Elevated matrix metalloproteinase-9 expression may contribute to the pathogenesis of bladder cancer

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Abstract. The present study investigated the potential association between matrix metalloproteinase-9 (MMP-9) expression and the pathogenesis of bladder cancer. The present study reviewed previous studies published in Chinese and English using predefined selection criteria, which identified high-quality studies concerning MMP-9 and bladder cancer. Statistical analyses of the data were conducted using Comprehensive Meta-Analysis software version 2.0. In total, 23 case-control studies were selected, which consisted of 1,040 bladder cancer patients and 244 healthy controls. The expression rates and protein levels of MMP-9 were significantly increased in bladder cancer patients compared with the healthy controls, which was demonstrated using immunohistochemistry (IHC) and enzyme-linked immunosorbent assay-based methods. Furthermore, the expression rate of MMP-9 in histological G1/G2 grade bladder cancer tumors was significantly decreased compared with G3 tumors. Subgroup analysis based on ethnicity demonstrated that the rate of MMP-9 protein expression between bladder cancer patients and healthy controls was significantly different in African, Asian and Caucasian patients, which was identified using IHC. The MMP-9 protein levels in bladder cancer patients and healthy controls were significantly different between Asian and Caucasian patients, but not African patients. The differences between MMP-9 expression in ethnic groups were also evident in the expression rate of MMP-9 identified in histological G1/G2 grade tumors in Asian and Caucasian patients compared with G3 grade tumors, which was not evident in African patients. In conclusion, the present meta-analysis results markedly indicate that MMP-9 expression is associated with clinicopathological features of bladder cancer, suggesting that MMP-9 may be a useful biomarker in the diagnosis and clinical management of bladder cancer, and may be a valuable therapeutic target.

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Abbreviations: ELISA, enzyme-linked immunosorbent assay; MMP, matrix metalloproteinase; IHC, immunohistochemistry; OR, odds ratio; CI, confidence interval

Key words: bladder cancer, matrix metalloproteinase-9, expression, association, meta-analysis, matrix metalloproteinase

Introduction

Worldwide, bladder cancer is the 7th most common cancer in men and the 17th most common cancer in women (1). Notably, in the developed world, bladder cancer ranks as the 4th and 9th most common cancer in men and women, respectively (2). An estimated 375,000 bladder cancer cases are reported each year around the world, with 68,810 novel cases and ~14,100 mortalities reported in the United States in 2013 (3). Transitional cell carcinoma is the most frequently occurring type of bladder cancer. Other bladder cancer types consist of adenocarcinoma, squamous cell carcinoma and small cell bladder cancer (4,5). Notably, the incidence of bladder cancer increases with age, particularly in men (6). Bladder cancer arises as a result of multistep alterations, among which metastasis is crucial (7). Epidemiological studies have demonstrated that several environmental factors may contribute to bladder cancer risk, including smoking, chronic inflammation, radiation exposure, anticancer drugs and aromatic amines, which are contained in dyes (6,8). The treatment of bladder cancer is based on multiple parameters, including the extent of the disease, bladder cancer stage and the results of a bladder cystoscopy, which evaluates the tumor (9). The currently available treatments are not effective and the mechanisms of initiation and progression of bladder cancer remain unresolved due to a lack of effective early diagnostic tools and clinical prognostic markers (10). Nevertheless, previous studies have identified a few markers that are associated with bladder cancer progression, including the tumor stage, grade, invasion, growth and metastasis (11). However, additional molecular targets that accurately predict bladder cancer progression are urgently required.

The matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases with proteolytic activity against extracellular matrix components (12), are involved in numerous physiological processes, including tissue remodeling, embryonic development and reproduction (13). However, the overexpression of MMPs is also observed in

