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Original Article

The *MIF -173G/C* gene polymorphism increase gastrointestinal cancer and hematological malignancy risk: evidence from a meta-analysis and FPRP test

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Abstract: The macrophage migration inhibitory factor (*MIF) -173G/C* gene polymorphism has been implicated in the susceptibility to cancer, but the results are not conclusive. So the aim of study to investigate the association between *MIF -173G/C* gene polymorphism and cancer risk by a comprehensive meta-analysis. We searched the PubMed, Embase, Wanfang and China National Knowledge Internet (CNKI) databases, with the last updated search being performed on May 24, 2015. The odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the association. Statistical analysis was performed by STATA 11.0 software. Finally, 7,253 participants from 15 studies were included in the meta-analysis. The results of meta-analysis indicated the significant association between *MIF -173G/C* gene polymorphism and cancer susceptibility, especially in Asians (C vs. G, OR: 1.22, 95% CI=1.00-1.50). In addition, the significant relationship between MIF -173G/C gene polymorphism and gastrointestinal tumors (CC+CG vs. GG, OR: 1.25, 95% CI=1.05-1.50), hematological malignancy (CC+CG vs. GG, OR: 1.27, 95% CI=1.03-1.56), gynecolgical tumors (CC vs. CG+GG, OR: 1.51, 95% CI=1.04-2.19) risk was found. However, to avoid the "false positive report", we investigated the significant associations observed in the present meta-analysis by the false positive report probabilities (FPRPs) test. Interestingly, the results of FPRP test indicated the *MIF -173G/C* gene polymorphism only associated with gastrointestinal cancer and hematological malignancy risk (FPRP=0.132, 0.067 respectively) at the level of a prior probability is 0.1. Therefore, the meta-analysis suggested *MIF -173G/C* gene polymorphism would be a risk factor for the gastrointestinal cancer and hematological malignancy.

Keywords: Cancer, *MIF*, polymorphism, susceptibility, meta-analysis, FPRP

Introduction

Cancer is still a major cause of death in the world. The previous studies found that many risk factors may play important role in the pathogenesis of cancer including age, gender, life-style and environmental pollution [1]. Additionally, lots of studies focused on investigating the association between gene variants and malignant tumor susceptibility. In recent years, the macrophage migration inhibitory factor (*MIF*) gene which is located on chromosome 22q11.2 has been widely studied. The *MIF* was first found in 1950s, and it was defined as a soluble factor produced by T-lymphocytes which could inhibit the directed migration of macrophages [2]. Subsequently, many other studies suggested the *MIF* was also expressed on anterior pituitary cells, monocytes, eosinophils and epithelial cells etc. [3-6]. Currently, the *MIF* was considered a pleiotropic cytokine, and it played a major role in innate immune response. In addition, the *MIF* also acted as an important regulator for many other inflammatory cytokines, such as interleukin (IL)-2, IL-4 and interferon (IFN)-γ [7, 8]. Furthermore, the *MIF* has been found that it played a critical role in the regulation of antitumor T-lymphocytes [9].

One important polymorphism named *-173G/C (rs755622)* has recently been indentified in *MIF* gene which involves a G→C substitution at

base pair 173 of the 50-flanking region [10]. Previous studies indicated that the *MIF -173G/C* polymorphism was associated with risk of peptic ulcer diseases, systemic lupus erythematosus (SLE), polycystic ovary syndrome (PCOS) and rheumatoid arthritis (RA) [11-14]. Interestingly, a growing number of evidences suggested that *MIF -173G/C* polymorphism played an important role in the pathogenesis of cancer. Ramireddy et al. found the *MIF -173G/C* polymorphism was associated with colorectal cancer and acute myelocytic leukemia (AML) susceptibility [15, 16], Yuan and colleagues reported the *MIF -173G/C* polymorphism could increase the risk of bladder cancer [17]. The *MIF -173G/C* polymorphisms may be associated with a higher risk of prostate cancer in Chinese [18]. However, there is no relationship between the *MIF -173G/C* polymorphism and risk of cervical cancer in Yuan's study [19].

