RESEARCH ARTICLE

The 2518 A/G Polymorphism in the MCP-1 Gene and Cancer Risk: A Meta-analysis

Liu-Qun Jia[&], Yong-Chun Shen[&], Shu-Jin Guo[&], Qian-Jing Hu, Cai-Shuang Pang, Tao Wang, Lei Chen, Fu-Qiang Wen*

Abstract

Background: The 2518 A/G polymorphism in the MCP-1 gene has been extensively studied for association swith cancer; however, results from replication studies have been inconsistent. The aim of this investigation was to determine links with risk of cancer by meta-analysis. Methods: We searched Pubmed, Embase, CNKI, Weipu and Wanfang databases, covering all case-control studies until March, 2013. Statistical analyses were performed using the Revman 5.0 software. Results: A total of 11 case-control studies met our inclusion criteria, including 1,422 cases and 2,237 controls. The results indicated that the MCP-1 2518 gene polymorphism had no association with cancer risk overall (GG vs.GA+ AA: OR = 0.89, 95%CI = 0.61–1.28, *P* = 0.52). However, in the subgroup analysis by ethnicity, a decrease of cancer risk was found in Asian populations (GG vs.GA+ AA: OR = 0.79, 95%CI = 0.63–0.99, *P* = 0.04). Conclusion: This meta-analysis suggested that the 2518A/G polymorphism of MCP-1 gene is associated with risk of cancer among Asian, but not in Caucasian populations.

Keywords: MCP-1 - cancer - polymorphism - meta-analysis - ethnicity

Asian Pacific J Cancer Prev, **14 (6)**, 3575-3579

Introduction

Chronic inflammation is known to be associated with the development and progression of different types of cancer (Balkwill et al., 2001). It is estimated that 15~20% of all human cancers are caused by chronic infection or chronic inflammatory responses (Mantovani et al., 2008). Altered regulation of chemokines and their receptors has recently been shown to play a crucial role in promoting tumor development and progression through distinct mechanisms, such as proliferation, angiogenesis, invasiveness, and recruitment of immune cells (Hanahan et al., 2000). Numerous studies have been performed on the association of genetic variants with cancer susceptibility and among them, the monocyte chemoattractant protein-1 (MCP-1) gene has been highlighted.

The human MCP-1 gene, which belongs to CC chemokine family, regulates the infiltration of monocytes, memory T cells and macrophages and other inflammatory cells by binding to the membrane CC chemokine receptor 2 (CCR2) (Rollins et al., 1991; O'Hayre et al., 2008). The -2518A/G polymorphism (rs1026611) in the MCP-1 gene can influence plasma MCP-1 concentration and has been suggested as a risk factor for cancers (Rovin et al., 1999; Shi et al., 2011). Numerous studies have been performed on the association of the -2518 A/G Polymorphisms in the MCP-1 gene with cancer susceptibility, but the results were inconclusive. In the present study, we performed a meta-analysis to investigate the association between this polymorphism and cancer risk. To our knowledge, this is the first genetic meta-analysis conducted with respect to the association between the MCP-1 polymorphism and cancer risk.

Materials and Methods

Study identification and selection

A systematic search of the literature was made by using the electronic database Medline (Pubmed), Pubmed, CNKI, Wanfang and Weipu database to identify articles that evaluated the association between polymorphism of MCP-1 gene and cancer risk (Last search was updated on March 27, 2013). The search terms were as follows: "cancer or tumor or carcinoma" in combination with "polymorphism or variant or mutation" and in combination with "Monocyte chemoattractant protein-1 or MCP-1 or CCL2 or Chemokine (C–C motif) ligand 2". The languages were limited to English and Chinese.

Inclusion criteria were defined as follows: (1) articles had to evaluate the association between MCP-1 -2518A/G polymorphism and cancer risk; (2) they were case-control studies; (3) sufficient data (genotype distributions for cases and controls) must be available to estimate an odds ratio (OR) with its 95% confidence interval (CI); and (4)

*Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China and Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu, China [&]Equal contributors *For correspondence: wenfuqiang_scu@126.com*

Table 1. Characteristics of the Case-control Studies Included in the Present Meta-analysis

