal cancer among mutant homozygote variants (TT vs. CC; homozygote model), with both fixed (OR = 1.38; 95%CI = 1.25–1.523; p= <0.001) and random (OR = 1.38; 95%CI = 1.10–1.72; p = 0.004) effect models (Fig. 3; Table 2).

Combined mutant genotypes (TT + CT vs. CC; dominant model) showed positive significant association with oesophageal cancer using both fixed (OR = 1.27; 95%CI = 1.18–1.36; p = <0.0001) and random (OR = 1.3; 95%CI = 1.12–1.53; p = 0.0007) effect models (Table 2). Similarly the recessive genotypes model (TT vs. CT + CC) also showed significant association with oesophageal cancer with both fixed (OR = 1.21; 95%CI = 1.12–1.31; p = <0.0001) and random (OR = 1.18; 95%CI = 1.0–1.38; p = 0.04) effect models (Table 2).

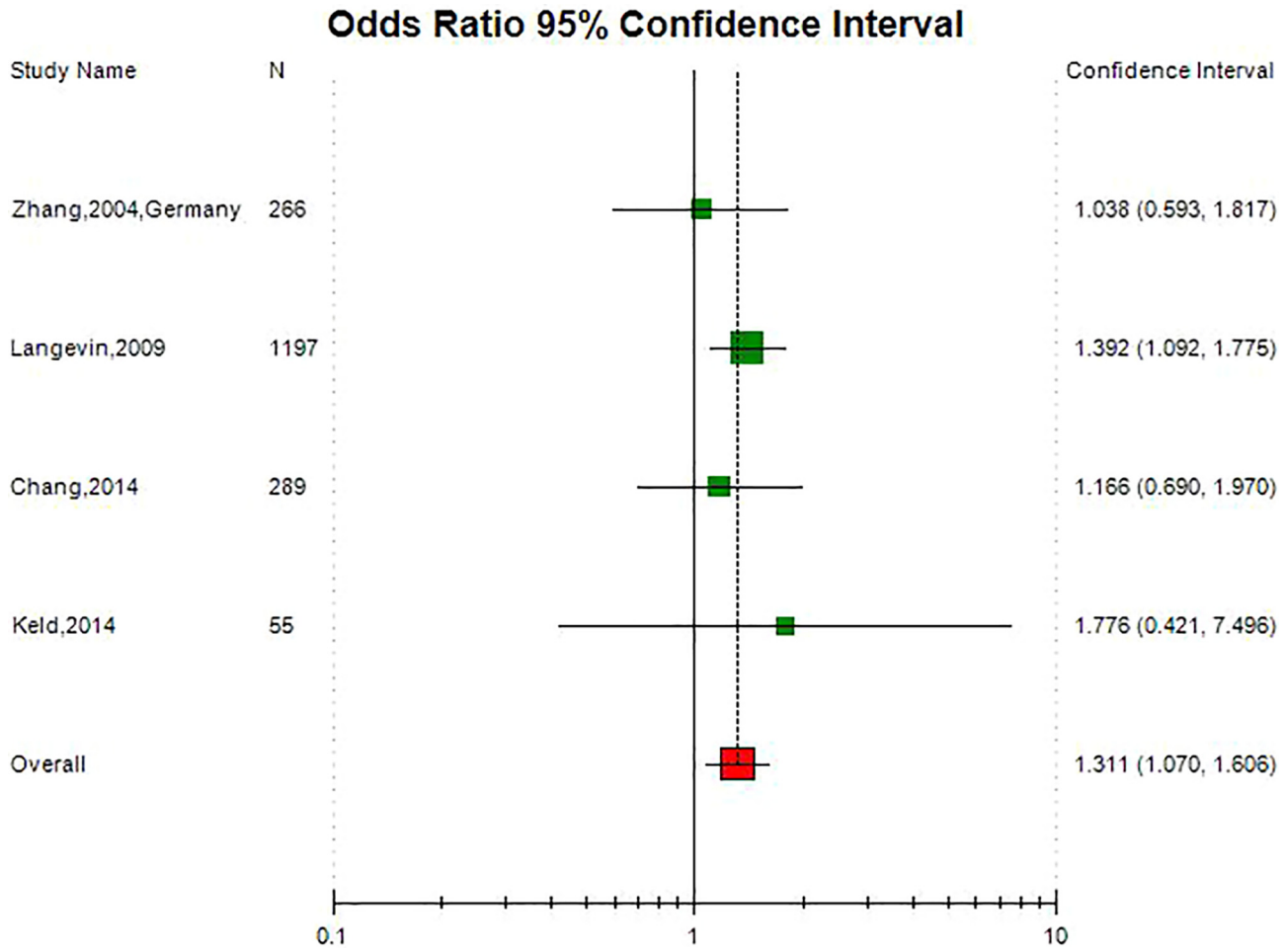

Fig. 5. Random effect forest plot of allele contrast model (T vs. C) of Caucasian studies.

3.3. Subgroup analysis

We also performed sub-group analysis based on ethnicity and source of controls. Out of 32 studies, 28 studies were from Asia and 4 studies were from Caucasian population. In Asian population (number of studies = 28; 5,308/6956 cases/controls), allele contrast meta-analysis showed significant association adopting both fixed (allele contrast: OR = 1.2; 95% CI = 1.13–1.26; p = <0.0001) and random (OR = 1.2; 95% CI = 1.04–1.35; p = 0.01) effect models. Combined mutant genotypes also showed significant association with fixed (dominant model: OR = 1.31; 95% CI = 1.20–1.4; p < 0.0001) and random (OR = 1.34; 95% CI = 1.11–1.61; p = 0.002) effect models (Fig. 4; Table 2). Results of Caucasian studies (number of studies = 16; 2916/4300 cases/controls) meta-analysis