Due to these inconclusive reports, we performed a meta-analysis to investigate the association of the *MIF -173G/C* polymorphism with risk of cancer. Because the meta-analysis uses a quantitative method to combine the results from different studies with the same topic, so it is a useful technique for investigating the risk factors of genetic diseases, and can provide more reliable conclusions. To our knowledge, this is the most recent meta-analysis was conducted to assess the association between the *MIF -173G/C* polymorphism and cancer susceptibility.

Materials and methods

Study selection

A systematic literature search in PubMed, Embase, Wanfang Database and China National Knowledge Internet (CNKI) were carried out to identify studies involving the association between the *MIF -173G/C* polymorphism and cancer risk on May 24, 2015. The key words were as follows: ('macrophage migration inhibitory factor' or '*MIF*') and ('cancer' or 'malignancy' or 'tumor', 'neoplasm' or 'cancinoma' or 'leukemia' or 'myeloma' or 'sarcoma' or 'lymphoma') and 'polymorphism' or 'variant' or 'mutation'). There is no language restriction.

The inclusion criteria were defined as follows: (1) the design had to be a case-control study; (2) studies evaluated the association between *MIF* gene polymorphism and malignant tumor risk; (3) the studies should be provided available data to count the odds ratio (OR) and 95% confidence interval (CI); (4) the object of study must be human. The following exclusive items were: (1) not designed as a case-control study; (2) reviews, abstracts or overlapping studies; (3) not reported the genotype frequencies or number in the studies.

Quality score assessment

The qualities of included studies were evaluated by the Newcastle-Ottawa Scale (Case control study), The Scale to assess quality based on three aspects including selection, comparability and exposure in the study. The total scores were ranged from 0 to 9. We have assessed the quality of the studies in a consensus meeting with all authors.

Date extraction

The independent reviewers (Xiang Tong and Bing Zheng) collected the each study's data according to the inclusive criteria. If there is a disagreement, the third author (Qiaoyi Tong) would assess those articles. First author, year of publication, ethnicity, country of origin, age, sample size, genotype distribution in cases and controls, types of cancer and genotyping method were extracted from each study.

Statistical methods

The current meta-analysis was performed with the STATA 11.0 software. We used the OR and 95% CI to investigate the strength of association between *MIF -173G/C* gene polymorphism and risk of cancer. The χ^2 based Q-test and I-squared (I^2) statistics test were used to calculate heterogeneity. The pooled OR should be counted by the random-effect model when the heterogeneity was considered statistically significant ($I^2 > 50\%$ and $P < 0.10$), otherwise the fixed-effect model was applied. The pooled OR was estimated on the association between *MIF -173G/C* gene polymorphism and cancer risk in gene and allele models (CC+CG vs. GG, CC vs. CG+GG, CC vs. GG, CG vs. GG and C vs. G). To evaluate the ethnicity and types of cancer-specific effect, subgroup analysis by ethnicity groups and types of cancer was carried out.

In addition, to investigate whether an association between *MIF -173G/C* gene polymorphism and cancer risk is "noteworthy", we also calcu-

