The association between the migration inhibitory factor –173G/C polymorphism and cancer risk: a meta-analysis

Abstract: Previous studies have suggested that macrophage migration inhibitory factor (MIF) –173G/C polymorphism may be associated with cancer risk. However, previous research has demonstrated conflicting results. Therefore, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and the meta-analysis on genetic association studies checklist, and performed a meta-analysis to investigate the association between MIF –173G/C polymorphisms and the risk of cancer. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were combined to measure the association between MIF promoter polymorphisms and cancer risk. The pooled ORs were performed for the dominant model, recessive model, allelic model, homozygote comparison, and heterozygote comparison. The publication bias was examined by Begg’s funnel plots and Egger’s test. A total of ten studies enrolling 2,203 cases and 2,805 controls met the inclusion criteria. MIF (–173G/C) polymorphism was significantly associated with increased cancer risk under the dominant model (OR=1.32, 95%, CI=1.00–1.74, P=0.01) and the heterozygote comparison (OR=1.38, CI=1.01–1.87, P=0.04). In subgroup analysis, MIF polymorphism and prostate were related to increased risk of prostate and non-solid cancer. In conclusion, MIF polymorphism was significantly associated with cancer risk in heterozygote comparison. The MIF –173G/C polymorphism may be associated with increased cancer risk.

Keywords: MIF, SNP, systematic review, cancer susceptibility

Introduction

Macrophage migration inhibitory factor (MIF) was first identified nearly 50 years ago and has been used as a cytokine and an enzyme. MIF is a member of the transferring growth factor-β (TGF-β) super family, which is expressed by a broad variety of cells, including B- and T-lymphocytes as well as endocrine, endothelial, and epithelial cells of diverse histogenetic origin. Presently, MIF is considered to play an important role in the pro- and anti-inflammatory response to infection since it is constitutively expressed and acts as an upstream regulator of many other inflammatory cytokines.

Recently, several studies have shown that MIF can promote tumor growth and viability by modulating immune responses and supporting tumor-associated angiogenesis. A few experiments suggested that MIF mRNA and MIF protein are overexpressed in a number of cancers. Tan et al reported that MIF is upregulated in patients with pancreatic cancer and causes dysfunction of insulin secretion in β-cells. Krockenberger et al reported that MIF is clearly overexpressed on the protein level in invasive cervical cancer compared to cervical dysplasia. Two polymorphisms in the promoter region of MIF have been reported in the past. One is a single nucleotide polymorphism (SNP)
at the nucleotide position −173 (G to C)\textsuperscript{10} and the other is a
tetranucleotide CATT repeat beginning at position −794.\textsuperscript{11}
The association between these two polymorphisms and dis-
eases has been extended to several inflammatory conditions
including Graves’ disease,\textsuperscript{12} idiopathic thrombocytopenic
purpura,\textsuperscript{13} and Vogt-Koyanagi-Harada (VKH) syndrome.\textsuperscript{14}
These studies indicate that these two polymorphisms of MIF
are associated with inflammatory diseases. Similarly, some
studies have reported that the polymorphism of MIF resulted
in an increased risk of cancer. With new studies about the
polymorphism of MIF and the risk of cancer emerging,
there has been no meta-analysis conducted regarding the
association between MIF promoter polymorphism and the
risk of cancer in recent times. The aim of this study is to
perform a meta-analysis of all available studies that analyze
the association between the polymorphism of MIF promoter
and the risk of cancer.

Materials and methods

Literature search

The preferred reporting items for systematic reviews and
meta-analyses (PRISMA) statement (Figure S1) and the
meta-analysis on genetic association studies checklist
(Figure S2) were followed in our meta-analysis. A com-
prehensive search of EMBASE, PubMed, Web of Science,
OVID, Cochrane Library, and China National Knowledge
Infrastructure (CNKI) was done from database inception
to July 22, 2014 without language restriction. The search
strategy was “macrophage migration inhibitory factor or
MIF” and “polymorphism or variant or mutation or geno-
type.” To complete our research, we also studied the review
articles and references of retrieved articles manually. The
literature review was performed independently by X Zhang
and J Wang and the disagreements were resolved through
consensus by all the authors.\textsuperscript{15,16}