also indicated significant association with both fixed and random effects model (allele contrast: OR = 1.14; 95% CI = 1.03–1.23; p = 0.009). The combined mutant genotype did not show significant association with fixed and random effect models (dominant model: OR = 1.14; 95% CI = 0.98–1.32; p = 0.09) (Table 2; Fig. 5).

Subgroup analysis based on source of controls was also done. Out of 32 studies, in 17 studies, controls were selected from hospital and in 16 studies controls were selected from the population. Allele contrast meta-analysis of hospital based group, showed significant association adopting fixed effects model (OR = 1.12; 95% CI = 1.03–1.20; p = 0.003) but random effects model did not show significant association (OR = 1.15; 95% CI = 0.98–1.35; p = 0.08) (Table 2; Fig. 6). In population based group, allele contrast meta-analysis showed significant association with both fixed (OR = 1.2; 95% CI = 1.15–1.29; p < 0.0001) and random (OR = 1.2; 95% CI = 1.03–1.39; p = 0.01) effects models (Table 2; Fig. 7).

3.4. Heterogeneity and sensitive analysis

A true heterogeneity existed for allele (P_{hetero} = <0.0001, Q = 152.43, df = 33, I^2 = 79.66%, t^2 = 0.07), homozygote (P_{hetero} = <0.0001, Q = 132.973, df = 33, I^2 = 76.69%, t^2 = 0.27), heterozygote (P_{hetero} = <0.0001, Q = 95.54, df = 33, I^2 = 67.52%, t^2 = 0.11), mutant genotypes (P_{hetero} = <0.0001, Q = 122.15, df = 33, I^2 = 74.62%, t^2 = 0.14) and recessive (P_{hetero} = <0.0001, Q = 105.62, df = 33, I^2 = 70.65%, t^2 = 0.13) comparisons. The '$I^{2\prime}$ value of more than 50% in both allele and genotype analysis shows high level of true heterogeneity.