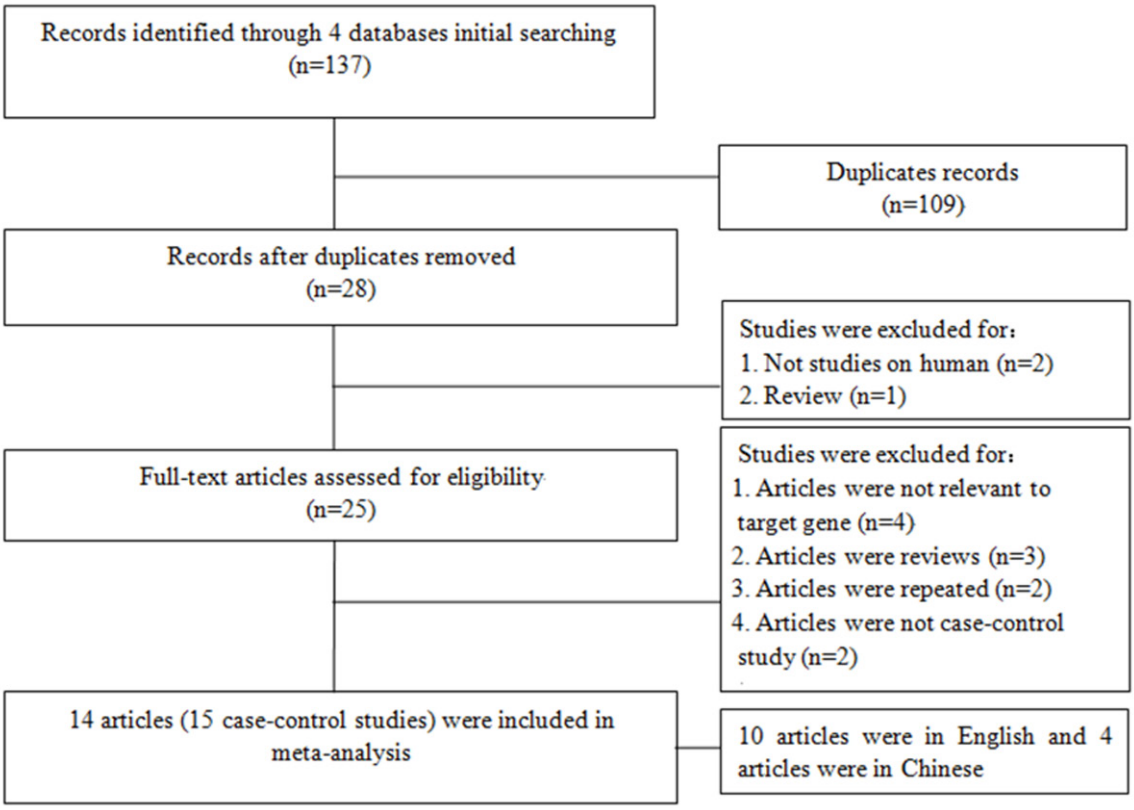

Figure 1. The flow diagram of included and excluded studies.

lated the false positive report probabilities (FPRPs) for all significant associations were found in the current meta-analysis by prior probabilities of 0.1. In the FPRP test, we set a FPRP cut-off value of 0.2 which suggested by the previous study [20], and only the results with FPRP < 0.2 were considered "noteworthy".

Publication bias was tested by several methods. Visual inspection of asymmetry in funnel plots was carried out. Besides, the Egger's test was also applied to assess the publication bias. Furthermore, the Hardy-Weinberg equilibrium (HWE) was assessed by the Chi-square test in control group of each study.

Results

Study characteristics

In total, 137 articles were identified after an initial search (**Figure 1**). After initial reading titles and abstracts, 112 articles were excluded. The remained 25 articles were further screened for full-text view. Four of them were excluded because they were assessed the other polymorphisms of *MIF* gene (such as +254C/T, +656C/G etc.) rather than *-173G/C* polymorphism, three articles were removed for they are reviews, two articles were not included since they were not designed as case-control study, and two articles were repeated. Finally, 15 case-control studies [15-19, 21-29] from 14 articles were identified in the meta-analysis. Among them, 10 papers were in English [15-18, 21-25, 27] and 4 articles [19, 26, 28, 29] were in Chinese. The characteristics of included studies are listed in **Tables 1**, **2**.