several diseases (14). The levels of particular MMPs, including the interstitial collagenase MMP-1, stromelysin-1 MMP-3, gelatinases MMP-2 and MMP-9 and stromelysin-3 MMP-11, are increased in tumor tissues, and promote the invasion of malignant cells, regulate tumor growth and metastasis and are associated with a poor overall survival rate (15). MMP-9 has multiple substrates; however, collagen type IV, the main component of basement membranes, is the most crucial MMP-9 substrate in a tumor microenvironment (16). The proteolytic activity of MMP-9 against collagen type IV not only promotes invasion and metastasis, but also releases matrix-bound growth factors and other signaling molecules to promote growth signaling, angiogenesis and an inflammatory response (9,17). Previous studies have revealed that MMP-9 is involved in the pathogenesis of bladder cancer (3,9,15,18); however, alternative studies fail to establish an association between MMP-9 expression and bladder cancer, leading to the conclusion that MMP-9 may not be an effective marker for bladder cancer detection (19,20). Due to the conflicting results of previous studies, the present study investigated the association between MMP-9 and the pathogenesis of bladder cancer using a retrospective meta-analysis.

Materials and methods

Literature search. The present study conducted a systematic literature search of studies published prior to October 2014, using PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD, USA), EBSCO Industries, Inc. (Birmingham, AL, USA), Ovid (New York, NY, USA), SpringerLink (Berlin, Germany), Wiley (London, UK), Web of Science (New York, NY, USA), Wanfang (Beijing, China), China National Knowledge Infrastructure (Beijing, China) and Chongqing VIP Information Co., Ltd (Chongqing, China) databases. The literature search was restricted to retrieving studies published in Chinese and English. The following search keywords were used: Matrix metalloproteinase; MMP; bladder cancer; urinary bladder neoplasms; neoplasms; bladder; malignant tumor of urinary bladder; cancer of bladder; bladder tumors; and urinary bladder cancer.

Study selection criteria. Published studies were selected based on the following inclusion criteria: The studies were case-control studies; the case group contained pathology-verified bladder cancer patients and the control group consisted of healthy individuals; the detection methods were enzyme-linked immunosorbent assays (ELISA) and immunohistochemistry (IHC); and the end results were defined as expression rates and protein levels of MMP-9 in bladder cancer tissues. The exclusion criteria were as follows: Studies that were letters, reviews and meta-analyses; studies that were not associated with MMP-9 and bladder cancer; non-human studies; and studies with incomplete data. When there were multiple studies written by the same author, the study with the most applicable information and largest number of cases was used.

Statistical analysis. Odds ratio (OR) at 95% confidence intervals (CI) were calculated using the fixed or random effects model. The significance of the overall effect size was estimated by the Z-test (21). Forest plots were created to demonstrate the differences in the OR at 95% CI between groups. The heterogeneity was assessed using a Galbraith radial plot (22) and Cochran's Q-test (21); heterogeneity was regarded as $P_h<0.05$. A Galbraith radial plot is a scatter plot of standardized estimates against reciprocals of standard errors, possibly with respect to a transformed scale, designed so that the original estimates may be compared and interpreted. Heterogeneity is indicated if the dot lies beyond the 95% CI, otherwise no heterogeneity existed. In addition, I^2 test was used to evaluate the degree of heterogeneity (24). If there was heterogeneity among studies ($P_h<0.05$ or $I^2>50\%$), a random effects model was applied; otherwise a fixed effects model was used (25). Sensitivity analysis was conducted to estimate the effects of a single study on the overall results. Publication bias was evaluated by classic fail-safe N, funnel plots and Egger's test (26-28). All statistical analyses were performed using Comprehensive Meta-Analysis software version 2.0 (Biostat, Inc., Englewood, NJ, USA).

Results

Baseline characteristics. The present literature search initially retrieved 358 relevant articles, 132 of which were studies published in Chinese and 253 were studies published in English. In total, 299 of the studies were not included, as follows: Duplicates, n=8; letters or reviews, n=12; non-human studies, n=15; and not relevant to the present study topic, n=264. The full text of the remaining studies (n=86) was reviewed. Additional studies were excluded as they were not case-control or cohort studies (n=19), were irrelevant to the present study (n=4) or possessed incomplete data (n=1). Overall, 23 case-control studies (15,18-20,29-47), published between 1998 and 2014, were selected for meta-analysis, and consisted of 1,040 bladder cancer patients and 244 healthy control individuals. Among the 23 studies, the study subjects in 3 studies were African, 14 studies enrolled Asian subjects and 6 studies enrolled Caucasian subjects. All sample sources from the study subjects were tissues, and the detection methods consisted of ELISA and IHC. Baseline characteristics of the studies are presented in Table I.