Selection criteria

Studies were included in the meta-analysis if the follow-
ing inclusion criteria were satisfied: 1) case-control studies
focused on association between the MIF promoter poly-
morphism and cancer risk, 2) studies enrolled more than
30 patients, 3) studies provided sufficient data to estimate
the odds ratio (OR) and 95% confidence intervals (CIs)
according to MIF promoter polymorphism, and 4) when study
patients overlapped with patients in other included studies,
we selected the first study published. The two researchers
(J Wang and X Zhang) independently read the titles and
abstracts and excluded the uncorrelated studies; then the
full-texts were examined by our review team. The studies
were selected according to the inclusion criteria.\textsuperscript{15,16}

Data abstraction

Two independent reviewers (X Zhang and J Wang) extracted the
following information: authors, year of publication, country,
tumor type, number of cases and controls analyzed, mean
value of age, source of controls (hospital-based controls or
population-based controls), and genotyping method. If both
univariate and multivariate analyses were reported, we utilized
the multivariate analysis because it involves observation and
analysis of more than one statistical outcome variable at a time
thus is more accurate. If articles provided insufficient data
(missing data, inconsistencies, or any other uncertainties), we
attempted to contact the first and corresponding authors for
necessary information via telephone or email.\textsuperscript{15,16}

Statistical analysis

ORs and corresponding 95% CIs were combined to measure
the association between MIF promoter polymorphisms and
cancer risk. Hardy–Weinberg equilibrium (HWE) for each
study was determined by the chi-square test. The pooled
ORs were calculated for the allelic model (mutation [M]
allele versus [vs] wild [W] allele), dominant model (WM +
MM vs WW), recessive model (MM vs WM + WW),
hozygote comparison (MM vs WW), and heterozygote
comparison (WM vs WW) respectively, and \( P<0.05 \) denoted
statistical significance. Statistical heterogeneity among the
studies was evaluated using the \( Q \)-test and \( I^2 \)-test. When
heterogeneity among the studies was observed, the pooled
OR was calculated by random-effect models. Sensitivity
analyses were performed to identify the potential influence
of the individual data set to the pooled ORs. Subgroup
analyses were conducted with respect to cancer type and
source of controls. The statistical significance was analyzed
by Student’s \( t \)-test. These analyses were performed by
Review Manager Version 5.1 software (http://ims.cochrane.
org/revman). Both Begg’s and Egger’s tests was performed
using R (http://cran.r-project.org/bin/windows/base).\textsuperscript{15,16}

Results

Characteristics of identified studies

Following an initial search, 166 studies were retrieved from
PubMed; 233 studies from EMBASE; 313 studies from
OVID; 266 studies from Web of Science; 50 studies
from Cochrane Library; 532 studies from CNKI; and five
additional review articles were added to make our search
comprehensive. After duplicated records were removed,
878 published studies were identified. We excluded 780 unrelated studies by reading the titles and abstracts. Next, we downloaded the full-text of the remaining 98 studies and excluded 65 unrelated studies. Of the remaining 33 studies considered for performing the meta-analysis, some studies were found to report incomplete data or report other associations between MIF and cancer. We tried our best to communicate with the first and corresponding authors to get the necessary data. Some authors were able to provide the necessary data for our study, while others did not. Ultimately, after further reviewing in detail, ten studies were included in our meta-analysis. Figure 1 shows in detail the selection process. These ten studies were published between 2005 and 2014. There were 2,203 cases and 2,805 controls included in our meta-analysis. Studies were carried out in People’s Republic of China, Taiwan, Japan, Iran, Italy, and USA. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used in seven studies. One study used polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP). The other two studies employed denaturing high-performance liquid chromatography (DHLPC) wave analysis and a Genetic Analyzer, respectively. Three studies assessed prostate cancer, three studies assessed leukemia and one each for gastric cancer, cervical cancer, colorectal cancer, and bladder cancer. The genotype distribution in one study deviated from HWE. The main characteristics of all the included studies are listed in Table 1.

Meta-analysis

Overall, ten prospective studies enrolling 2,203 cases and 2,805 controls were included in our meta-analysis. A statistically significant association between MIF (−173G/C) polymorphism and cancer risk was found under the dominant model (OR = 1.32, CI = 1.00–1.74, P = 0.01) (Figure 2) and the heterozygote comparison (OR = 1.38, CI = 1.01–1.87, P = 0.04) (Figure S3). There was no statistical significant association under the recessive model (OR = 0.98, 95% CI 0.67–1.45, P = 0.93) (Figure S4), homozygote comparison (OR = 1.02, 95% CI 0.64–1.63, P = 0.93) (Figure S5), and allelic model (OR = 1.32, 95% CI 1.00–1.74, P = 0.05) (Figure S6). Furthermore, in our subgroup analysis, a significant association was found in the prostate group under the dominant model (OR = 3.34, 95% CI 2.24–4.97, P < 0.001), allelic model