Meta-analysis results

All 3,324 cases and 3,929 controls from 14 articles were included in the meta-analysis. Except for two studies reported by Ramireddy et al. [15, 16] not according with the HWE, the other studies met the HWE in the control groups. The χ^2 and I^2 test suggested a moderate heterogeneity (I^2=80.2%, P < 0.1) in the dominant model (CC+CG vs. GG), so we used a

Table 1. Characteristics of case-control studies included in meta-analysis

Author	Year	Coutry	Ethnicity	Cases/Controls	Age	Tumor	Type
Arisawa T	2008	Japan	Asian	229/428	63.0±10.7/54.7±18.8	Gastric cancer	Gastrointestinal tumors
Cai KK	2013	China	Asian	98/80	67.8±5.76/60.2±4.9	Prostate cancer	Urologic tumors
Ding GX	2009	China	Asian	259/301	52.0±1.5/51.6±0.8	Prostate cancer	Urologic tumors
Li HX	2012	China	Asian	296/319	44.0±16.6/44.3±15.9	Gastric cancer	Gastrointestinal tumors
Meyer-Siegler KL	2007	America	Caucasian	131/128	70.2±0.9/64.4±1.1	Prostate cancer	Urologic tumors
Ramireddy L (A)	2014	China	Asian	256/256	53.44/55.8	AML[a]	Hematological malignancies
Ramireddy L (C)	2014	China	Asian	192/256	62.1/55.8	Colorectal cancer	Gastrointestinal tumors
Wu S	2011	China	Asian	250/147	49.1±9.4/48.0±10.8	Cervical cancer	Gynecolgical tumors
Xue Y	2010	China	Asian	346/516	NA[b]	ALL[c]	Hematological malignancies
Yuan L (C)	2012	China	Asian	455/447	46.4±8.9/45.5±9.8	Cervical cancer	Gynecolgical tumors
Yuan L (O)	2012	China	Asian	130/145	50.1±13.3/50.9±12.4	Ovarian cancer	Gynecolgical tumors
Yuan QB	2012	China	Asian	325/345	NA	Bladder cancer	Urologic tumors
Zhou SZ (GD)	2005	China	Asian	104/104	58.5±11.2/59.3±10.6	Gastric cancer	Gastrointestinal tumors
Zhou SZ (SX)	2005	China	Asian	102/102	59.6±10.1/61.3±9.6	Gastric cancer	Gastrointestinal tumors
Ziino O	2005	Italy	Caucasian	151/355	NA	ALL	Hematological malignancies

[a]Acute myelocytic leukemia; [b]Not available; [c]Acute lymphocytic leukemia.

Table 2. Distributions of *MIF -173G/C* genotypes in case and control group

Author	Year	Case					Control					Method	Score
		CC	CG	GG	C	G	CC	CG	GG	C	G		
Arisawa T	2008	12	94	123	118	340	23	144	261	190	666	PCR-SSCP[d]	9
Cai KK	2013	18	43	37	79	117	6	32	42	44	116	PCR-RFLP[e]	8
Ding GX	2009	18	75	166	111	407	0	45	256	45	557	PCR-RFLP	8
Li HX	2012	27	101	168	155	437	12	114	193	138	500	PCR-RFLP	8
Meyer-Siegler KL	2007	/	/	/	152	110	/	/	/	57	199	PCR-sequencing	7
Ramireddy L (A)	2014	8	80	168	96	416	14	56	186	84	428	RT-PCR[f]	8
Ramireddy L (C)	2014	4	63	125	71	313	14	56	186	84	428	RT-PCR	8
Wu S	2011	91	117	42	299	201	39	68	40	146	148	PCR-RFLP	8
Xue Y	2010	10	108	228	128	564	13	134	369	160	872	PCR-RFLP	8
Yuan L (C)	2012	19	135	301	173	737	11	155	281	177	717	PCR-RFLP	8
Yuan L (O)	2012	1	40	89	42	218	4	61	80	69	221	PCR-RFLP	8
Yuan QB	2012	20	99	206	139	511	21	149	175	191	499	PCR-RFLP	7
Zhou SZ (GD)	2005	30	52	22	112	96	16	60	28	92	116	PCR-RFLP	8
Zhou SZ (SX)	2005	32	39	31	103	101	28	46	28	102	102	PCR-RFLP	8
Ziino O	2005	0	34	117	34	268	2	76	277	80	630	DHLPC[g] Wave	7

