

RESEARCH ARTICLE

Contribution of Macrophage Migration Inhibitory Factor -173G/C Gene Polymorphism to the Risk of Cancer in Chinese Population

Cheng-Di Wang^{1&}, Tai-Ming Li^{2&}, Zheng-Ju Ren³, Yu-Lin Ji^{1*}, Liu-Shou Zhi^{1*}

Abstract

Background: Macrophage migration inhibitory factor (MIF) -173G/C (rs755622) gene polymorphism has been associated with cancer risk. Previous studies have revealed that MIF -173G/C gene polymorphism may increase cancer in the Chinese population, while results of individual published studies remain inconsistent and inconclusive. We performed this meta-analysis to derive a more precise estimation of the relationship. **Materials and Methods:** We conducted a search on PubMed, Embase, MEDLINE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang, Weipu on Dec 31, 2014. Odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the association. A total of eight studies including 2,186 cases and 2,285 controls were involved in this meta-analysis. **Results:** The pooled results indicated the significant association between MIF -173G/C polymorphism and the risk of cancer for Chinese population (CC + CG vs GG: OR=1.14, 95% CI=1.02-1.27, heterogeneity<0.01; P =0.023; CC vs CG+GG: OR=1.12, 95% CI=1.02-1.23, heterogeneity<0.01; P =0.017; CC vs GG: OR=1.18, 95% CI=1.04-1.33, heterogeneity<0.01; P =0.008; CG vs GG: OR=1.03, 95% CI=0.91-1.15, heterogeneity<0.01; P =0.656; C vs G: OR=1.24, 95% CI=1.14-1.25, heterogeneity<0.01; P <0.001). Subgroup analysis showed that in patients with “solid tumors”, heterogeneity was very large (OR=0.94, 95% CI=0.83-1.06, heterogeneity=0.044; p=0.297). Within “non-solid tumors”, the association became even stronger (OR=6.62, 95% CI=4.32-10.14, heterogeneity<0.001; p<0.001). **Conclusions:** This study suggested that MIF -173G/C gene polymorphism may increase cancer in the Chinese population. Furthermore, more larger sample and representative population-based cases and well-matched controls are needed to validate our results.

Keywords: Macrophage migration inhibitory factor (MIF) - cancer - polymorphism - Chinese

Asian Pac J Cancer Prev, 16 (11), 4597-4601

Introduction

China is the most populous country in the world, where cancer is a major public health. Cancer was the second leading cause of death, and the incidence and mortality keep increasing (Chen et al., 2015). During the transformation from normal cells to cancer cells, the genes which regulate cell growth and differentiation are overturned. Among the well-known oncogenes such as MIF (Babu et al., 2012), COMT (Du et al., 2014), XRCCI (Chen et al., 2015), EGFR (Chen et al., 2015) and so forth. Of which, the MIF gene is one of the most involved genes that cause cancer.

The macrophage migration inhibitory factor (MIF) was initially described as a soluble factor produced by T lymphocytes which could inhibit the directed migration of macrophages. Nowadays, MIF is accepted as a pleiotropic cytokine that is a crucial regulator of innate immunity and a regulator of inflammation because it is not only constitutively released from a variety of immune cells, but also widely expressed in other cells (Yuan

et al., 2013). Up to date, previous studies have reported the potential association between MIF -173G/C gene polymorphism and risk of cancer (Meyer-Siegler et al., 2007; Arisawa et al., 2008), such as prostate cancer patients have increased Mif mRNA expression or MIF protein levels in prostate tissue (Meyer-Siegler et al., 2002). However, while others have reported a lack of association (Ziino et al., 2005). The aim of this study is to conduct a meta-analysis of all published studies that derive a more precise estimation of the association between MIF promoter polymorphism and the incidence of cancer in Chinese population.