![Flow diagram summarizing the selection of eligible studies.](image-url)
| Study                  | Year | Country             | Tumor Type          | Cases | Controls | Age                      | Source of controls | Genotyping method | HWE    |
|-----------------------|------|---------------------|---------------------|-------|----------|--------------------------|--------------------|------------------|--------|
| Ramireddy et al       | 2014 | Taiwan              | Acute myeloid leukemia | 256   | 256      | Mean age: cases: 53.4 controls: 55.8 | HB                 | PCR-RFLP         | 0.06   |
| Leukemia              |      |                     |                     |       |          |                          |                    |                  |        |
| Wu et al              | 2011 | People's Republic of China | Cervical cancer | 250   | 147      | Mean age: cases: 49.08±9.405 controls: 47.99±10.750 | PB                 | PCR-RFLP         | 0.28   |
| Ziino et al           | 2005 | Italy               | Acute lymphoblastic leukemia | 151   | 355      | NR                       | PB                 | PCR-DHLPC Wave analysis | 0.05   |
| Razzaghi et al        | 2012 | Iran                | Prostate cancer     | 61    | 71       | NR                       | PB                 | PCR-RFLP         | 0.88   |
| Ramireddy et al       | 2014 | Taiwan              | Colorectal cancer   | 192   | 256      | Mean age: cases: 62.1 controls: 55.8 | PB                 | PCR-RFLP         | 0.13   |
| CRC                   |      |                     |                     |       |          |                          |                    |                  |        |
| Meyer-Siegler et al   | 2007 | USA                 | Prostate cancer     | 131   | 128      | Mean age: cases: 70.16±0.89 controls: 64.39±1.09 | PB                 | PCR-A310 Genetic analyzer | –      |
| Yuan et al            | 2012 | People's Republic of China | Bladder cancer     | 325   | 345      | Cases: ≤55 years: 66 persons, >55 years: 259 persons; controls: ≤55 years: 83 persons, >55 years: 262 persons | PB                 | PCR-RFLP         | 0.94   |
| Arisawa et al         | 2007 | Japan               | Gastric cancer      | 232   | 430      | Mean age: cases: 62.99±10.73 controls: 54.72±18.84 | HB                 | PCR-SSCP         | 0.81   |
| Xue et al             | 2010 | People's Republic of China | Acute lymphoblastic leukemia | 346   | 516      | Cases: <6 years: 156 persons, ≥6 years: 190 persons; controls: <6 years: 251 persons, ≥6 years: 265 persons | PB                 | PCR-RFLP         | 0.8    |
| Ding et al            | 2009 | People's Republic of China | Prostate cancer     | 259   | 301      | Cases: ≤70 years: 123 persons, >70 years: 136 persons; controls: ≤70 years: 153 persons, >70 years: 148 persons | HB                 | PCR-RFLP         | 0.01   |

**Abbreviations:** HB, hospital-based; PB, population-based; HWE, Hardy–Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; DHLPC, denaturing high-performance liquid chromatography; PCR-SSCP, polymerase chain reaction-single strand conformation polymorphism; NR, no report.
(OR=2.94, 95% CI 1.91–4.54, P<0.001), and heterozygote comparison (OR=2.39, 95% CI 1.65–3.47, P<0.001). MIF (−173G/C) polymorphism was also significantly associated with non-solid cancer risk under the dominant model (OR=1.27, 95% CI 1.03–1.56, P=0.03) and heterozygote comparison (OR=1.32, 95% CI 1.06–1.63, P=0.01). Table S1 presents the results of overall and subgroup analyses.

Sensitivity analysis

We performed sensitivity analysis by omitting one study at a time and calculating the pooled ORs again. However, the results did not show any significant statistical differences when studies were omitted. Therefore, the stability of the study was not influenced by any individual study. Table S2 presents the sensitivity analysis in the dominant model.

Publication bias

Both Begg’s funnel plot and Egger’s test were carried out to evaluate the publication bias of the studies. The results are presented in Figure 3 and Table 2. Publication bias was found under the dominant model (P=0.0286) according to Begg’s funnel plot. When Egger’s test was performed, publication bias was found under the recessive model (P=0.0075) and homozygote comparison (P=0.03). Results indicate that there may be publication bias existing in our meta-analysis. Table 2 presents the results of Begg’s funnel plot and Egger’s test under the five genetic models.