Firest Author	Year	Country	Ethnicity	Cancer	Cases/Controls	Genotyping method
Bektas-Kayhan K	2012	Turkey	Caucasian	Oral cancer	129/140	PCR-RFLP
Chen MK	2011	China	Asian	Oral cancer	216/344	PCR-RFLP
Hsin-Hung Wu	2013	China	Asian	Cervical cancer	86/253	PCR-RFLP
Kruszyna L	2011	Poland	Caucasian	Breast cancer	160/323	PCR
Kucukgergin C	2012	Turkey	Caucasian	Prostate cancer	156/152	PCR-RFLP
Kucukgergin C	2012	Turkey	Caucasian	Bladder cancer	142/197	PCR-RFLP
Narter KF	2010	Turkey	Caucasian	Bladder cancer	72/76	PCR-RFLP
Singh	2012	India	Asian	Bladder cancer	200/200	PCR-RFLP
Vázquez-Lavista LG	2009	Mexico	Latino	Bladder cancer	47/126	PCR-RFLP
Yang L	2010	China	Asian	Lung cancer	112/82	PCR-RFLP
Yeh CB	2010	China	Asian	Liver cancer	102/344	PCR-RFLP

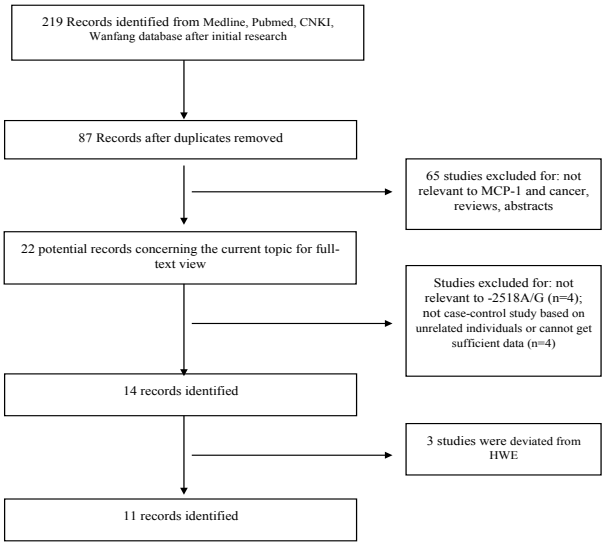

Figure 1. The Flow Diagram of Included and Excluded Studies

the distribution of genotypes in the control group was consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: (1) abstracts and reviews, (2) genotype frequency not reported, and (3) Repeat or overlapping publications.

Data extraction

Two reviewers independently checked all potentially relevant studies and reached a consensus on all items. In case of disagreement, a third author would assess these articles. The following data were collected from each study: first author, year of publication, ethnicity, definition of cases, source of control, genotyping methods, total number of cases and controls, and genotype distributions in cases and controls.

Statistical analysis

The strength of association between MCP-1 -2518A/G polymorphism and cancer risk was assessed by OR with the corresponding 95% CI. The genetic model evaluated for pooled OR of the polymorphism was recessive genetic model (GG vs. GA+AA). Dominant genetic models (GG+AG vs. AA) and G vs. A model were also used to assess the association with the risk of cancer. The OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity among studies was assessed by a χ^2-based Q statistic, with statistical significance set at $p < 0.05$. When the p value was <0.05, the pooled OR was calculated by the fixed-effects model; otherwise a random-effects model was used. The significance of the pooled OR was determined by a Z-test and $p < 0.05$ was considered statistically significant. To evaluate the ethnicity-specific effects, subgroup analyses was performed by ethnic group. Publication bias was analyzed by Begg's funnel plots and Egger's test. Sensitivity analysis was performed by sequentially excluding individual study to assess the stability of the results. HWE was tested by Pearson's χ^2 test ($P < 0.05$ means deviated from HWE). All statistical tests were performed using Revman 5.0 software and STATA 12.0 software.