Materials and Methods

Identification and eligibility of relevant studies

Relevant articles included in the meta-analysis were systematically searched on PubMed, Embase, MEDLINE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang, Weipu on Dec 31, 2014. Search terms were as follows: “MIF or Macrophage

¹Department of Respiratory Medicine, ²Department of Pediatric Surgery, ³Department of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China &Equal contributors *For correspondence: jiyulinscu@sina.cn liushouzhiscu@sina.cn

Table 1. Characteristics and Genotype Distributions of Included Case-control Studies

First author	Year	Cancer type	Region	Genotyping method	Case	Control	Case			Control		
							CC (%)	CG (%)	GG (%)	CC (%)	CG (%)	GG (%)
Ding	2009	Prostate Cancer	Nanjing	PCR-RFLP	259	301	18 (7.0)	75 (29.0)	166 (64.0)	0 (0.00)	45 (15.0)	256 (85.0)
Xue	2010	acute lymphoblastic leukemia	Nanjing	PCR-RFLP	346	516	228 (65.9)	108 (31.2)	10 (2.9)	369 (71.5)	134 (26.0)	13 (2.5)
WU	2011	cervical cancer	Shanxi	PCR	250	147	91(36.4)	117(46.8)	42(16.8)	39(26.5)	68(46.3)	40(27.2)
Yuan	2012	bladder cancer	Nanjing	PCR-RFLP	325	345	20 (6.1)	99 (30.5)	206 (63.4)	21 (6.1)	149 (43.2)	175 (50.7)
Gu	2012	non-small-cell lung carcinoma	Shanghai	PCR	262	145	11 (4.2)	83 (31.7)	168 (64.1)	7 (4.8)	51 (35.2)	87 (60.0)
Li	2012	Gastric cancer	Henan	PCR_RFLP	296	319	27(9.1)	101(34.1)	168(56.8)	12(3.8)	114(35.7)	193(60.5)
Ramireddy	2014	Acute Myeloid Leukemia	Taiwan	PCR	256	256	8(3.1)	80(31.2)	168(65.6)	186 (72.7)	56 (21.9)	14 (5.5)
Ramireddy	2014	Colorectal Cancer	Taiwan	PCR	192	256	4(2.1)	63(32.8)	125(65.1)	14(5.5)	56(21.8)	186(72.7)

migration inhibitory factor (MIF)", "polymorphism, mutation, or variant", "China or Chinese", "cancer or carcinoma". There was no language restriction. The eligible studies had to meet the following criteria: *i*) Studies had to assess the association between MIF promoter polymorphism and the cancer risks in Chinese population originally; *ii*) The design had to be a case-control study or cohort study; *iii*) genotype distributions in both cases and controls were available; *iv*) the results were expressed as odds ratio (OR) and corresponding 95 % confidence interval (95%CI). And major reasons for exclusion of studies were as follows: *i*) not for MIF promoter polymorphism and the cancer risks in Chinese population; *ii*) studies with duplicate unusable data or overlapping participants; *iii*) animal studies, review articles, meta-analyses, conference abstracts or editorial articles. When more than one of the same patient population was included in several publications, the study with the largest sample size or with the latest publication date was selected.

Data extraction

Two independent reviewers (ChengDi Wang and Taiming Li) extracted data independently complying with the inclusion criteria. In case of conflicting evaluation, a third reviewer (Zhengju Ren) was consulted and consensus was reached after a discussion. In the present meta-analysis, the following variables were collected for each study: *i*) the first author's name, year of publication, region, subject source control was stratified to population-based studies and hospital-based studies, cancer type, genotyping method; *ii*) design type, sample size of the study case and control groups.

