Original Article
MSH3 rs26279 polymorphism increases cancer risk: a meta-analysis

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Abstract: Previous studies have investigated the association of *mutS homolog 3* (*MSH3*) rs26279 G > A polymorphism with the risk of different types of cancers including colorectal cancer, breast cancer, prostate cancer, bladder cancer, thyroid cancer, ovarian cancer and oesophageal cancer. However, its association with cancer remains conflicting. We performed a comprehensive meta-analysis to derive a more precise estimation of the relationship between *MSH3* rs26279 G > A polymorphism and cancer susceptibility. Systematically searching the PubMed and EMBASE databases yielded 11 publications with 12 studies of 3282 cases and 6476 controls. The strength of the association was determined by crude odds ratios (OR) and 95% confidence intervals (CI). Overall, pooled risk estimates demonstrated that *MSH3* rs26279 G > A was significantly associated with an increased overall cancer risk under all the genetic models (GG vs. AA: OR = 1.27, 95% CI = 1.09-1.48, *P* = 0.002; AG vs. AA: OR = 1.10, 95% CI = 1.00-1.21, *P* = 0.045; GG vs. AG + AA: OR = 1.23, 95% CI = 1.06-1.42, *P* = 0.005; AG + GG vs. AA: OR = 1.13, 95% CI = 1.04-1.24, *P* = 0.006; G vs. A: OR = 1.13, 95% CI = 1.05-1.20, *P* = 0.001). The association was more evident for colorectal cancer and breast cancer. Moreover, the significant association was also observed in the following subgroups: Europeans, Asians, population-based studies, hospital-based studies, and studies comprising relatively large sample size (≥ 200). Our meta-analysis results demonstrated that *MSH3* rs26279 G > A polymorphism is associated with an increased risk of overall cancer, especially for the colorectal cancer and breast cancer.

Keywords: *MSH3*, polymorphism, cancer, meta-analysis

Introduction

Cancer is a complex multistep disease. Genetic aberrations may contribute to the development of cancer through interaction with environment factors [1]. Genetic aberrations can occur during the process of DNA replication and homologous recombination or as a result of DNA damage, owing to exposure to various exogenous and endogenous factors such as UV, ionizing radiation, and products of lipid peroxidation. In order to protect against DNA aberrations and maintain the integrity of the genome, human body possesses four major DNA repair, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR) and mismatch repair (MMR) pathways [2].

As one of fundamentally biological pathway, the MMR system plays an important role in cell cycle regulation and apoptosis, answerable for a variety of DNA damage [3, 4]. It is primarily responsible for recognizing and correcting base-base mismatches and insertion/deletion loops generated during DNA replication and homologous recombination [5, 6].

Additionally, a fraction of mismatches can arise from DNA damage. If not properly repaired, these mismatches may enhance spontaneous mutation rates and lead to the occurrence of microsatellite repeat instability in cells, thereby contributing to carcinogenesis. Therefore, MMR plays a critical role in maintaining the integrity of the genome. In humans, there are seven mismatch repair genes including *MSH2* (*mutS homolog 2*), *MSH3*, *MSH6*, *MLH1* (*mutL homolog 1*), *PMS1* (*postmeiotic segregation increased 1*), *PMS2* and *MLH3*. The *MSH2*, *MSH3* and *MSH6* genes are MutS homologs, while the rest of genes are MutL homologes [7]. Unlike homo-

oligomers in prokaryotes, MMR proteins form heterodimers in human. The function of MutS is to recognize and bind to mismatched DNA fragments, and thereafter initiate MMR. There are two kinds of MutS homodimers, MSH2-MSH6 (MutSα) and MSH2-MSH3 (MutSβ) in human. The MutSα searchs for single base mismatches and short insertion/deletion loops, while the MutSβ are able to detect large insertion/deletion loops [6, 8].