Discussion

In our meta-analysis, ten studies enrolling 2,203 cases and 2,805 controls were included. The results indicated that MIF −173G/C polymorphism was significantly associated with cancer risk.

MIF is known as a major regulator of inflammation and a central upstream mediator of innate immune response, and functions as a key mediator to counter-regulate the inhibitory effects of glucocorticoids within the immune system.27 There are numerous studies suggesting that MIF polymorphism might be associated with the risk of immune disease. Liu et al reported that MIF polymorphism is associated with new-onset Graves’ disease in a Taiwanese Chinese population.21 Hao et al carried out a meta-analysis to investigate the association between MIF polymorphism and the risk of inflammatory bowel disease (IBD).28 They found that MIF −173G/C polymorphism contributed to the susceptibility of IBD.

MIF is also involved in cancer growth and progression. The elevated MIF and mRNA levels have been observed in many tumor cells and pre-tumor states. Krockenberger et al found that MIF was significantly overexpressed on both the protein level and the mRNA level in invasive cervical cancer and MIF protein was overexpressed in SiHa and CaSki cervical cancer cell lines.9 Huang et al reported that MIF expression levels in hepatocellular carcinoma tissues and cell lines were significantly up-regulated compared with adjacent normal tissues or a normal liver cell line.29 Moreover, several studies suggested that MIF polymorphism might be associated with the risk of cancer. Only one study reported that MIF −173G/C polymorphism is associated with a decreased risk of cancer.23 All the other studies reported the opposite conclusion. We also found a meta-analysis that investigated the association between the MIF −173G/C polymorphism and cancer risk.30 However, there were only five studies included in that meta-analysis, and the result was only under the dominant model. In recent times, some new studies have been emerging; for instance, Yuan et al reported that MIF −173G/C polymorphism is associated with new-onset Graves’ disease.
decreased cancer risk.\(^2\) This conclusion contradicted with the conclusion in the previous meta-analysis. Therefore, we added new studies in our meta-analysis and calculated ORs in the dominant model, recessive model, homozygote comparison, heterozygote comparison, and allelic model. In our meta-analysis, we found that MIF\(^{-173}G/C\) polymorphism is significantly associated with cancer risk in the dominant model (OR\(=1.32\), 95% CI 1.00–1.74, \(P=0.01\)) and heterozygote comparison (OR\(=1.38\), 95% CI 1.01–1.87, \(P=0.04\)). There were no significant associations between MIF\(^{-173}G/C\) polymorphism and cancer risk in the recessive model (OR\(=0.98\), 95% CI 0.67–1.45, \(P=0.93\)), homozygote comparison (OR\(=1.02\), 95% CI 0.64–1.63, \(P=0.93\)), and allelic model (OR\(=1.32\), 95% CI 1.00–1.74, \(P=0.05\)). Drawing from these results, we conclude from our meta-analysis that MIF\(^{-173}G/C\) polymorphism might increase the risk of cancer.

There are several limitations in our meta-analysis. First, publication bias exists in the current meta-analysis. If the future studies find that MIF polymorphism was not associated with cancer risk, then publication bias might cause false outcomes. Second, there were some studies lacking in necessary data to calculate ORs under different genetic models. Although we had tried our best to communicate with the first and corresponding authors, some were unable to reply. Third, the patients included in the meta-analysis were limited. It was difficult for us to perform subgroup analyses and obtain specific results. Additionally, only papers published in English or Chinese were included in our meta-analysis, and

Table 2 A summary of \(P\)-values for Begg’s funnel plot and Egger’s test in five genetic models

| Model                  | Begg’s funnel plot | Egger’s test |
|------------------------|--------------------|--------------|
| Dominant model         | 0.0286             | 0.1128       |
| Recessive model        | 0.1361             | 0.0075       |
| Homozygote comparison  | 0.1361             | 0.03         |
| Heterozygote comparison| 0.4767             | 0.2992       |
| Allelic model          | 0.7614             | 0.2373       |

Figure 3 Publication bias in this meta-analysis.
Notes: (A) Begg’s funnel plots of MIF\(^{-173}G/C\) polymorphism in dominant model. (B) Egger’s test of MIF\(^{-173}G/C\) polymorphism in dominant model.
Abbreviation: MIF, migration inhibitory factor.
eligible studies written in other languages that could have fulfilled our study criterion were not included.

Conclusion
Our meta-analysis concluded that MIF –173G/C polymorphism might increase the risk of cancer. Given the above limitations, more studies are needed to confirm the association between MIF polymorphism and the risk of cancer.