Statistical analysis

The strength of the relationships between MIF promoter polymorphism and the cancer risks in Chinese population were assessed using OR and corresponding 95%CI. The pooled OR and 95%CI were counted in dominant model (CC+CG vs GG) and other models (CC vs CG+GG, CC vs GG, CG vsGG and C vs G) for MIF -173G/C polymorphism. The heterogeneity was calculated through the χ^2 -based Q-test and I^2 statistics test. If the *P*-value of heterogeneity was >0.10 , a fixed-effect model was used; otherwise, a random-effect model was used. The significance of the pooled OR was determined by the Z-test, and $P < 0.05$ was considered as statistically significant. Begg's test and Egger's test were applied to investigate the publication bias. All the statistical analysis was performed using STATA11.0 (Stata Corporation, College Station, Texas, USA).

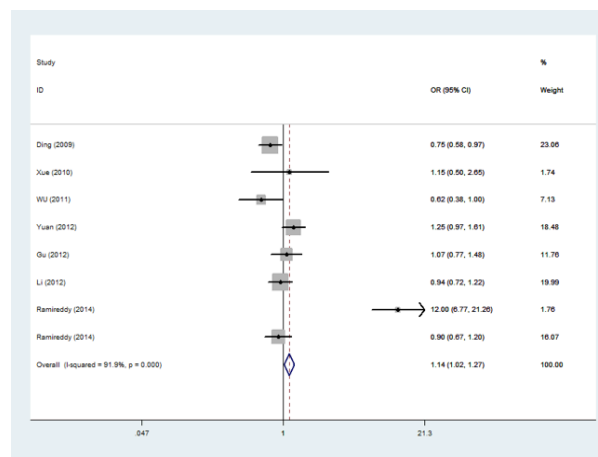


Figure 1. Overall Meta-analysis for the Association between MIF -173G/C Gene Polymorphism and the Cancer Risk in Chinese Population (CC+CG vs GG). CI, Confidence Interval; OR, Odds Ratio. Heterogeneity chi-squared = 86.64 (d.f. = 7) p = 0.000 I-squared (variation in OR attributable to heterogeneity) = 91.9% Test of OR=1: z = 2.28 p = 0.023

Results

Study characteristics

A total of 71 results were retrieved after first search in PubMed, Embase, MEDLINE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang, Weipu databases. After our careful selection, 8 case-control studies considering 2, 186 cases and 2, 285 controls were included in the current study (Ding et al., 2009; Xue et al., 2010; Wu et al., 2011; Yuan et al., 2012; Gu et al., 2012; Li et al., 2012; Ramireddy et al., 2014; Ramireddy et al., 2014). Two studies were conducted on leukemia patients and were thus classified as "non-solid tumors" whereas the remaining six studies examined either cancer or carcinoma, and thus were classified as "solid tumors". The characteristics of included studies are shown in Table 1.

Quantitative synthesis

The association between MIF promoter polymorphism and the cancer risks in Chinese population was analyzed in a total of 2, 186 cases and 2, 285 controls from eight case-control studies. Overall, The pooled results indicated the significant association between MIF -173G/C polymorphism and the risk of cancer for Chinese population (CC+CG vs GG: OR=1.14, 95%CI=1.02-1.27, heterogeneity < 0.01 ; $P = 0.023$, Figure 1; CC vs

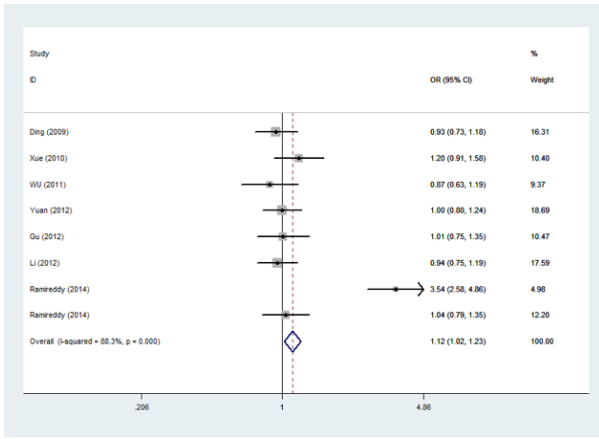


Figure 2. Overall Meta-analysis for the Association between MIF -173G/C Gene Polymorphism and the Cancer Risk in Chinese Population (CC vs CG+GG). CI, Confidence Interval; OR, Odds Ratio. Heterogeneity chi-squared = 59.88 (d.f. =7) p = 0.000 I-squared (variation in OR attributable to heterogeneity) = 88.3% Test of OR=1 : z= 2.39 p = 0.017