The *MSH3* gene is located at chromosome 5q11-13 and encodes a protein of 1137 amino acid residues [9]. Some potentially functional single-nucleotide polymorphisms (SNPs) of *MSH3* may have influence the DNA repair capacity and thereby predispose individuals to a variety of cancers. Thus far, at least 180 SNPs have been reported in MSH3 gene (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4437). Among all of these SNPs, rs26279 G > A polymorphism are frequently investigated and have been thought to be involved in carcinogenesis in recent years. Some studies suggested that this variant was associated with the risk of cancer including colorectal cancer [10, 11], breast cancer [12-14], prostate cancer [15, 16], bladder cancer [17], thyroid cancer [18], ovarian cancer [19] and oesophageal cancer [20]. However, the association of interest remains inconclusive. Hence, to provide a more precise estimation of the association between *MSH3* rs26279 G > A polymorphism and the risk of cancer, we conducted a meta-analysis with all eligible case-control studies.

Materials and methods

Identification of eligible relevant studies

A systematic literature search was conducted throughout the Pubmed and EMBASE database to find studies assessing the association between *MSH3* rs26279 G > A polymorphism and the risk of cancer prior to May 30, 2015. The following keywords were used to identify relevant studies "MSH3 or hMSH3", "variant or polymorphism" and "cancer or carcinoma or neoplasm or tumor". Additional related studies have been also identified by hand screening. The search was limited to human studies written in Chinese and English.

Inclusion and exclusion criteria

Inclusion criteria were listed in the following paragraph: (a) a case-control design study evaluating the association between *MSH3* rs26279 G > A polymorphism and cancer risk; (b) sufficient raw data for estimating odds ratios (ORs) and their 95% confidence intervals; and (c) the genotype distribution in the control group of the studies should be in accordance with the Hardy-Weinberg equilibrium (HWE). Exclusion criteria included: (a) case-only study; (b) reviews and duplicate data.

Data extraction

After selection of eligible studies according to the inclusion criteria and exclusion criteria, two of the researchers independently collected information from all eligible publications. The following data was extracted from each study: the last name of the first author, publication year, country, ethnicity, cancer type, source of control (hospital-based or population-based), genotyping methods, genotype counts of cases and controls for *MSH3* rs26279 G > A polymorphism. The stratification analysis was conducted by cancer type (If one type of cancer was only investigated in a study, the cancer type would be merged into the "other type"), ethnicity (Asians, Europeans and Africans), control source (hospital-based and population-based) and sample size (number of cases < 200 and ≥ 200).

Statistical analysis

Crude ORs with the corresponding 95% CIs were employed to estimate the strength of association between the *MSH3* rs26279 G > A polymorphism and cancer risk. The following genetic models were chosen: homozygous model (GG vs. AA), heterozygous model (AG vs. AA), recessive model (GG vs. AG + AA), dominant model (AG + GG vs. AA) and allele comparison (G vs. A). Goodness-of-fit chi-square test was used to check whether there was deviation from Hardy-Weinberg equilibrium in control subjects of each included study. The heterogeneity of studies was tested by Chi squared-based Q-test, with a *P* value of more than 0.10 denoting a lack of between-study heterogeneity. In the absence of heterogeneity, we used the fixed-effects model (the Mantel-Haenszel