Results

Study inclusion and characteristics

Figure 1 outlines the process of selecting studies. Briefly, a total of 219 articles were identified after an initial search from the Pubmed, Embase, CNKI, Weipu and Wanfang database. After excluded the duplicate articles, 87 articles were identified. Then 65 studies excluded for being not relevant to MCP-1 polymorphisms and cancer risk, or abstracts and reviews. After reading full texts of the remaining 22 articles, 4 studies which did not concern -2518A/G polymorphism were excluded, 3 studies which concern prognosis were excluded, and 1 study which did not have normal control group was excluded. After HWE test, 3 articles (Saenz-Lopez et al., 2008; Attar et al., 2010; Gu et al., 2011) were deviated from HWE. Thus, a total of 11 case– control studies were extracted (Vazquez-Lavista et al., 2009; Narter et al., 2010; Yang et al., 2010; Yeh et al., 2010; Chen et al., 2011; Kruszyna et al., 2011; Kucukgergin et al., 2012a; Kucukgergin et al., 2012b; Bektas-Kayhan et al., 2012; Singh et al., 2012; Wu et al., 2013). The characteristics of each case–control study are listed in Table 1. Briefly, a total of 11 case–control studies were identified met our inclusion criteria, including 1422 cases and 2237 controls. There were 5 studies of Asian and 5 studies of Caucasian and 1 study of Latino. The cancer types included bladder cancer (n=4), oral cancer (n=2), prostate cancer (n=1), cervical cancer (n=1), breast cancer (n=1), liver cancer (n=1) and lung cancer (n=1). The characteristics of each study included in this meta-analysis are presented in Table 1. Genotype frequencies and HWE examination results are listed in Table 2.

Table 2. Distributions of MCP-1 Genotype and Allele among Cancer Patients and Controls

	Cancer			Control			Cancer		Control		HWE
Firest Author	AA	AG	GG	AA	AG	GG	A	G	A	G	*P* value
Bektas-Kayhan K	67	56	6	94	45	1	190	68	233	47	0.07
Chen MK	49	112	55	80	172	92	210	222	332	356	0.98
Hsin-Hung Wu	16	52	18	33	132	88	84	88	198	308	0.13
Kruszyna L	89	54	17	154	145	24	232	88	453	193	0.2
Kucukgergin C	78	67	11	64	71	17	223	89	205	105	0.68
Kucukgergin C	67	54	21	96	83	18	188	96	275	119	0.99
Narter KF	48	16	8	40	33	3	112	32	113	39	0.23
Singh	83	101	16	81	97	22	267	133	259	141	0.38
Vázquez-Lavista LG	9	35	3	18	71	37	53	41	107	145	0.08
Yang L	34	48	30	10	38	34	116	108	58	106	0.9
Yeh CB	23	48	31	80	172	92	94	110	332	356	0.98

Table 3. Summary of Results from Different Comparative Genetic Models

			GG vs. GA+AA		GG+GA vs. AA		G vs. A	
-2518A/G	N	Case/Control	OR (95%CI)	*P**	OR (95%CI)	*P**	OR (95%CI)	*P**
Total	11	1422/2237	0.89 (0.61, 1.28)	0.52	0.85 (0.68, 1.08)	0.18	0.89 (0.74, 1.06)	0.18
Subgroup by Ethnicity								
Latino	5	716/1223	0.79 (0.63, 0.99)	0.04	0.81 (0.58, 1.14)	0.23	0.83 (0.65, 1.05)	0.13
Asian	5	659/888	1.44 (0.99, 2.08)	0.05	0.91 (0.62, 1.34)	0.64	1.03 (0.77, 1.37)	0.85
Subgroup by cancer type								
Bladder cancer	4	461/599	0.89 (0.32, 2.45)	0.82	0.89 (0.69, 1.16)	0.39	0.88 (0.66, 1.17)	0.38

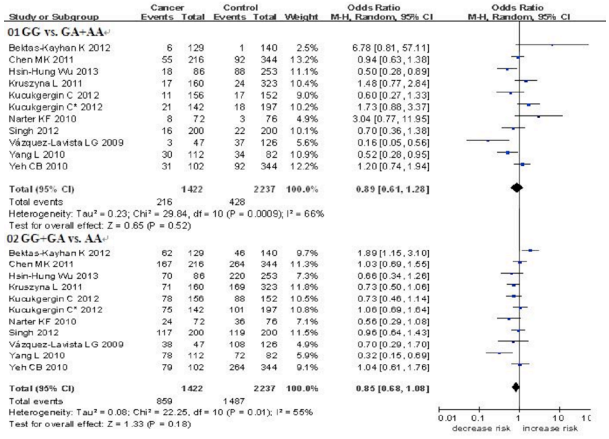

Figure 2. Meta-analysis with A Random-effects Model for the Association Between Cancer Risk and the MCP-1 -2518A/G Polymorphism (GG vs. GA+AA) and (GG vs.GA+ AA)