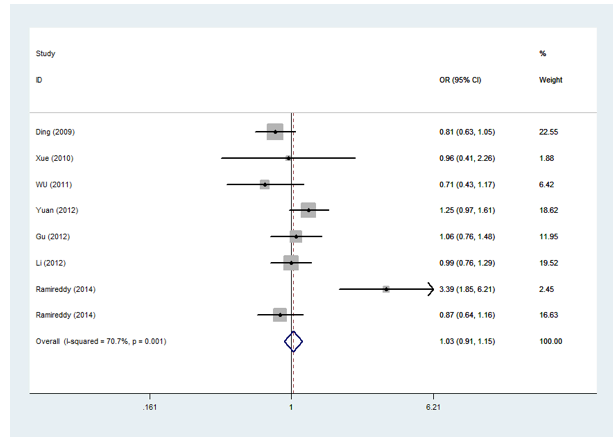


Figure 4. Overall Meta-analysis for the Association between MIF -173G/C Gene Polymorphism and the Cancer Risk in Chinese Population (CG vs GG) CI, Confidence Interval; OR, Odds Ratio. Heterogeneity chi-squared = 23.89 (d.f. =7) p=0.001 I-squared (variation in OR attributable to heterogeneity) =70.7% Test of OR=1 : z=0.45 p = 0.656

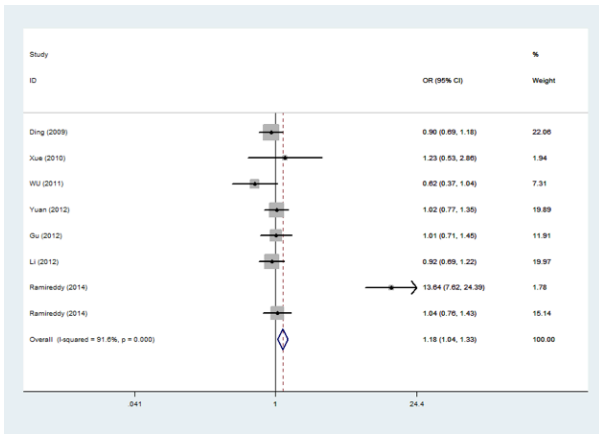


Figure 3. Overall Meta-analysis for the Association between MIF -173G/C Gene Polymorphism and the Cancer Risk in Chinese Population (CC vs GG) CI, Confidence Interval; OR, Odds Ratio. Heterogeneity chi-squared =82.87 (d.f.=7) p=0.000 I-squared (variation in OR attributable to heterogeneity) =91.6% Test of OR=1: z=2.66 p=0.008

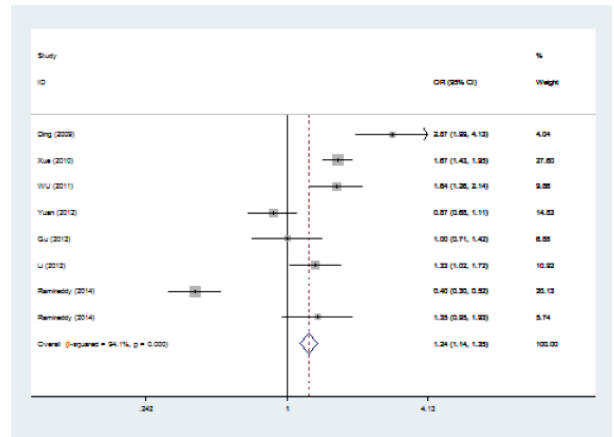


Figure 5. Overall Meta-analysis for the Association between MIF -173G/C Gene Polymorphism and the Cancer Risk in Chinese Population (C vs G) CI, Confidence Interval; OR, Odds Ratio. Heterogeneity chi-squared=119.23 (d.f. =7) p=0.000 I-squared (variation in OR attributable to heterogeneity)=94.1% Test of OR=1: z= 4.81 p=0.000