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

Surname	Year	Country	Ethnicity	Cancer type	Control source	Genotype method	NO. of cases				NO. of control				MAF	HWE
							All	AA	AG	GG	All	AA	AG	GG		
Berndt	2007	USA	European	Colorectal	PB	TaqMan	229	101	101	27	2081	1063	851	167	0.28	0.855
Conde	2009	Portugal	European	Breast	HB	TaqMan	286	121	129	36	544	246	240	58	0.33	0.962
Hirata	2008	Japan	Asian	Prostate	HB	SSCP/PCR-RFLP	110	60	43	7	110	72	31	7	0.20	0.160
Jafary	2012	Iran	Asian	Prostate	PB	SSCP	18	12	5	1	60	34	18	8	0.28	0.043
Kawakami	2004	Japan	Asian	Bladder	PB	SSCP	99	53	38	8	101	66	28	7	0.21	0.112
Orimo	2000	Japan	Asian	Colorectal	PB	SSCP	19	10	8	1	89	55	28	6	0.22	0.360
Shi	2008	China	Asian	Thyroid	HB	PCR-RFLP	204	120	68	16	204	130	60	14	0.22	0.062
Smith	2008	USA	European	Breast	HB	MassARRAY	321	154	123	44	409	198	175	36	0.30	0.762
			African	Breast	HB	MassARRAY	52	21	23	8	72	33	29	10	0.34	0.383
Song	2006	UK	European	Ovarian	PB	TaqMan	1310	663	525	122	2003	1064	771	168	0.28	0.093
Terrazzino	2012	Italy	European	Breast	HB	TaqMan	89	41	36	12	196	93	86	17	0.31	0.646
Vogelsang	2012	South Africa	African	Oesophageal	HB	TaqMan	545	204	256	85	607	230	295	82	0.38	0.410

SSCP, single-strand conformational polymorphism; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphisms; HB, hospital based; PB, population based; MAF, Minor Allele Frequency; HWE: Hardy-Weinberg equilibrium.

Table 2. Meta-analysis of the association between rs26279 polymorphism and cancer risk

Variables	N (case/control)	Homozygous			Heterozygous			Recessive			Dominant			Allele		
		GG vs. AA			AG vs. AA			GG vs. (AG + AA)			(AG +GG) vs. AA			G vs. A		
		OR (95% CI)	P^{het}	I^2 (%)	OR (95% CI)	P^{het}	I^2 (%)	OR (95% CI)	P^{het}	I^2 (%)	OR (95% CI)	P^{het}	I^2 (%)	OR (95% CI)	P^{het}	I^2 (%)
All	12 (3282/6476)	1.27 (1.09-1.48)	0.943	0.0	1.10 (1.00-1.21)	0.675	0.0	1.23 (1.06-1.42)	0.925	0.0	1.13 (1.04-1.24)	0.787	0.0	1.13 (1.05-1.20)	0.863	0.0
Cancer type																
Colorectal	2 (248/2170)	1.65 (1.06-2.58)	0.593	0.0	1.27 (0.96-1.68)	0.676	0.0	1.48 (0.97-2.26)	0.542	0.0	1.33 (1.02-1.74)	0.856	0.0	1.28 (1.05-1.56)	0.921	0.0
Breast	4 (748/1221)	1.42 (1.05-1.91)	0.910	0.0	1.00 (0.83-1.22)	0.783	0.0	1.40 (1.06-1.86)	0.746	0.0	1.08 (0.90-1.30)	0.940	0.0	1.13 (0.98-1.30)	0.998	0.0
Prostate	2 (128/170)	0.88 (0.34-2.27)	0.324	0.0	1.44 (0.86-2.40)	0.266	19.0	0.79 (0.31-2.01)	0.430	0.0	1.32 (0.82-2.14)	0.160	49.2	1.15 (0.78-1.71)	0.123	58.0
Other	4 (2158/2915)	1.18 (0.97-1.43)	0.986	0.0	1.09 (0.97-1.23)	0.391	0.1	1.15 (0.95-1.38)	0.995	0.0	1.11 (0.99-1.25)	0.470	0.0	1.10 (1.01-1.20)	0.642	0.0
Ethnicity																
European	5 (2235/5233)	1.32 (1.10-1.58)	0.580	0.0	1.08 (0.97-1.21)	0.650	0.0	1.28 (1.07-1.52)	0.500	0.0	1.12 (1.01-1.25)	0.752	0.0	1.13 (1.04-1.22)	0.735	0.0
Asian	5 (450/564)	1.14 (0.69-1.88)	0.851	0.0	1.40 (1.06-1.85)	0.730	0.0	1.02 (0.62-1.67)	0.902	0.0	1.35 (1.04-1.75)	0.619	0.0	1.23 (0.99-1.52)	0.574	0.0
African	2 (597/679)	1.18 (0.84-1.65)	0.900	0.0	1.00 (0.79-1.27)	0.560	0.0	1.18 (0.86-1.61)	0.929	0.0	1.04 (0.83-1.31)	0.601	0.0	1.07 (0.91-1.25)	0.729	0.0
Control source																
PB	5 (1675/4334)	1.24 (1.00-1.54)	0.480	0.0	1.14 (1.01-1.30)	0.549	0.0	1.18 (0.96-1.45)	0.596	0.0	1.16 (1.03-1.31)	0.409	0.0	1.13 (1.03-1.24)	0.314	15.7
HB	7 (1607/2142)	1.30 (1.05-1.61)	0.976	0.0	1.05 (0.91-1.21)	0.601	0.0	1.28 (1.04-1.57)	0.908	0.0	1.10 (0.96-1.26)	0.830	0.0	1.12 (1.01-1.23)	0.968	0.0
Sample size																
≥200	6 (2895/5848)	1.27 (1.08-1.50)	0.704	0.0	1.08 (0.97-1.19)	0.672	0.0	1.24 (1.06-1.44)	0.683	0.0	1.12 (1.01-1.23)	0.753	0.0	1.12 (1.04-1.20)	0.763	0.0
<200	6 (387/628)	1.25 (0.78-2.00)	0.880	0.0	1.31 (0.99-1.74)	0.613	0.0	1.15 (0.73-1.81)	0.850	0.0	1.30 (1.00-1.69)	0.651	0.0	1.21 (0.99-1.49)	0.702	0.0