In allele contrast meta-analysis, sensitivity analysis performed by exclusion of the studies in which control population was not in Hardy Weinberg equilibrium and studies with small sample size (n ⟨1 0 0). Control population of seven studies [24,25,42,46–48,52], were not in HW equilibrium and heterogeneity did not decrease after exclusion of these studies (p = <0.0001, I^2 = 79.55%). Exclusion of six studies involving small sample size, <100 (Wu et al. [39], n = 93; Kureshi et al. [22], n = 34; Zhang et al. [46] (Kazakh), n = 94; Zhang et al. [46] (Han), n = 84; Ekiz et al. [5], n = 26; Keld et al., [28], n = 44), heterogeneity did not decrease (P < 0.0001, I^2 = 82.55%), but odds ratio was increased (OR = 1.23; 95%CI = 1.14–1.26;p < 0.0001).

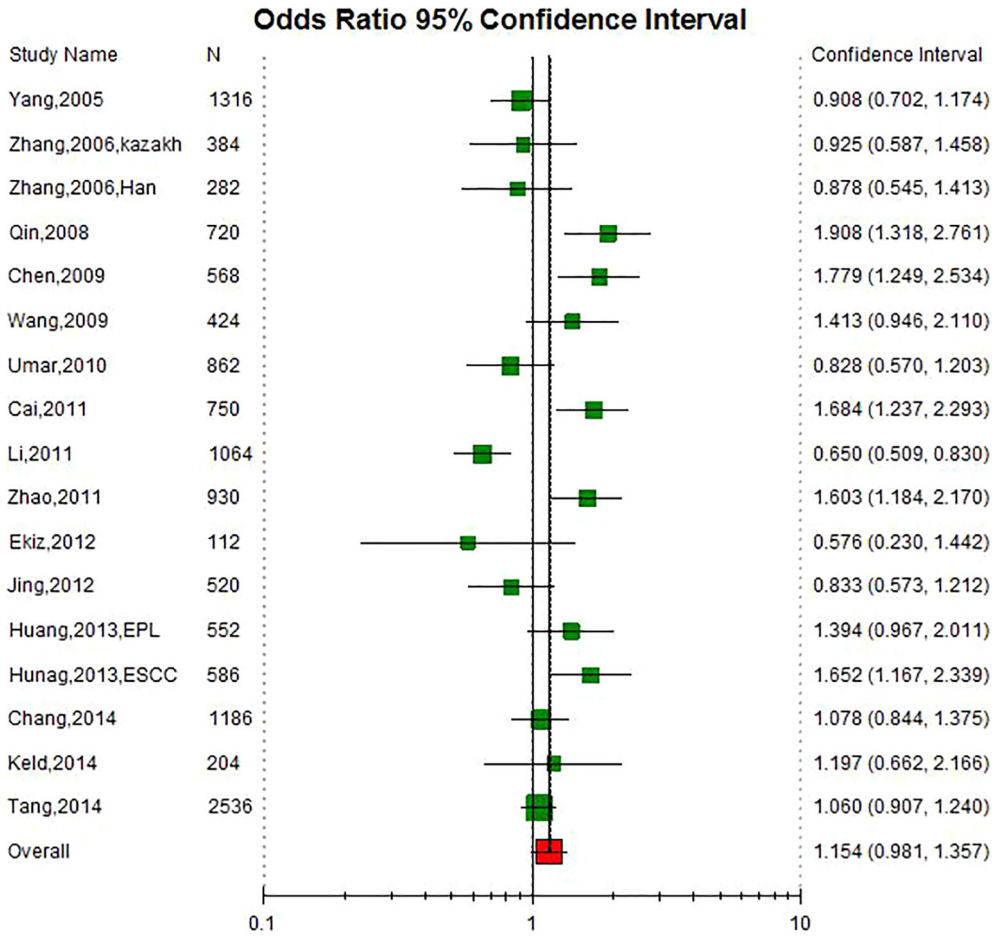

Fig. 6. Random effect forest plot of allele contrast model (T vs. C) of studies included hospital based control population.