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Disclosure
The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 A summary of ORs for the overall and subgroup analyses of MIF polymorphism and cancer risk

| Subgroups          | Dominant model (ORs) | 95% CI       | P-value | Recessive model (ORs) | 95% CI       | P-value | Allelic model (ORs) | 95% CI       | P-value |
|--------------------|----------------------|--------------|---------|-----------------------|--------------|---------|---------------------|--------------|---------|
| Overall            | 1.57                 | 1.1–2.24     | 0.01    | 0.98                  | 0.67–1.45    | 0.93    | 1.32                | 1.00–1.74    | 0.05    |
| Prostate cancer    | 3.34                 | 2.24–4.97    | <0.001  | –                     | –            | –       | 2.94                | 1.91–4.54    | <0.001  |
| Other cancer       | 1.2                  | 0.9–1.59     | 0.21    | 0.98                  | 0.67–1.45    | 0.93    | 1.12                | 0.92–1.36    | 0.27    |
| Solid cancer       | 1.78                 | 1.04–3.04    | 0.04    | 1.04                  | 0.64–1.69    | 0.88    | 1.44                | 0.94–2.22    | 0.1     |
| Non-solid cancer   | 1.27                 | 1.03–1.56    | 0.03    | 0.81                  | 0.40–1.66    | 0.57    | 1.17                | 0.98–1.40    | 0.07    |
| Asian              | 1.41                 | 0.97–2.06    | 0.07    | 0.98                  | 0.67–1.45    | 0.93    | 1.32                | 0.96–1.81    | 0.1     |
| Caucasian          | 2.13                 | 0.78–5.81    | 0.14    | –                     | –            | –       | 1.34                | 0.67–2.71    | 0.41    |
| HB                 | 1.8                  | 1.06–3.04    | 0.03    | 0.8                   | 0.45–1.44    | 0.46    | 1.67                | 0.90–3.12    | 0.1     |
| PB                 | 1.49                 | 0.93–2.37    | 0.1     | 1.06                  | 0.64–1.75    | 0.82    | 1.15                | 0.87–1.52    | 0.32    |
| Subgroups          | Homozygote comparison (ORs) | 95% CI       | P-value | Heterozygote comparison (ORs) | 95% CI       | P-value |
| Overall            | 1.02                 | 0.64–1.63    | 0.93    | 1.38                  | 1.01–1.87    | 0.04    |
| Prostate cancer    | –                    | –            | –       | 2.39                  | 1.65–3.47    | <0.001  |
| Other cancer       | 1.02                 | 0.64–1.63    | 0.93    | 1.23                  | 0.90–1.68    | 0.19    |
| Solid cancer       | 1.05                 | 0.56–2.00    | 0.87    | 1.44                  | 0.88–2.35    | 0.15    |
| Non-solid cancer   | 0.9                  | 0.47–1.75    | 0.76    | 1.32                  | 1.06–1.63    | 0.01    |
| Asian              | 1.02                 | 0.64–1.63    | 0.93    | 1.4                   | 0.97–2.01    | 0.07    |
| Caucasian          | –                    | –            | –       | 1.23                  | 0.77–1.98    | 0.23    |
| HB                 | 0.88                 | 0.50–1.56    | 0.67    | 1.75                  | 1.22–2.51    | 0.002   |
| PB                 | 1.08                 | 0.56–2.10    | 0.82    | 1.2                   | 0.81–1.79    | 0.35    |

Abbreviations: ORs, odds ratios; MIF, migration inhibitory factor; CI, confidence interval; HB, hospital-based; PB, population-based.

Table S2 The influence of individual study on ORs in dominant model

| Study omitted          | Year | OR  | 95% CI | P-value | Heterogeneity |
|------------------------|------|-----|--------|---------|---------------|
| None                   |      | 1.57| 1.10–2.24| 0.01    | 87            | P<0.001 |
| Ramireddy et al<sup>1</sup> | 2014 | 1.60| 1.07–2.39| 0.02    | 88            | P<0.001 |
| Leukemia               |      |     |        |         |               |         |
| Wu et al<sup>3</sup>   | 2011 | 1.55| 1.05–2.27| 0.03    | 88            | P<0.001 |
| Ziino et al<sup>4</sup> | 2005 | 1.65| 1.12–2.43| 0.01    | 88            | P<0.001 |
| Razzaghi et al<sup>5</sup> | 2012 | 1.54| 1.06–2.24| 0.02    | 88            | P<0.001 |
| Ramireddy et al<sup>6</sup> | 2014 | 1.60| 1.07–2.37| 0.02    | 88            | P<0.001 |
| CRC                    |      |     |        |         |               |         |
| Meyer-Siegler et al<sup>7</sup> | 2007 | 1.40| 1.01–1.93| 0.04    | 83            | P<0.001 |
| Yuan et al<sup>8</sup>  | 2012 | 1.75| 1.31–2.35| 0.0002  | 77            | P<0.001 |
| Arisawa et al<sup>9</sup> | 2007 | 1.61| 1.07–2.42| 0.02    | 88            | P<0.001 |
| Xue et al<sup>10</sup>  | 2010 | 1.62| 1.07–2.44| 0.02    | 88            | P<0.001 |
| Ding et al<sup>11</sup> | 2009 | 1.44| 1.03–2.03| 0.04    | 84            | P<0.001 |