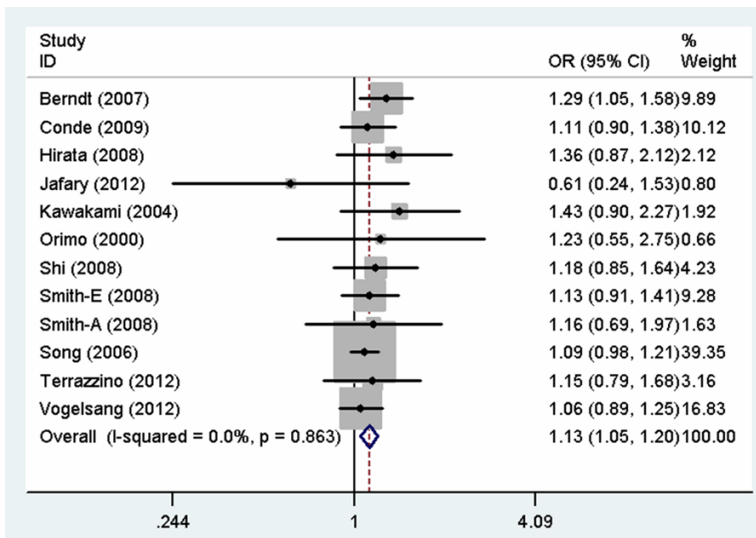HB, hospital based; PB, population based.

Figure 1. Forest plot for the association between *MSH3* rs26279 G > A polymorphism and cancer risk (G vs. A).