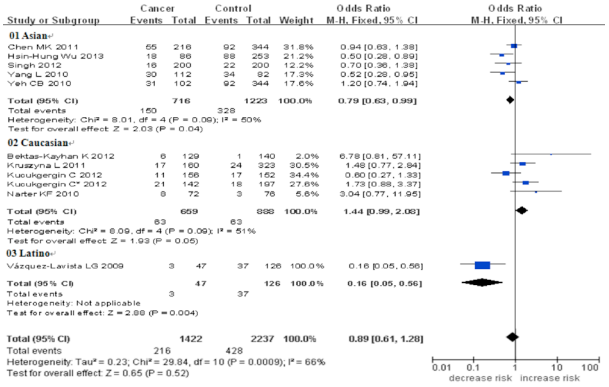

Figure 3. Meta-analysis for the Association Between Cancer Risk and the MCP-1 -2518A/G Polymorphism (GG vs. AA + GA): Subgroup Analysis by Ethnicity. The Asian and Caucasian population subgroups were analyzed by fixed-effect model, while the total was analyzed by random-effect model

Quantitative data synthesis

A total of 1422 cases and 2237 controls in 11 case-control studies were included. We analyzed the heterogeneity of GG vs.GA+ AA for all 11 studies and the value of χ^2 was 29.34 with 10 degrees of freedom and P=0.0009. Thus, we chose the random-effects model to synthesize the data. Overall, OR was 0.89 (95%CI = 0.61–1.28) and the test for overall effect Z value was 0.65 (P = 0.52) for GG vs. GA +AA model (Figure 2). We also analyzed the GG+GA vs. AA model and G vs. A model. OR was 0.85 (95%CI = 0.68–1.08) and the test for overall effect Z value was 1.33 (P = 0.18) for GG+GA vs. AA model (Figure 2), OR was 0.89 (95%CI = 0.74–1.06) and the test for overall effect Z value was 1.33 (P = 0.18) for G vs. A model. These result showed no association between polymorphisms of MCP -2518A/G gene and cancer risk. In the subgroup analysis by ethnicity (GG vs. GA +AA), OR was 0.79 (95%CI = 0.63–0.99, p=0.04) among Asians and was 1.44 (95%CI = 0.99–2.08, p=0.05) among Caucasian (Figure 3). The results suggested that the GG homozygote had a 21% decrease risk of cancer compared with those individuals with GA or AA in Asians. In the subgroup analysis by cancer type, only bladder cancer was investigated in four studies (Vazquez-Lavista et al., 2009; Narter et al., 2010; Kucukgergin et al., 2012b; Singh et al., 2012), and the pooled OR was 0.89 (95%CI = 0.32–2.45, p=0.82) for GG vs. GA +AA model , showed no association.

A summary of results from other comparisons is listed in Table 3.

Publication bias

Publication bias was analyzed by using the Begg's funnel plots and and Egger's test. The shape of the funnel plots was seemed symmetrical in the GG vs. GA+AA comparison genetic model, suggesting the absence

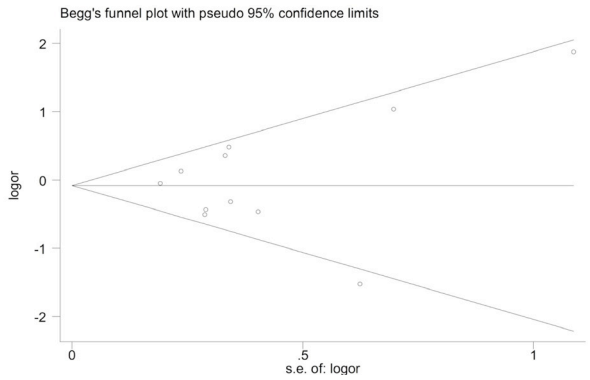

Figure 4. Begg's Funnel Plot for Publication Bias in Selection of Studies on the MCP-1 -2518A/G Polymorphism (GG vs. AA + GA)

of publication bias (Figure 4). The Egger's test was performed to provide statistical evidence of funnel plot asymmetry. The result indicated a lack of publication bias (t=0.40, *P*=0.700).