CG+GG; OR=1.12, 95%CI=1.02-1.23, p=0.017, Figure 2; CC vs GG; OR=1.18, 95%CI=1.04-1.33, p=0.008, Figure 3; CG vs GG; OR=1.03, 95%CI=0.91-1.15, p=0.656, Figure 4; C vs G; OR=1.24, 95%CI=1.14-1.35, p<0.001, Figure 5).

The shape of the funnel plots seemed symmetrical, and no publication bias was detected in the Egger's test (figure not shown).

Subgroup analysis showed that in patients with "solid tumors", heterogeneity was very large (OR=0.94, 95%CI=0.83-1.06, p=0.044; p=0.297, Figure 6). Within "non-solid tumors", there was also significant association between the MIF -173G/C polymorphism and cancer (OR=6.62, 95%CI=4.32-10.14, p<0.001; p<0.001).

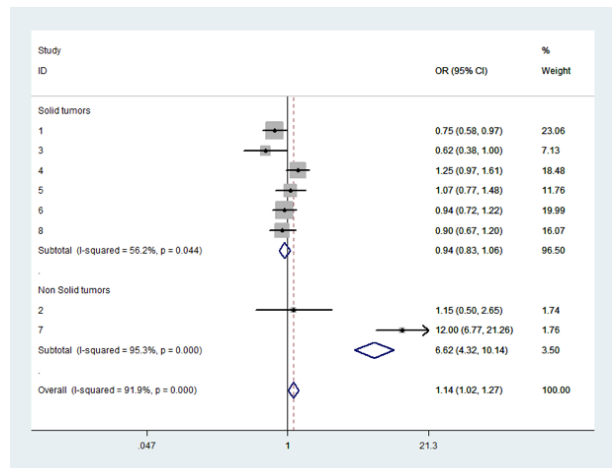


Figure 6. Overall Analysis Using Subgroup Analyses for Patients with "Non-Solid" vs "Solid" Tumors are Shown (CC+CG vs GG). CI, confidence interval; OR, odds ratio

Discussion

The MIF gene is available on chromosome 22q11, and -173G/C polymorphism involves a G to C substitution at base pair 173 of the 50-flanking region (Tong et al., 2015). Nowadays, MIF is thought as a pleiotropic cytokine, which is connected with many inflammatory response and plays a crucial role in regulation of T-cell activation, the innate immune response (Vera et al., 2011). Recent studies have revealed MIF expression was associated with tumor grading and a SNP of the MIF promoter (-173) was functionally connected with its expression (De Benedetti., 2003). Accordingly, MIF is a main modulator of inflammation and a possible connection between inflammation and cancer (Balkwill et al., 2010). Previous studies have considered the relationship between increased expression of Mif mRNA and cancer (Meyer-Siegler et al., 2005; Rendon et al., 2007; Verjans et al., 2009). Although many studies have reported the association between MIF -173G/C polymorphism and cancer risk, there is no meta-analysis to comprehensively evaluate the relationship of MIF -173G/C gene polymorphism with cancer risk in Chinese population up to date. Hence, we performed a study to investigate the association.