Figure 2. Forest plot for the association between *MSH3* rs26279 G > A polymorphism and cancer risk (GG vs. AA).
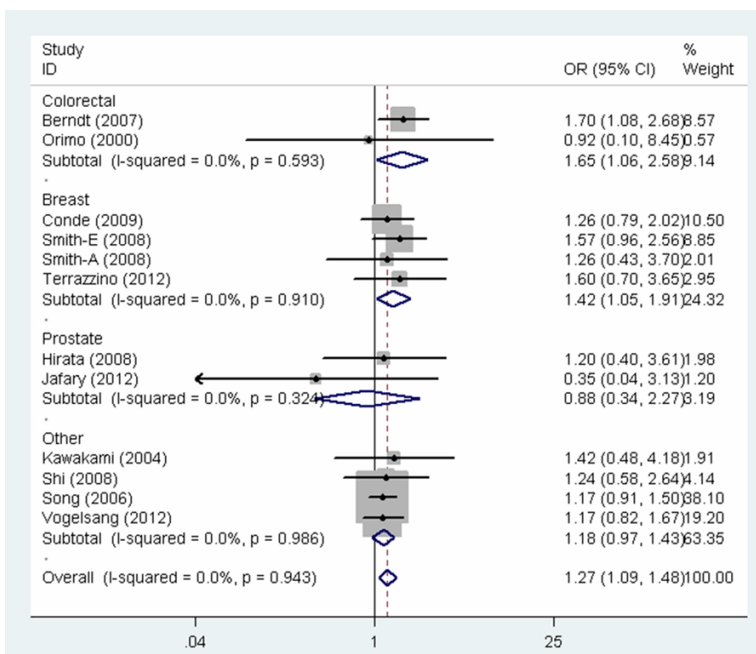
statistically significant as $P < 0.05$ without further special notification.

Results

Study characteristics

A total of 68 articles were initially retrieved from the Pubmed and EMBASE electronic databases. Among these, 46 studies were excluded after preliminary screening of titles and abstracts. The remaining 22 publications underwent full-text reviews. Of these, 3 studies were excluded because they did not contain *MSH3* rs26279 G > A polymorphism [24-26], five non-case-control studies [27-31] and 3 studies without detailed information were also eliminated [32-34]. In the study By Jafary et al. genotype distribution of *MSH3* rs26279 G > A polymorphism was not in agreement with HWE. However, this study was included in our meta-analysis, because another SNP, rs1805355 in this study was in HWE. Finally, 11 publications with 12 studies, comprising 3282 cases and 6476 controls were included to examine the association of *MSH3* rs26279 G > A polymorphism with cancer risk [10-20].

As summarized in **Table 1**, all publications were case-control studies. Overall, there were 2 studies conducted on colorectal cancer, 4 on breast cancer, 2 on prostate cancer and 4 on others. Regarding ethnicity, 5, 5, and 2 studies were performed among Europeans, Asians, and Africans, respectively. Five studies were population-based, while 7 studies were hospital-based. Moreover, these studies were also stratified by sample size: 6 studies with sample size < 200 and 6 studies with sample size ≥ 200.

method) [21]. Otherwise, we would apply the random-effects model (the DerSimonian and Laird method) to the analysis [22]. The potential publication bias was examined by Egger's linear regression test [23]. All the analyses were tested with the STATA software (version 11.0; Stata Corporation, College Station, TX). All *P* values were two-sided, and we referred to
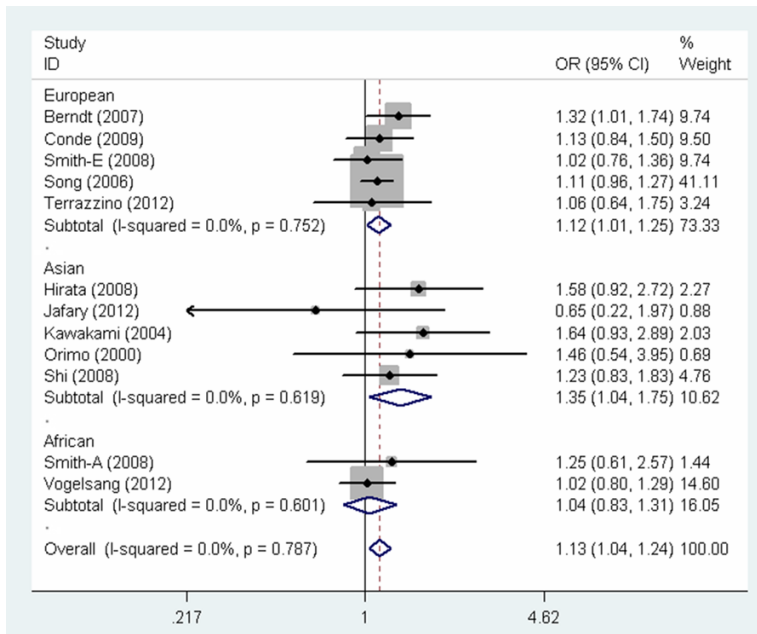
Figure 3. Forest plot for the association between *MSH3* rs26279 G > A polymorphism and cancer risk (AG + GG vs. AA).