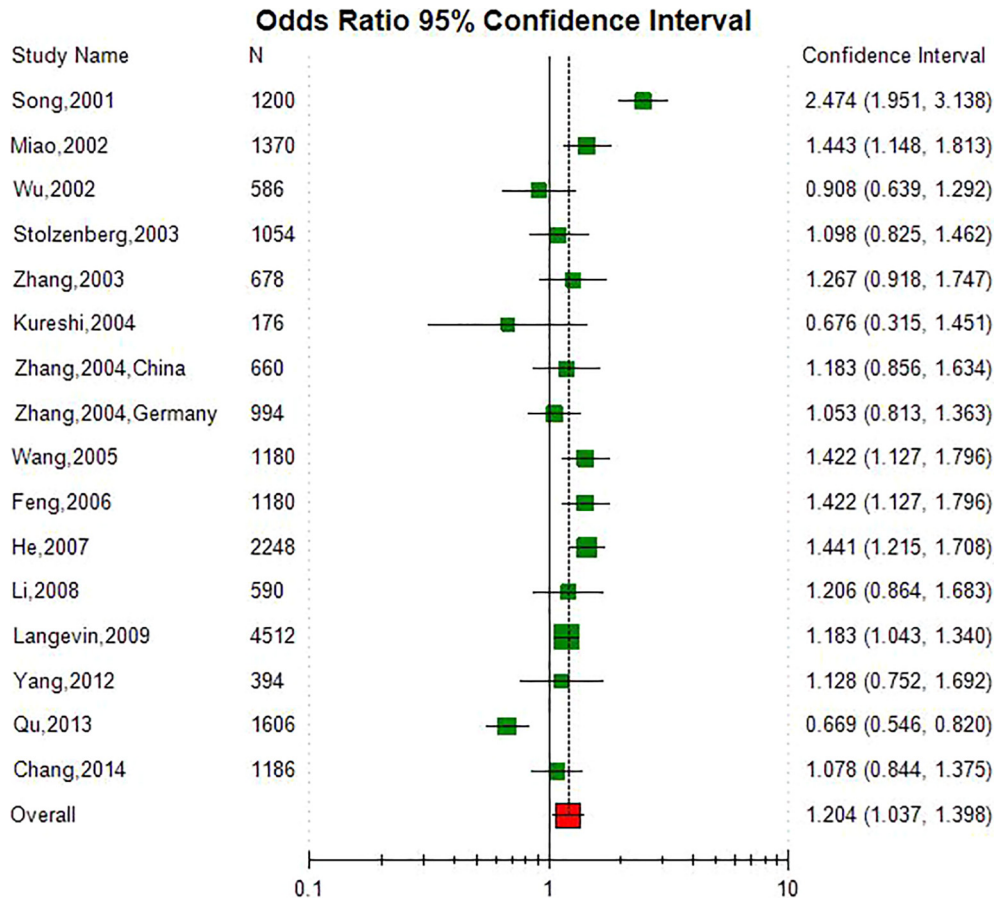

Fig. 7. Random effect forest plot of allele contrast model (T vs. C) of studies included population based control population.