In the present study, the overall results showed that MIF gene polymorphism could increase the cancer risk in Chinese population (CC+CG vs GG; OR=1.14, 95%CI=1.02-1.27, pheterogeneity<0.01; P=0.023; C vs G:OR=1.24, 95%CI=1.14-1.35, pheterogeneity<0.001; P<0.001). It reveals that individuals with the variant C allele are at almost 24% higher risk of cancer risk. Due to large heterogeneity in the results, sub-group analysis indicated that there is a strong relationship between Mif promoter genotypes containing dominant model (CC+CG vs GG). In patients with "solid tumors", heterogeneity was very large (OR=0.94, 95%CI=0.83-1.06, pheterogeneity=0.044; p=0.297, Figure 6). Within "non-solid tumors", there was also significant association between the MIF -173G/C polymorphism and cancer (OR=6.62, 95%CI=4.32-10.14, pheterogeneity<0.001; p<0.001). However, a significant heterogeneity between articles studies was indicated in this study, which may have reasons according to following aspects: *i*) different types of cancer; *ii*) different genetic and demographic characteristics of included populations; *iii*) different genotyping methods and different quality of each included study.

There exists several remained limitations in this meta-analysis. Firstly, the sample size of included published articles was small, so sufficient data was unavailable. Secondly, other clinical data such as location, age, gender, source of control, et al were not analyzed due to the lack of information in the original studies (Zhu et al., 2013). Thirdly, the focus of the recent articles was limited to the MIF -173 G/C promoter and did not include -794 CATT repeat polymorphisms because of the very small numbers of studies. Finally, the gene-gene and gene-environment interactions were not discussed for the MIF gene polymorphisms, also due to lack of original information. Despite the limitations as above, we have minimized the bias through the whole process as follows: well-met our inclusion criteria, data selection and statistical analysis of

included case-control studies in the control of publication bias and sensitivity. In this way, the reliability of the results is guaranteed.

In conclusion, our study suggested that the MIF -173G/C polymorphism may increase the risk of cancers in Chinese population. high-quality case-control studies with large sample sizes are warranted to validate our results.

References

- Arisawa T, Tahara T, Shibata T, et al (2008). Functional promoter polymorphisms of the macrophage migration inhibitory factor gene in gastric carcinogenesis. *Oncology reports*, **19**, 223-8.
- Babu SN, Chetal G, Kumar S (2012). Macrophage migration inhibitory factor: A potential marker for cancer diagnosis and therapy. *Asian Pac J Cancer Prev*, **13**, 1737-44.
- Balkwill F, Mantovani A (2010). Cancer and inflammation: implications for pharmacology and therapeutics. *Clin Pharmacol Ther*, **87**, 401-6.
- Bloom BR, Bennett B (1966). Mechanism of a reaction *in vitro* associated with delayed-type hypersensitivity. *Science*, **153**, 80-2.
- Chen W, Zheng R, Zeng H, Zhang S, et al (2015). Annual report on status of cancer in China, 2011. *Chin J Cancer Res*, **27**, 2-12
- De Benedetti F, Cristina M, Vivarelli M, et al (2003). Functional and prognostic relevance of the -173 polymorphism of the macrophage migration inhibitory factor gene in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum*, **48**, 1398-407.
- Ding GX, Zhou SQ, Xu Z, et al (2009). The association between MIF-173 G>C polymorphism and prostate cancer in southern Chinese. *J Surg Oncol*, **100**, 106-110.
- Du JZ, Dong YL, Wan GX, et al (2014). Lack of Association between the COMT rs4680 polymorphism and ovarian cancer risk: evidence from a meta-analysis of 3,940 individuals. *Asian Pac J Cancer Prev*, **15**, 7941-5.
- Gu S, Wu Q, Zhao X, et al (2012). Association of CASP3 polymorphism with hematologic toxicity in patients with advanced non-small-cell lung carcinoma treated with platinum-based chemotherapy. *Cancer Sci*, **103**, 1451-59.
- Li H, Zang J, Wang P, et al (2012). Gastric cancer susceptibility in gastric cancer relatives: attributable risks of Macrophage migration inhibitory factor promoter polymorphism and Helicobacter pylori. *Cytokine*, **60**, 346-351.
- Meyer-Siegler KL, Bellino MA, Tannenbaum M (2002). Macrophage migration inhibitory factor evaluation compared with prostate specific antigen as a biomarker in patients with prostate carcinoma. *Cancer*, **94**, 1449-56.
- Meyer-Siegler KL, Iczkowski KA, Vera PL (2005). Further evidence for increased macrophage migration inhibitory factor expression in prostate cancer. *BMC cancer*, **5**, 73.
- Meyer-Siegler KL, Vera PL, Iczkowski KA, et al (2007). Macrophage migration inhibitory factor (MIF) gene polymorphisms are associated with increased prostate cancer incidence. *Genes and immunity*, **8**, 646-52.
- Ramireddy L, Chen WT, Peng CT, et al (2014). Association Between Genetic Polymorphism of the MIF Gene and Colorectal Cancer in Taiwan. *J Clin Lab Anal*, **00**, 1-7
- Ramireddy L, Lin CY, Liu SC, et al (2014). Association study between macrophage migration inhibitory factor-173 polymorphism and acute myeloid leukemia in Taiwan. *Cell Biochem Biophys*, **70**, 1159-65.
- Rendon BE, Roger T, Teneng I, et al (2007): Regulation of