Discussion

It is proved that chronic inflammation is known to be associated with the development and progression of different types of cancer. Chemokines, which play an important role in inflammation, are families of cytokines that are important mediators of leukocyte trafficking (Yoshie et al., 2001). MCP-1 is a member of the C–C beta chemokine family that is produced by macrophages, fibroblasts, and endothelial cells to stimulate chemo taxis of monocyte/macrophages and other inflammatory cells. A growing number of studies have studied the relationship between polymorphism and cancer risk. However, the results from different published studies were inconsistent. Thus, we performed this meta-analysis to comprehensively analyze these associations. To our knowledge, this is the first meta-analysis to date investigating the association between the MCP-1 -2518A/G polymorphism and cancer risk.

The present meta-analysis indicated that the polymorphism of MCP-1 -2518A/G gene had no association with cancer risk. We analysis several models, including codominant model and recessive model, but found no association between polymorphism and cancer risk. The present study included kinds of cancer, which may influence the result, so we did a subgroup analysis of bladder cancer. However, the result indicated no association as well.

Ethnicity is one of the important factors for the development of cancer; different cancer pathogenesis is inherited among different ethnic populations. In this meta-analysis, data were also stratified by ethnicities. A significant association was found among Asians but not in Caucasians, indicating the importance of ethnic differences for this polymorphism among different ethnic populations. However, when we analyzed the Caucasians population, OR was 1.44 and p value was 0.05, indicating a potential association and had a increase cancer risk, which was contrary to Asian population.

The objective of a meta-analysis is to integrate the results from comparable studies on the same topic, in order to increase sample size and statistical power, and to draw more valid conclusions. However, there are several confounding factors that may influence the results of a meta-analysis, including publication bias and quality of the analysis. Therefore, strict inclusion and exclusion criteria were used in order to reduce selection bias. Only those studies published as articles were included. In this study, publication bias was analyzed by Begg's funnel plots and Egger's test. We did not detect a significant publication bias, suggesting our results may be reliable.

We should mention the importance of heterogeneity and publication bias, which may affect the reliability of results in meta- analysis. Significant heterogeneity existed in overall comparisons and subgroup analysis, which may affect the result. Possible reasons of heterogeneity included different kinds of cancers, ethnicity and bias of selected cases. There was significant heterogeneity in the overall comparisons, which may weaken the corresponding conclusions. When subgroup analyses by ethnicity, the heterogeneity among Asian and Caucasian populations was effectively reduced or removed. Possible explanations may be the differences in genetic backgrounds and environmental exposures among populations of different ethnicities. Other possible reasons of heterogeneity included different kinds of cancers and bias of selected cases.

Some limitations should be discussed in this meta-analysis. First, only published studies in the selected databases were included in this meta-analysis. Thus, it is possible that some studies that were not included in these databases or some unpublished studies with null results were not identified, and this may bias our results. Second, due to the limitation of original information, we could not analyze gene-gene and gene-environment interactions. Third, most of the included studies were from Asian and Caucasian populations; thus, these results may be applicable to only these ethnic groups, and additional studies are warranted to evaluate the effect of this functional polymorphism on cancer risk in different populations, especially in Africans. Fourth, the sample sizes of several included studies are rather small and they do not have adequate ability to assess the association between the -2518A/G polymorphism in the MCP-1 gene and cancer risk, and may affect the statistical power to detect publication bias. However, there are also several advantages in this meta-analysis. First, a meta-analysis of the association of MCP-1 -2518A/G polymorphism with cancer risk is statistically more powerful than any single study. Second, the methodological issues for meta-analysis such as heterogeneity, publication bias, and stability of results were all well investigated.

To our knowledge, this is the first meta-analysis that has assessed the relationship between the -2518A/G polymorphism in the MCP-1 gene and cancer risk. Our results indicated that the -2518A/G polymorphism was significantly associated with decreased risk of cancer among Asian population, and which maybe contrary among Caucasian population. In the future, additional case-control studies should be performed to validate our findings.

Acknowledgements

We are indebted to the authors of the primary studies included in this meta-analysis; without their contributions, this work would not have been possible. In addition, we are grateful to Mrs. Jiuling Guo and to Mr. Jiuchang Guo for kindly giving suggestions on how to revise the manuscript.

References

Attar R, Agachan B, Kuran SB, et al (2010). Association of CCL2 and CCR2 gene variants with endometrial cancer in Turkish women. *In Vivo*, **24**, 243-8.

Balkwill F, Mantovani A (2001). Inflammation and cancer: back to Virchow? *Lancet*, **357**, 539-45.