Meta-analysis results

The overall findings of the meta-analysis of the associations between *MSH3* rs26279 G > A polymorphism and cancer risk were shown in **Table 2**. Pooled risk estimates indicated that *MSH3* rs26279 G > A polymorphism was associated with an increased risk of cancer under all the genetic models (GG vs. AA: OR = 1.27, 95% CI = 1.09-1.48, *P* = 0.002; AG vs. AA: OR = 1.10, 95% CI = 1.00-1.21, *P* = 0.045; GG vs. AG + AA: OR = 1.23, 95% CI = 1.06-1.42, *P* = 0.005; AG + GG vs. AA: OR = 1.13, 95% CI = 1.04-1.24, *P* = 0.006; G vs. A: OR = 1.13, 95% CI = 1.05-1.20, *P* = 0.001, **Figure 1**). Next, when the analysis was stratified by cancer type, the same study also revealed a significant increase in the risk of colorectal cancer (GG vs. AA: OR = 1.65, 95% CI = 1.06-2.58, *P* = 0.027, **Figure 2**; AG + GG vs. AA: OR = 1.33, 95% CI = 1.02-1.74, *P* = 0.034; G vs. A: OR = 1.28, 95% CI = 1.05-1.56, *P* = 0.014) and breast cancer (GG vs. AA: OR = 1.42, 95% CI = 1.05-1.91, *P* = 0.023, **Figure 2**; GG vs. AG + AA: OR = 1.40, 95% CI = 1.06-1.86, *P* = 0.020), but not prostate cancer. Stratified analysis by ethnicity further elucidated that the pooled odds ratio for the association with cancer risk was statistically significant among Europeans (GG vs. AA: OR = 1.32, 95% CI = 1.10-1.58, *P* = 0.003; GG

vs. AG + AA: OR = 1.28, 95% CI = 1.07-1.52, *P* = 0.006; AG + GG vs. AA: OR = 1.12, 95% CI = 1.01-1.25, *P* = 0.028, **Figure 3**; G vs. A: OR = 1.13, 95% CI = 1.04-1.22, *P* = 0.003) and Asians (AG vs. AA: OR = 1.40, 95% CI = 1.06-1.85, *P* = 0.018, AG + GG vs. AA: OR = 1.35, 95% CI = 1.04-1.75, *P* = 0.024, **Figure 3**), while no significant association was observed among African populations. Moreover, there was a significant association with increased cancer risk in population-based studies and hospital-based studies. Lastly, association was also observed in subgroup with studies with no less than 200 cases.

Heterogeneity and sensitivity analyses

No significant heterogeneity was detected for the meta-analysis of *MSH3* rs26279 G > A polymorphism and overall cancer risk (GG vs. AA: *P* = 0.943; AG vs. AA: *P* = 0.675; GG vs. AG + AA: *P* = 0.925; AG + GG vs. AA: *P* = 0.787; G vs. A: *P* = 0.863). The sensitivity analysis provided the evidence of the stability of the meta-analysis, since no single study was found to influence the pooled ORs qualitatively.