- human lung adenocarcinoma cell migration and invasion by macrophage migration inhibitory factor. *J Biol Chem*, **282**, 29910-8.
- Tong X, He J, Liu S, et al (2015). Macrophage migration inhibitory factor -173G/C gene polymorphism increases the risk of renal disease: a meta-analysis. *Nephrology*, **20**, 68-76
- Vera PL, Meyer-Siegler K L (2011). Association between macrophage migration inhibitory factor promoter region polymorphism (-173 G/C) and cancer: a meta-analysis. *BMC Res Notes*, **4**, 395
- Verjans E, Noetzel E, Bektas N, et al (2009). Dual role of macrophage migration inhibitory factor (MIF) in human breast cancer. *BMC cancer*, **9**, 230.
- Wu S, Lian J, Tao H, et al (2011). Correlation of macrophage migration inhibitory factor gene polymorphism with the risk of early-stage cervical cancer and lymphatic metastasis. *Oncol Lett*, **2**, 1261-67.
- Xue Y, Xu H, Rong L, et al (2010). The MIF -173G/C polymorphism and risk of childhood acute lymphoblastic leukemia in a Chinese population. *Leuk Res*, **34**, 1282-86.
- Yang HY, Yang SY, Shao FY, et al (2015). Updated assessment of the association of the XRCC1 Arg399Gln Polymorphism with lung cancer risk in the Chinese population. *Asian Pac J Cancer Prev*, **16**, 495-500.
- Yuan Q, Wang M, Zhang Z, et al (2012). Macrophage migration inhibitory factor gene -173G>C polymorphism and risk of bladder cancer in southeast China: a case-control analysis. *Mol Biol Rep*, **39**, 3109-15.
- Yuan T, Tang C, Chen M, et al (2013). Influence of the human MIF promoter polymorphism on hepatocellular carcinoma prognosis. *Genetics and Molecular Research*, **12**, 6629-35
- Zheng CL, Qiu C, Shen MX, et al (2015). Prognostic impact of elevation of vascular endothelial growth factor family expression in patients with non-small cell lung cancer: an updated meta-analysis. *Asian Pac J Cancer Prev*, **16**, 1881-95
- Zhu LX, Ho SC, Wong TK (2013). Effectiveness of health education programs on exercise behavior among patients with heart disease: a systematic review and meta-analysis. *J Evid Based Med*, **6**, 265-301.
- Ziino O, D'Urbano LE, Benedetti FD, et al (2005). The MIF-173G/C polymorphism does not contribute to prednisone poor response in vivo in childhood acute lymphoblastic leukemia. *Leukemia*, **19**, 2346-7.