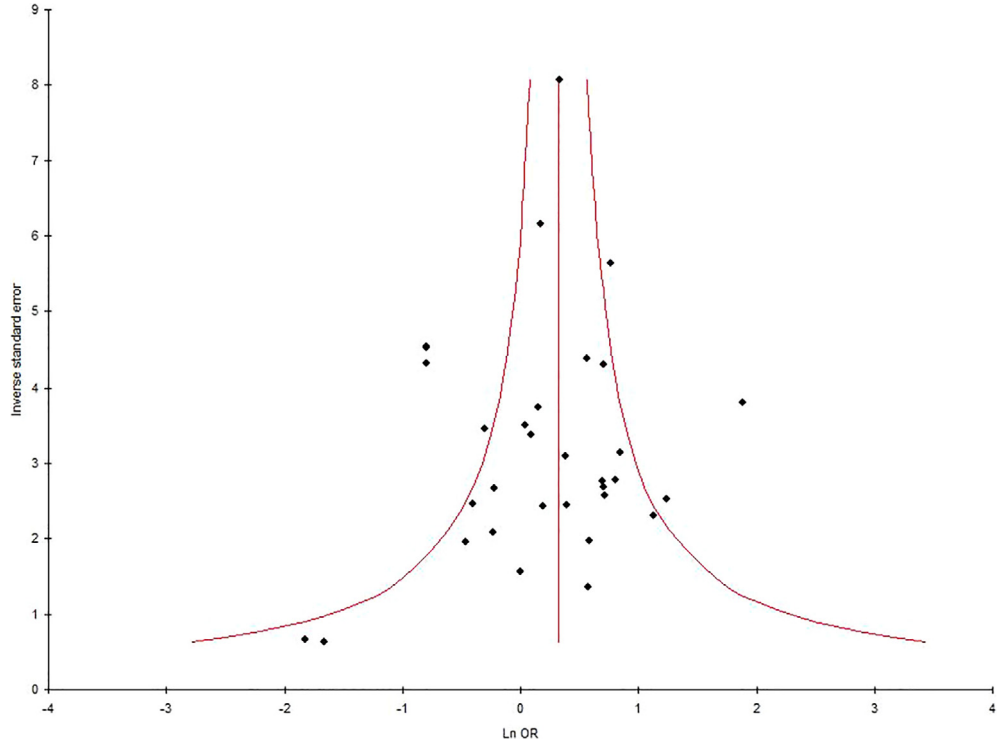

Fig. 8. Funnel plots of precision by OR of *MTHFR* C677T allele contrast model (T vs. C).

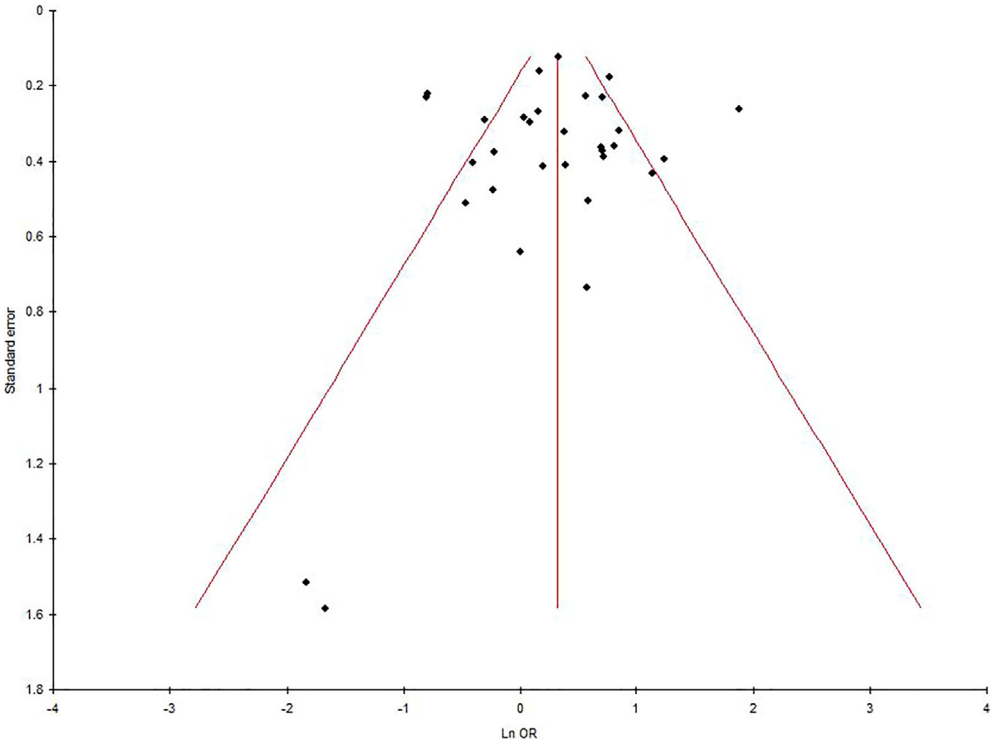

Fig. 9. Funnel plots of standard error by OR of *MTHFR* C677T allele contrast model (T vs. C).