Publication bias

We used Begg's funnel plot and Egger's test to estimate the publication bias of literatures. No evidence of publication bias was observed under all the genetic models (GG vs. AA: *P* = 0.910; AG vs. AA: *P* = 0.292; GG vs. AG + AA: *P* = 0.672; AG + GG vs. AA: *P* = 0.339 and G vs. A: *P* = 0.443). These results suggested that no publication bias influenced the evaluation of the association between *MSH3* rs26279 G > A polymorphism and cancer susceptibility.

Discussion

Human *MSH3* gene is located on chromosome 5q11-13 and encodes MSH3 protein containing 1137 amino acids residus [9]. The MSH3 protein is one of the essential components of mismatch repair (MMR) system that is critical to maintaining genome stability [35]. MMR defi-

ciency has been reported to associate with increased risk of several types of cancer [6]. Loss of MSH3 protein expression is associated with colorectal cancer progression [36]. Until now, there are numerous publications investigating the association of *MSH3* polymorphisms and cancer susceptibility. *MSH3* rs26279 G > A polymorphism is most wildly studied for its association with cancer risk among those genetic variation. However the results were controversy. For example, Berndt et al. found that *MSH3* rs26279 G > A polymorphism significantly increased the risk of developing colorectal cancer [10]. In contrast, Smith et al. did not observe any significant association between *MSH3* rs26279 G > A polymorphism and the risk of breast cancer [13].

To the best of our knowledge, this is the first meta-analysis exploring the relationship of MSH3 rs26279 G > A polymorphism with overall cancer susceptibility. In the current study, *MSH3* rs26279 G > A polymorphism was found to confer 10% to 27% increase in the risk of overall cancer under different genetic models. These findings further substantiated that *MSH3* rs26279 G > A polymorphism may play an important role in carcinogenesis. Germline mutation in the *MSH3* gene, leading to inactivation of MMR, can increase the risk for cancer susceptibility [5, 37]. Stratified analysis by cancer type found that there was 28% to 65% increase in the risk of colorectal cancer under homozygous, dominant and allele models, including 2 studies of 2418 subjects. Frameshift mutations in MSH3 gene play an important role in the development of colorectal cancer with microsatellite instability [38-40]. Similarly, this variant was also related to a 40% to 42% increase in the risk of breast cancer under homozygous and recessive models (4 studies with 1969 subjects), but no risk effect was found on prostate cancer (2 studies with 298 subjects). Our results suggested that *MSH3* rs26279 G > A polymorphism may play a differential role in the carcinogenesis of different types of cancers [16]. Moreover, we did not evaluate the association of this polymorphism and the rest of types of cancers (e.g., prostate cancer), since the relatively small number of studies and subjects could only provide very limited statistical power. Stratified analysis by ethnicity indicated significant association between *MSH3* rs26279 G > A polymorphism and around 12% and 35% higher cancer risk among Europeans and Asians respectively, whereas, no association was not found among Africans. Many factors may contribute to the differences between different ethnic groups, such as environment, gene, lifestyle and eating habits [41]. However, these finding should be considered carefully because of small sample size. For instance, only 2 studies conducted among Africans were included in the meta-analysis.

Despite the significant findings, there are still several limitations in the current meta-analysis. Firstly, due to failure to acquire original data, our results were based on single factor estimates without adjustment for other factors, such as individual's age, smoking and drinking status. Secondly, only 12 studies with 3282 cases and 6476 controls were included to estimate the relationship between *MSH3* rs26279 G > A polymorphism and cancer risk. As a result, the study has no sufficient statistical power to evaluate the association with the risk of certain type of cancer, especially for prostate cancer. Finally, because we only searched studies written in Chinese and English language, related publications in other language might be omitted.

Conclusions

This meta-analysis results suggests that the presence of *MSH3* rs26279 G > A polymorphism may increase the risk of overall cancer, especially for the colorectal cancer and breast cancer. However, large studies with well matched cancer-free controls, involving different types of cancers, are necessary to verify these finding and provide more information about gene-gene and gene-environment interactions in carcinogenesis.

Disclosure of conflict of interest

None.

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