Abbreviations: OR, odds ratio; CI, confidence interval.
## PRISMA 2009 Checklist

| Section/topic                      | # | Checklist item                                                                                                                                                                                                 | Reported on page |
|-----------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| **Title**                         |   |                                                                                          |                  |
| Title                             | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                             | **Title**        |
| **Abstract**                      |   |                                                                                          | **Abstract**     |
| Structured summary                | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |                  |
| **Introduction**                  |   |                                                                                          |                  |
| Rationale                         | 3 | Describe the rationale for the review in the context of what is already known.                                                                     | **Introduction** |
| Objectives                        | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICO).                                                          | **Introduction** |
| **Methods**                       |   |                                                                                          | **Methods**      |
| Protocol and registration         | 5 | Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.                                           | **NA**           |
| Eligibility criteria              | 6 | Specify study characteristics (eg, PICO, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.                                      | **Literature search and selection criteria** |
| Information sources               | 7 | Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                             | **Literature search and selection criteria** |
| Search                            | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                             | **Literature search and selection criteria** |
| Study selection                   | 9 | State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                   | **Data abstraction** |
| Data collection process           | 10| Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                              | **Data abstraction** |
| Data items                        | 11| List and define all variables for which data were sought (eg, PICO, funding sources) and any assumptions and simplifications made.                                                                           | **Statistical analysis** |
| Risk of bias in individual studies| 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | **Data abstraction** |
| Summary measures                  | 13| State the principal summary measures (eg, risk ratio, difference in means).                                                                            | **Statistical analysis** |
| Synthesis of results              | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I²) for each meta-analysis.                                                              | **Statistical analysis** |
| Risk of bias across studies       | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).                                                                    | **Statistical analysis** |

(Continued)
| Section/topic                               | #  | Checklist item                                                                 | Reported on page |
|--------------------------------------------|----|--------------------------------------------------------------------------------|------------------|
| Additional analyses                        | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Statistical analysis |
| Results                                    |    |                                                                                |                  |
| Study selection                            | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1         |
| Study characteristics                      | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICO, follow-up period) and provide the citations. | Table S1         |
| Risk of bias within studies                | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 2 and Figure 3 |
| Results of individual studies              | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 2         |
| Synthesis of results                       | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures S1–S4   |
| Risk of bias across studies                | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Table S2         |
| Additional analysis                        | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Figure 3 and Table 2, Tables 1 and S2 |
| Discussion                                 |    |                                                                                |                  |
| Summary of evidence                        | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Discussion       |
| Limitations                                | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Discussion       |
| Conclusions                                | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Discussion       |
| Funding                                    |    |                                                                                | Acknowledgment   |
| Funding                                    | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |                  |