Association between MMP-9 and bladder cancer. The results of the Galbraith radial plot and Cochran's Q-test demonstrated that the OR estimates for all included studies were within the 95% CI of the OR from the main analysis, suggesting no heterogeneity existed in the rate of MMP-9 protein expression between bladder cancer patients and healthy control individuals (case vs. control, $P_h=0.448$ and $I^2=0.430\%$; histological G1/G2 vs. G3 grade, $P_h=0.357$ and $I_2=8.58\%$). Therefore, a fixed effects model was applied. The MMP-9 protein levels demonstrated heterogeneity between bladder cancer patients and healthy control individuals, with 4 studies beyond the 95% CI ($P_h<0.001$ and $I^2=95.212\%$). Therefore, a random effects model was used (Fig. 1). Meta-analysis results demonstrated that the expression rates of MMP-9 in bladder cancer patients were significantly increased compared with the healthy control individuals (OR, 18.589; 95% CI, 11.630-29.711; P<0.001). MMP-9 protein levels in patients with bladder cancer were markedly higher compared with the healthy control individuals, which was at a statistically significant level [standardized mean difference

Table I. Characteristics of studies on the levels of MMP-9 protein expression in bladder cancer patients and healthy control individuals, and the expression levels of MMP-9 in patients with a histological G1/G2 grade tumor compared with patients with a G3 grade tumor.

First author, year (Ref.)	Country	Diagnosis	Detection method	Mean (range) age, years	Gender, n		Positive MMP-9 expression, n		Histological grade of tumors, n		MMP-9 levels, μg/l		Ref.
					Male	Female	Patients	Controls	G1/G2	G3	Patients	Controls	
Zhao *et al*, 2014	China	BUCC	IHC	62.2 (37-81)	48	12	60	15	47	13	0	0	(29)
Eissa *et al*, 2013	Egypt	BUCC	IHC	61.5 (26-83)	35	11	46	20	36	10	0	0	(15)
Ramón de Fata *et al*, 2013	Spain	BC	ELISA	NA	NA	NA	0	0	0	0	31	11	(41)
Gunes *et al*, 2013	Turkey	BC	ELISA	57.0 (40-67)	57	33	0	0	0	0	90	40	(18)
Zheng *et al*, 2012	China	BTCC	IHC	62.7 (30-84)	24	16	40	10	28	12	0	0	(42)
Urquidi *et al*, 2012	USA	BC	ELISA	69.5 (22-90)	55	9	0	0	0	0	64	63	(19)
Goodison *et al*, 2012	USA	BC	ELISA	69.5 (22-90)	55	9	0	0	0	0	64	41	(20)
Chen *et al*, 2011	China	BUCC	IHC	57.9 (37-76)	53	26	79	18	58	21	0	0	(39)
Zhang *et al*, 2010	China	BC	IHC	(43-72)	44	10	54	15	38	16	0	0	(36)
Zhu *et al*, 2009	China	BTCC	IHC	62.7 (30-84)	24	16	40	10	28	12	0	0	(47)
Zhu *et al*, 2009	China	BTCC	IHC	(38-72)	32	14	46	14	35	11	0	0	(33)
Zhang *et al*, 2009	China	BTCC	IHC	59.2 (35-76)	52	13	65	10	45	20	0	0	(34)
Eissa *et al*, 2007	Egypt	BC	ELISA	57.0 (25-82)	104	50	154	30	0	0	0	0	(31)
Tang *et al*, 2007	China	BTCC	ELISA	59.0 (27-78)	65	21	86	10	62	24	0	0	(45)
Zhong *et al*, 2006	China	BTCC	ELISA	56.4 (31-76)	31	7	0	0	0	0	38	16	(46)
Wu *et al*, 2005	China	BTCC	IHC	64.5 (31-80)	48	8	56	5	40	16	0	0	(43)
Sun *et al*, 2005	China	BTCC	ELISA	(32-80)	54	14	68	10	48	20	38	20	(44)
Wang *et al*, 2004	China	BC	IHC	58.0 (26-84)	50	15	65	19	45	20	0	0	(38)
Guo *et al*, 2004	China	BTCC	IHC	57.2	44	10	54	10	37	17	0	0	(37)
Eissa *et al*, 2003	Egypt	BC	ELISA	58.0 (30-78)	NA	NA	73	21	22	38	0	0	(32)
Nutt *et al*, 2003	UK	BC	ELISA	NA	NA	NA	28	12	0	0	0	0	(40)
Guan *et al*, 2003	China	BTCC	ELISA	62.0	37	15	0	0	0	0	52	32	(35)
Bianco *et al*, 1998	USA	BC	NA	(40-89)	51	14	26	15	10	16	0	0	(30)