[d]Polymerase chain reaction-single strand conformation polymorphism; [e]Polymerase chain reaction-restricted fragment length polymorphisms; [f]Real time-polymerase chain reaction; [g]Denaturing high performance liquid chromatography.

random-effect model to investigate the pooled OR. In totally analysis, no significant association between the *MIF -173G/C* gene polymorphism and malignant tumor susceptibility in gene models (CC+CG vs. GG, OR: 1.21, 95% CI=0.95-1.53; CC vs. CG+GG, OR: 1.32, 95% CI=0.94-1.84; CC vs. GG, OR: 1.36, 95% CI=0.93-2.00; CG vs. GG, OR: 1.15, 95% CI=0.91-1.45). However, there is a significant association between *MIF -173G/C* gene polymorphism and risk of cancer in allele model (C vs. G, OR: 1.32, 95% CI=1.04-1.68, P=0.02). No publication bias was checked in either the funnel plot or the Egger's test (t=1.33, P=0.21).

Interestingly, as the results are summarized in **Table 3**, the statistically significant association between the *MIF -173G/C* gene polymorphism and cancer risk was found in Asians (C vs. G, OR: 1.22, 95% CI=1.00-1.50), but not among Caucasians. Additionally, we also conducted the subgroup analysis by types of cancer. The

Table 3. Summary the results of subgroup analysis from different comparative genetic models

Gene models		Ethnicity		Type			
		Asians	Caucasians	Gastrointestinal	Urologic	Hematological	Gynecolgical
CC+CG vs. GG							
	OR[h]	1.22	1.03	1.25	1.50	1.27	0.96
	95% CI[i]	0.95-1.57	0.65-1.63	1.05-1.50	0.48-4.69	1.03-1.56	0.54-1.71
CC vs. CG+GG							
	OR	1.33	0.47	1.35	2.98	0.71	1.51
	95% CI	0.95-1.87	0.02-9.78	0.82-2.23	0.65-13.73	0.38-1.35	1.04-2.19
CC vs. GG							
	OR	1.39	0.47	1.37	3.48	0.79	1.56
	95% CI	0.94-2.04	0.02-9.91	0.83-2.28	0.55-22.19	0.42-1.50	0.73-3.30
CG vs. GG							
	OR	1.16	1.06	1.21	1.29	1.32	0.91
	95% CI	0.91-1.49	0.67-1.68	1.01-1.47	0.46-3.63	1.07-1.65	0.55-1.50
C vs. G							
	OR	1.22	2.20	1.23	2.12	1.16	0.98
	95% CI	1.00-1.50	0.47-10.30	1.07-1.41	0.82-5.50	0.97-1.40	0.63-1.53

[h]Odd ratio; [i]Confidence interval.