Figure S1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist
Notes: Data from Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 6(6):e1000097. For more information, visit: www.prisma-statement.org.
| # | Item                                                                 | Section name and paragraph number within manuscript |
|---|---------------------------------------------------------------------|-----------------------------------------------------|
| 1 | Provide a detailed justification for the polymorphism studied; if a single polymorphism was analyzed, give details as to why others were not included in the meta-analysis. | Para 2 of Introduction                                 |
| 2 | Provide a detailed justification for the population(s) and clinical condition studied. | Para 2 of Introduction                                 |
| 3 | Provide full details of the search strategy employed; outline the full electronic search strategy – specific combination of keywords and any limits applied- for at least one database. Specify whether synonyms of polymorphisms/genes (eg, SNP number) were searched. | Para 1 of Materials and methods                         |
| 4 | Report full details on the inclusion and exclusion criteria applied for selecting studies. Please list the excluded articles and the reasons for exclusion of each article in a supplementary file. | Para 1 of Materials and methods, Para 1 of Results |
| 5 | Provide details on how the quality of the studies included in the analyses was assessed. | Para 2 of Materials and methods                         |
| 6 | Describe steps taken to contact study authors to identify additional studies and to request missing data. | Para 3 of Materials and methods                         |
| 7 | Describe how environmental effects were adjusted for, if this adjustment was not conducted, outline the reasons for this. | Para 4 of Materials and methods                         |
| 8 | Describe the methods of handling heterogeneity/between-study variance. | Para 4 of Materials and methods                         |
| 9 | Describe how the Hardy–Weinberg equilibrium and linkage disequilibrium were assessed. | Para 4 of Materials and methods                         |
| 10 | Describe and justify the choice of model for the analyses (per-allele vs per-genotype vs genetic model-free, random effects vs fixed effects). | Para 4 of Materials and methods                         |
| 11 | Describe whether a sensitivity analysis has been completed. | Para 4 of Materials and methods                         |
| 12 | Describe whether an assessment of the effects of population stratification has been conducted. | Para 3 of Materials and methods                         |
| 13 | Describe whether study-specific results have been assessed and if so the reasons for this (eg, forest plot). | Para 4 of Materials and methods                         |
| 14 | Include flow diagram for the studies included in the meta-analysis as the first figure for the manuscript | Para 1 of Results                                     |
| 15 | Report details on allele/genotype prevalence. | Para 2 of Results                                     |
| 16 | Report the effect size estimates and P-values for each analysis. | Para 2 of Results                                     |
| 17 | Discuss the limitations of the meta-analysis, including genotyping errors/bias and publication bias. | Para 4 of Discussion                                  |
| 18 | If the meta-analysis identifies an association within a subgroup of the population studied but not another, discuss the implications of these results, and if applicable the possibility of subgroup-specific publication bias. | Para 3 of Discussion                                  |
| 19 | Discuss the suitability of the sample size employed to the research question and the power of the study. | Para 3 and Para 4 of Discussion                        |

**Figure S2** Meta-analysis on genetic association studies checklist

**Abbreviations:** Para, paragraph; SNP, single nucleotide polymorphisms.
| Study or subgroup | Experimental Events | Control Events | Weight | Odds ratio M–H, random, 95% CI |
|------------------|---------------------|----------------|--------|------------------------------|
| Arisawa et al9   | 23                  | 12             | 229    | 1.03 (0.50, 2.10)            |
| Ramireddy et al CRC | 4                  | 14             | 256    | 0.37 (0.12, 1.14)            |
| Ramireddy et al Leukemia | 8          | 14             | 256    | 0.56 (0.23, 1.35)            |
| Wu et al9        | 91                  | 39             | 147    | 1.58 (1.01, 2.48)            |
| Xue et al10      | 10                  | 13             | 516    | 1.15 (0.50, 2.66)            |
| Yuan et al8      | 20                  | 21             | 345    | 1.81 (0.54, 1.90)            |
| **Total (95% CI)** | **1,797**           | **1,749**      | **100.0%** | **0.98 (0.67, 1.45)** |

Favors experimental Favors control

**Heterogeneity:** \( \tau^2 = 0.09; \chi^2 = 8.55, df = 5 (P = 0.13); I^2 = 42\% \)

Test for overall effect: \( Z = 0.09 (P = 0.93) \)

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| Study or subgroup | Experimental Events | Control Events | Weight | Odds ratio M–H, random, 95% CI |
|------------------|---------------------|----------------|--------|------------------------------|
| Arisawa et al9   | 106                 | 45             | 428    | 1.35 (0.97, 1.86)            |
| Ding et al11     | 93                  | 45             | 301    | 3.19 (2.12, 4.78)            |
| Ramireddy et al CRC | 67                | 70             | 256    | 1.42 (0.95, 2.13)            |
| Ramireddy et al Leukemia | 88            | 70             | 256    | 1.39 (0.95, 2.03)            |
| Razzaggi et al8  | 19                  | 13             | 71     | 2.02 (0.90, 4.53)            |
| Meyer-Siegler et al7 | 76           | 29             | 128    | 4.72 (2.75, 8.10)            |
| Wu et al8        | 208                 | 107            | 147    | 1.85 (1.13, 3.03)            |
| Xue et al10      | 118                 | 147            | 516    | 1.30 (0.97, 1.74)            |
| Yuan et al8      | 119                 | 170            | 345    | 0.59 (0.44, 0.81)            |
| Ziino et al4     | 34                  | 78             | 355    | 1.03 (0.65, 1.63)            |
| **Total (95% CI)** | **2,200**           | **2,803**      | **100.0%** | **1.57 (1.10, 2.24)** |