The patient group had increased MMP-9 protein levels and positive MMP-9 expression compared with control group. MMP-9, matrix metalloproteinase-9; BUCC, bladder uroepithelium cell carcinoma; BC, bladder cancer; BTCC, transitional cell carcinoma of the bladder; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay; NA, not avaliable.

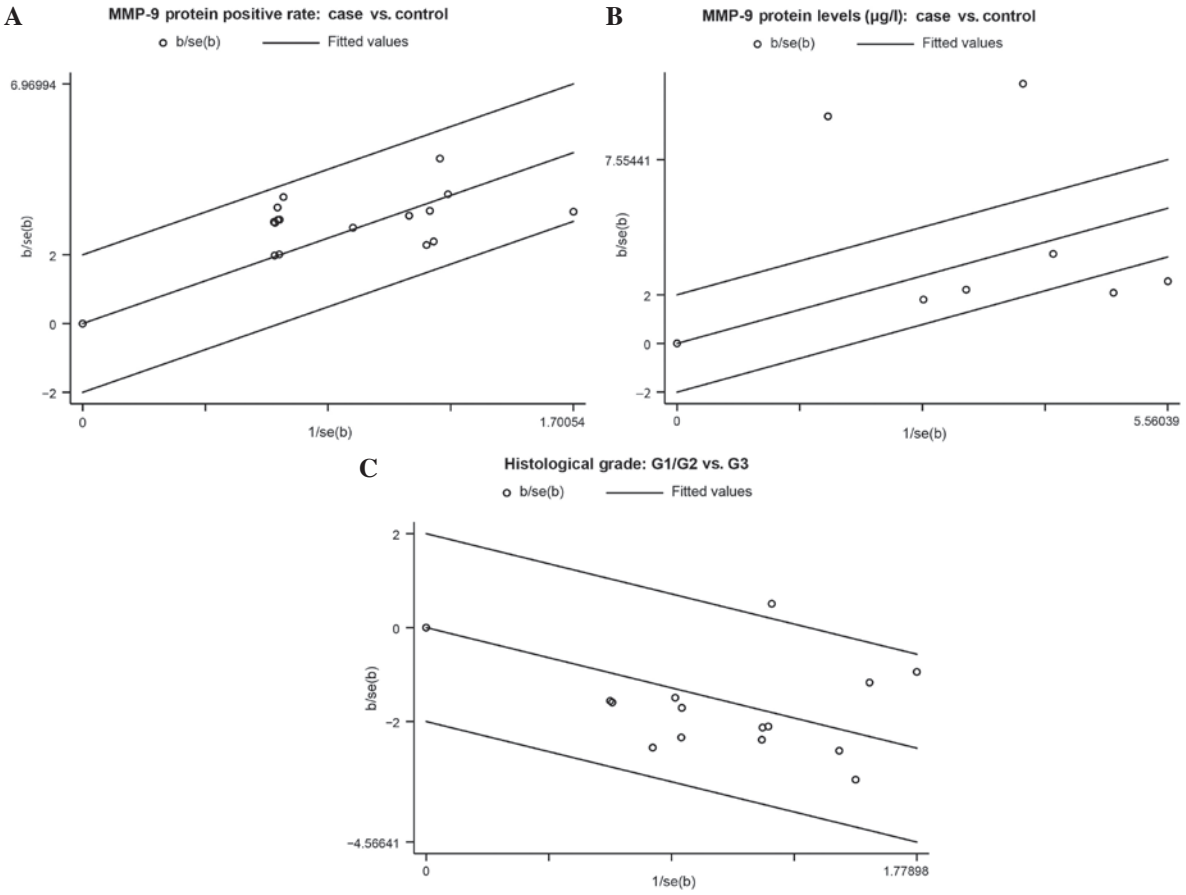


Figure 1. Galbraith radial plots for the heterogeneity of studies in terms of the association between (A) the expression rate and (B) protein levels of MMP-9 and the pathogenesis of bladder cancer, and (C) the expression rate of MMP-9 and the histological grade G1/G2 and G3 of tumors. MMP-9, matrix metalloproteinase-9.