Bektas-Kayhan K, Unur M, Boy-Metin Z, Cakmakoglu B (2012). MCP-1 and CCR2 gene variants in oral squamous cell carcinoma. *Oral Dis*, **18**, 55-9.

Chen MK, Yeh KT, Chiou HL, et al (2011). CCR2-64I gene polymorphism increase susceptibility to oral cancer. *Oral Oncol*, **47**, 577-82.

Gu H, Ni M, Guo X, et al (2011). The functional polymorphism in monocyte chemoattractant protein-1 gene increases susceptibility to gastric cancer. *Med Oncol*, **28**, S280-5.

Hanahan D, Weinberg RA (2000). The hallmarks of cancer. *Cell*, **100**, 57-70.

Kruszyna L, Lianeri M, Rubis B, et al (2011). CCL2 -2518 A/G single nucleotide polymorphism as a risk factor for breast cancer. *Mol Biol Rep*, **38**, 1263-7.

Kucukgergin C, Isman FK, Cakmakoglu B, Sanli O, Seckin S (2012a). Association of polymorphisms in MCP-1, CCR2, and CCR5 genes with the risk and clinicopathological characteristics of prostate cancer. *DNA Cell Biol*, **31**, 1418-24.

Kucukgergin C, Isman FK, Dasdemir S, et al (2012b). The role of chemokine and chemokine receptor gene variants on the susceptibility and clinicopathological characteristics of bladder cancer. *Gene*, **511**, 7-11.

Mantovani A, Allavena P, Sica A, Balkwill F (2008). Cancer-related inflammation. *Nature*, **454**, 436-44.

Narter KF, Agachan B, Sozen S, Cincin ZB, Isbir T (2010). CCR2-64I is a risk factor for development of bladder cancer. *Genet Mol Res*, **9**, 685-92.

O'Hayre M, Salanga CL, Handel TM, Allen SJ (2008). Chemokines and cancer: migration, intracellular signalling and intercellular communication in the microenvironment. *Biochem J*, **409**, 635-49.

Rollins BJ, Walz A, Baggiolini M (1991). Recombinant human MCP-1/JE induces chemotaxis, calcium flux, and the respiratory burst in human monocytes. *Blood*, **78**, 1112-6.

Rovin BH, Lu L, Saxena R (1999). A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. *Biochem Biophys Res Commun*, **259**, 344-8.

Saenz-Lopez P, Carretero R, Cozar JM, et al (2008). Genetic polymorphisms of RANTES, IL1-A, MCP-1 and TNF-A genes in patients with prostate cancer. *BMC Cancer*, **8**, 382.

Shi CL, Yu CH, Zhang Y, et al (2011). Monocyte chemoattractant protein-1 modulates invasion and apoptosis of PC-3M prostate cancer cells via regulating expression of VEGF, MMP9 and caspase-3. *Asian Pac J Cancer Prev*, **12**, 555-9.

Singh V, Srivastava P, Srivastava N, et al (2012). Association of inflammatory chemokine gene CCL2I/D with bladder cancer risk in North Indian population. *Mol Biol Rep*, **39**, 9827-34.

Vazquez-Lavista LG, Lima G, Gabilondo F, Llorente L (2009). Genetic association of monocyte chemoattractant protein 1 (MCP-1)-2518 polymorphism in Mexican patients with transitional cell carcinoma of the bladder. *Urology*, **74**, 414-8.

Wu HH, Lee TH, Tee YT, et al (2013). Relationships of Single Nucleotide Polymorphisms of Monocyte Chemoattractant Protein 1 and Chemokine Receptor 2 With Susceptibility and Clinicopathologic Characteristics of Neoplasia of Uterine Cervix in Taiwan Women. *Reprod Sci*.

Yang L, Shi GL, Song CX, Xu SF (2010). Relationship between genetic polymorphism of MCP-1 and non-small-cell lung cancer in the Han nationality of North China. *Genet Mol Res*, **9**, 765-71.

Yeh CB, Tsai HT, Chen YC, et al (2010). Genetic polymorphism of CCR2-64I increased the susceptibility of hepatocellular carcinoma. *J Surg Oncol*, **102**, 264-70.

Yoshie O, Imai T, Nomiyama H (2001). *Chemokines in immunity. Adv Immunol*, **78**, 57-110.