Favors experimental Favors control

**Heterogeneity:** \( \tau^2 = 0.27; \chi^2 = 68.73, df = 9 (P < 0.00001); I^2 = 87\% \)

Test for overall effect: \( Z = 2.51 (P = 0.01) \)

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| Study or subgroup | Experimental Events | Control Events | Weight | Odds ratio M–H, random, 95% CI |
|------------------|---------------------|----------------|--------|------------------------------|
| Arisawa et al9   | 94                  | 45             | 405    | 1.39 (0.99, 1.94)            |
| Ding et al11     | 75                  | 45             | 301    | 2.57 (1.69, 3.90)            |
| Ramireddy et al CRC | 63                | 56             | 242    | 1.67 (1.09, 2.56)            |
| Ramireddy et al Leukemia | 80            | 66             | 242    | 1.58 (1.06, 2.36)            |
| Razzaggi et al8  | 17                  | 13             | 71     | 1.81 (0.79, 4.12)            |
| Wu et al8        | 117                 | 68             | 108    | 1.64 (0.97, 2.77)            |
| Xue et al10      | 108                 | 134            | 503    | 1.30 (0.96, 1.77)            |
| Yuan et al8      | 99                  | 149            | 324    | 0.56 (0.41, 0.78)            |
| Ziino et al4     | 34                  | 76             | 353    | 1.06 (0.67, 1.68)            |
| **Total (95% CI)** | **1,904**           | **2,549**      | **100.0%** | **1.38 (1.01, 1.87)** |

Favors experimental Favors control

**Heterogeneity:** \( \tau^2 = 0.17; \chi^2 = 40.16, df = 8 (P < 0.00001); I^2 = 80\% \)

Test for overall effect: \( Z = 2.04 (P = 0.04) \)

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**Figure S3** Forest plot of MIF –173G/C polymorphism and cancer risk in heterozygote comparison.

**Abbreviations:** MIF, migration inhibitory factor; CI, confidence interval.

**Figure S4** Forest plot of MIF –173G/C polymorphism and cancer risk in recessive model.

**Abbreviations:** MIF, migration inhibitory factor; CI, confidence interval.

**Figure S5** Forest plot of MIF –173G/C polymorphism and cancer risk in homozygote comparison.

**Abbreviations:** MIF, migration inhibitory factor; CI, confidence interval.
Table 6 Forest plot of MIF-173G/C polymorphism and cancer risk in allelic model.

| Study or subgroup | Experimental Events | Control Events | Weight M–H, random, 95% CI | Odds ratio M–H, random, 95% CI |
|------------------|---------------------|----------------|----------------------------|--------------------------------|
| Arisawa et al | 118              | 458            | 190                        | 856                           | 12.2%   | 1.22 (0.93, 1.58) |
| Ding et al | 111              | 518            | 45                          | 602                           | 11.0%   | 3.38 (2.33, 4.88) |
| Ramireddy et al CRC | 71          | 384            | 84                          | 512                           | 11.3%   | 1.18 (0.82, 1.64) |
| Ramireddy et al Leukemia | 96        | 512            | 84                          | 512                           | 11.6%   | 1.18 (0.86, 1.62) |
| Razzaghi et al | 21               | 122            | 13                          | 142                           | 7.0%    | 2.06 (0.99, 4.32) |
| Wu et al | 299              | 500            | 146                         | 294                           | 11.9%   | 1.51 (1.13, 2.02) |
| Xue et al | 128              | 692            | 160                         | 1,032                         | 12.3%   | 1.24 (0.96, 1.60) |
| Yuan et al | 139              | 650            | 191                         | 690                           | 12.3%   | 0.71 (0.55, 0.91) |
| Zino et al | 34               | 302            | 80                          | 710                           | 10.4%   | 1.00 (0.86, 1.53) |
| **Total (95% CI)** | 4,138           | 5,350          | 100.0%                      | 1.32 (1.00, 1.74)             |

Total events: 1,017; 993
Heterogeneity: $I^2=0.15$; $Q=52.00$, $df=8$ ($P<0.00001$); $P=85$
Test for overall effect: $Z=2.95$ ($P<0.05$)

Figure S6 Forest plot of MIF −173G/C polymorphism and cancer risk in allelic model.

**Abbreviations:** MIF, migration inhibitory factor; CI, confidence interval.

**References**

1. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 6(6):e1000097.

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