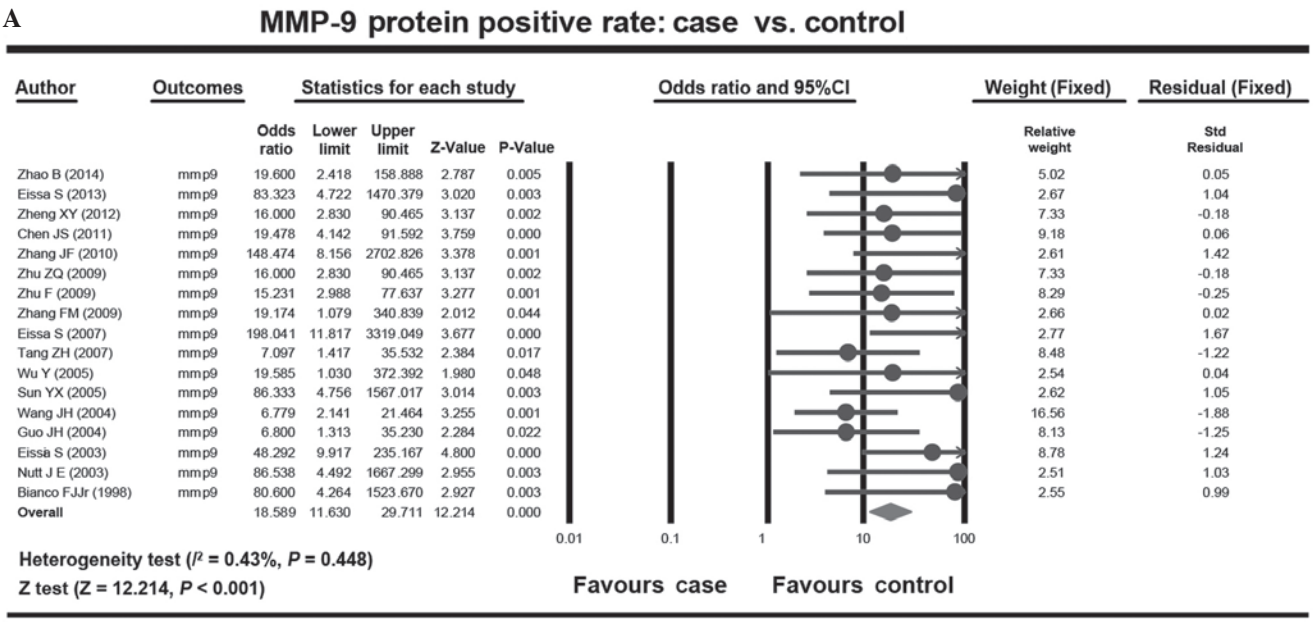
(SMD), 1.517; 95% CI, 0.631-2.403; P=0.001]. Furthermore, among histological grades, the expression rates of MMP-9 in tumor histological G1/G2 grade was significantly decreased compared with G3 grade (OR, 0.236; 95% CI, 0.154-0.362; P<0.001; Fig. 2). Subgroup analysis based on ethnicity demonstrated that the rates of MMP-9 protein expression between bladder cancer patients and healthy controls were significantly different in African (OR, 18.022; 95% CI, 5.074-64.010; P<0.001), Asian (OR, 16.433; 95% CI, 9.760-27.668; P<0.001) and Caucasian patients (OR, 133.553; 95% CI, 17.352-1027.937; P<0.001). The MMP-9 protein levels in bladder cancer patients and healthy controls were significantly different in Asian (SMD, 2.256; 95% CI, 0.168-4.345; P=0.034) and Caucasian (SMD, 1.060; 95% CI, 0.003-2.117; P=0.049) study subjects. Furthermore, the expression rates of MMP-9 between G1/G2 and G3 tumors demonstrated significant differences in Asian (OR, 0.175; 95% CI, 0.107-0.288; P<0.001) and Caucasian patients (OR, 0.044; 95% CI, 0.004-0.484; P=0.011), while there was no clear difference in African patients (OR, 0.803; 95% CI, 0.326-1.975; P=0.632; Fig. 3).