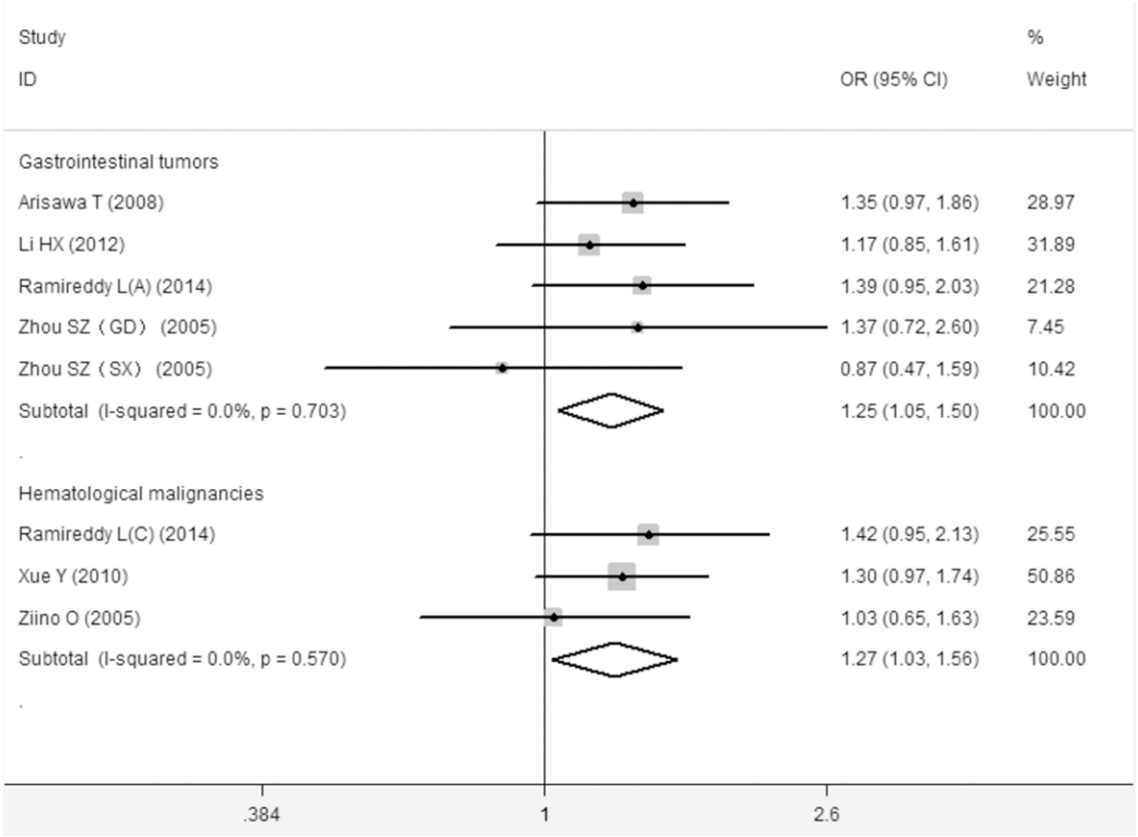

Figure 2. The association between the *MIF -173G/C* polymorphism and gastrointestinal cancer and hematological malignancy risk (CC+CG vs. GG).

results suggested the *MIF -173G/C* gene polymorphism has a significant associated with gastrointestinal cancer (CC+CG vs. GG, OR: 1.25, 95% CI=1.05-1.50; CG vs. GG, OR: 1.21,

Table 4. The results of FPRP test about all significant associations observed in the meta-analysis

Gene models	OR	95% CI	Power	*P* value	Prior probability=0.1 FPRP value
CC+CG vs. GG					
Gastrointestinal	1.25	1.05-1.50	0.975	0.016	0.132
Hematological	1.27	1.03-1.56	0.944	0.023	0.067
CC vs. CG+GG					
Gynecolgical	1.51	1.04-2.19	0.486	0.030	0.356
CG vs. GG					
Gastrointestinal	1.21	1.01-1.47	0.985	0.055	0.334
Hematological	1.32	1.07-1.65	0.869	0.015	0.132
C vs. G					
Overall	1.32	1.04-1.68	0.851	0.024	0.203
Asians	1.22	1.00-1.50	0.975	0.059	0.354
Gastrointestinal	1.23	1.07-1.41	0.998	0.003	0.026

95% CI=1.01-1.47; C vs. G, OR: 1.23, 95% CI=1.07-1.41) (**Figure 2**), hematological malignancy (CC+CG vs. GG, OR: 1.27, 95% CI=1.03-1.56; CG vs. GG, OR: 1.32, 95% CI=1.07-1.65) (**Figure 2**), and gynecological cancer (CC vs. CG+GG, OR: 1.51, 95% CI=1.04-2.19) risk. Unfortunately, there is no association between the *MIF -173G/C* gene polymorphism and urologic cancer risk.

FPRP test results

Furthermore, we investigated the significant associations observed in the present meta-analysis by the FPRP test. As listed in **Table 4**, according to the results of FPRP test, we found the *MIF -173G/C* gene

was only associated with gastrointestinal cancer and hematological malignancy risk (FPRP=0.132, 0.067 respectively). And the significant associations of overall-group, Asians-group and gynecological cancer in the present meta-analysis were proved to be false positive at the level of a prior probability is 0.1.