3.5. Publication bias

Funnel plots, Begg's and Egger's test were performed to estimate the risk of publication bias. The shape of funnel plots in all contrast models were symmetrical (Table 2; Figs. 8 and 9). In addition, the P values of Egger's test were more than 0.05, which provided statistical evidence for the symmetry of funnel plots in the meta-analysis (p = 0.82 for T vs. C; p = 0.80 for TT vs CC; and p = 0.18 for CT vs. CC; p = 0.39 for TT + CT vs. CC; p = 0.37 for TT vs. CT + CC) (Table 2). Begg's test results also did not show publication bias (p = 0.44 for T vs. C; p = 0.41 for TT vs CC; and p = 0.91 for CT vs. CC; p = 0.44 for TT + CT vs. CC; p = 0.09 for TT vs. CT + CC).

4. Discussion

Meta-analysis of thirty-two case control association studies revealed that there was a modest significant association between MTHFR C677T polymorphism and susceptibility of esophageal cancer. It was reported very well that folate deficiency and MTHFR C677T polymorphism increased the risk of different types of cancer [10,16–20,58,59]. MTHFR polymorphisms have been shown to modulate risk of cancer with the association being that MTHFR isoforms increase homocysteine levels, which consequently increase the cancer risk [60] by increasing DNA damage and mutations in tumor suppressor genes.

Folate functions as methyl donor in the one carbon metabolism pathway, an essential process in DNA synthesis, repair and methylation and dysregulation of the folate metabolic pathway either due to deficiency of folate or MTHFR C677T polymorphism could result in carcinogenesis [10,61]. There are two important mechanisms by which folate deficiency may influence the risk of cancer: (i) by inducing misincorporation of uracil into DNA, which can lead to chromosomal breaks and mutations [60,62,63], and/or (ii) by causing aberrant DNA methylation, resulting in altered expression of critical proto-oncogenes and tumor suppressor genes.

Meta-analysis is a powerful tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits but also provide more reliable results than a single case-control study. Several meta-analysis were published which investigated the association between folate pathway genes polymorphisms and different disease/disorders like- down syndrome [64–66], cleft lip and palate [67,68], recurrent pregnancy loss [69], male infertility [70], neurodegenerative disorders [71], psychiatric disorders [72–75], and different cancers [76–80].

Seven meta-analyses [51,81–86] examined the effect of MTHFR C677T polymorphism on esophageal cancer risk, but no consistent conclusion was achieved. The discrepancy of results may be due to the difference in ethnic background and environmental exposure as well as dietary intake of folate, smoking status and use of alcohol.

In interpretation of results of present meta-analysis, some limitations should be considered like- (i) crude OR was used, (ii) higher heterogeneity was present, (iii) only four databases were searched for articles, (iv) single gene polymorphism was considered, (vi) all case control studies were from Asian and Caucasian populations, African studies were not included and (vii) gene-gene and gene-environment interactions were not considered.

In conclusion, present meta-analysis supports the hypothesis that MTHFR C677T polymorphism may play a role in the etiology of esophageal cancer. Large studies that assess the interrelations between folate intake, MTHFR polymorphism, alcohol intake and smoking are needed to further clarify the role of MTHFR polymorphism in the development of esophageal cancer.

Conflict of interest

None.

Financial Disclosures

None.

Author's Contribution

VR: Concept and design, drafting the article, interpretation of data; PK: Interpretation of data, article drafting.

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