Discussion

Although a number of anti-cancer drugs are developing in recent decades, the malignancies was still the top leading cause of death worldwide. Previous studies have estimated the total size of new cancer cases is expected to increase by 29% in developed countries while an increase of 73% in developing countries, and with up to 15 million new cases in 2020 [30, 31]. In addition, Rastogi et al. showed the mortality rate caused by cancer will increase about 5-fold greater in the developing countries, and the global cancer mortality is expected to increase by 104% in 2020 [32]. What and how can we do?

Lots of studies focused on the aspects of pathogenesis, influence factors and prognosis of cancer. Previous studies have suggested the risk factors including unhealthy life style, environmental pollution, radiation, infection and immunity dysfunction etc. [33-37]. Furthermore, plenty of studies paid more attention to the role of host genetic variants in mechanism of cancer [38-41]. Lots of studies have reported the association between the *MIF -173G/C* gene polymorphism and cancer risk [18, 21, 25]. However, there is no well comprehensive meta-analysis to assess the association between *MIF -173G/C* gene polymorphism and risk of malignant tumor until now, and we conducted a meta-analysis to investigate the precise relationship. To avoid the false positive about results of the meta-analysis, we also investigated the FPRP for all significant associations shown in the current meta-analysis by set as the prior probabilities is 0.1.

By the meta-analysis, we found the *MIF -173G/C* gene polymorphism could increase the risk of cancer among Asians but not in Caucasians. And the mutational heterozygote could increase the risk of gastrointestinal cancer and hematological malignancy, while the homozygote could increase the gynecological cancer susceptibility. Interestingly, we just found that the *MIF -173G/C* gene polymorphism actually could increase the risk of gastrointestinal cancer and hematological malignancy by the FPRP test. The results of FPRP test means the significant associations of overall-group, Asians-group and gynecological cancer observed in the present meta-analysis may be a false positive association.

The results of current study are different with the previous results [42]. The following reasons may be explained the contradictory results: (1)

only 5 studies were identified in previous study, the results of previous study have insufficient power to reveal a reliable association. However, there are 14 articles were included in the present meta-analysis, our results would more accurately shown the real relationship between *MIF -173G/C* gene polymorphism and cancer risk; (2) except for performed the totally analysis, we also conducted the subgroup meta-analyses to reduce the specific effects from the ethnicity and types of cancer. (3) Furthermore, a large number of previous significant candidate gene association studies have turned out to be "false-positive reports" [43, 44]. Therefore, to assess whether the significant associations between *MIF -173G/C* gene polymorphism and cancer risk is "noteworthy" in the current study, we also investigated the significant associations observed in the meta-analysis by the FPRP test. Overall, the results of present study are more close to real value.

There were several limitations of the present meta-analysis. First, only published articles were included in a few datebases, so a publication bias may have occurred. Sencond, the complexity of cancer susceptibility in most cases probably does not depend on one single factor or on one single gene variant, but rather on many gene variants or gene-environment interaction, similar to the polygenic mode of inheritance in complex disorders. However, due to lacking of sufficient data for each included study, we failed to perform further analysis the confounding factors, such as gender, gene-environment/gene-gene interactionand age which might have influence on our pooled results. Third, the included studies of meta-analysis maily from Asians, so the results possible only applicable to the Asians. There is a need to perform larger sample size studies in other ethnic groups. What's more, the small number of participants included in the subgroup analysis, so we must be cautious when referring to the pooled results. Despite of these limitations, we minimized the likelihood of bias through the whole process by creating a detailed protocol, by performing study identification, statistical analysis and data selection, as well as in the control of publication bias. Anyway, the reliability of the results is guaranteed.

In conclusion, the present study suggested the *MIF -173G/C* gene polymorphism may be an independent risk to contribute the gastrointestinal cancer and hematological malignancy susceptibility. Need to more well designed studies with larger sample size focusing on ethnicities or cancer types be conducted to confirm the results in the future.

Disclosure of conflict of interest

None.

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