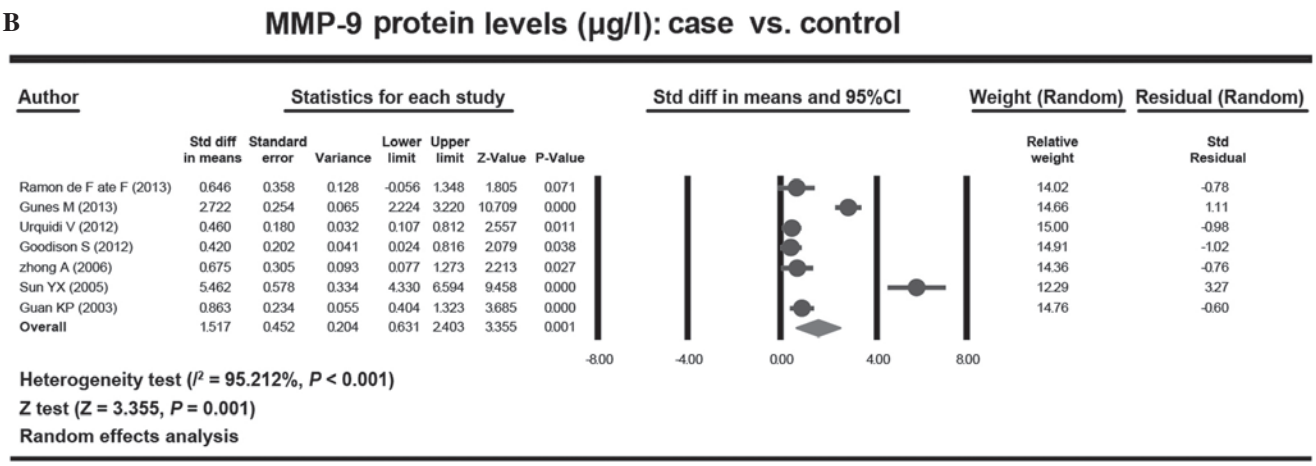
The results of the sensitivity analysis suggested that no study had a significant effect on the polled OR (Fig. 4). The funnel plot demonstrated no evidence of clear asymmetry, suggesting no publication bias regarding the MMP-9 protein levels in bladder cancer patients and healthy individuals. This was additionally confirmed by classic fail-safe N and the Egger's test (P=0.11). The funnel plot, classic fail-safe N and Egger's test demonstrated the existence of a publication bias regarding the expression rates of MMP-9 in bladder cancer patients compared with the expression rates in the healthy control individuals (P<0.05). Furthermore, publication bias in the selected studies, regarding the expression rates of MMP-9 in histology G1/G2 tumor grade and G3 grade, were identified (P<0.05; Fig. 5).

Discussion

In the developed world, bladder cancer is the 4th most common malignancy among men (2). Epidemiological studies have demonstrated that several environmental factors may increase the risk of bladder cancer, including smoking, chronic inflammation, radiation exposure, anticancer drugs and aromatic amines, which are contained in dyes (2,6).

The present study conducted a meta-analysis to investigate the association between MMP-9 and bladder cancer. The present results revealed that the expression rates of MMP-9 in bladder cancer patients were significantly increased compared with the expression rates in the healthy control individuals, suggesting that the MMP-9 protein is associated with the pathogenesis of bladder cancer. Furthermore, MMP-9 protein levels in patients with bladder cancer were significantly increased compared with the protein levels in the healthy control individuals, suggesting that the MMP-9 protein may be associated with a risk of bladder cancer. MMPs degrade various components of the extracellular matrix, which is important in numerous biological processes, including embryogenesis and





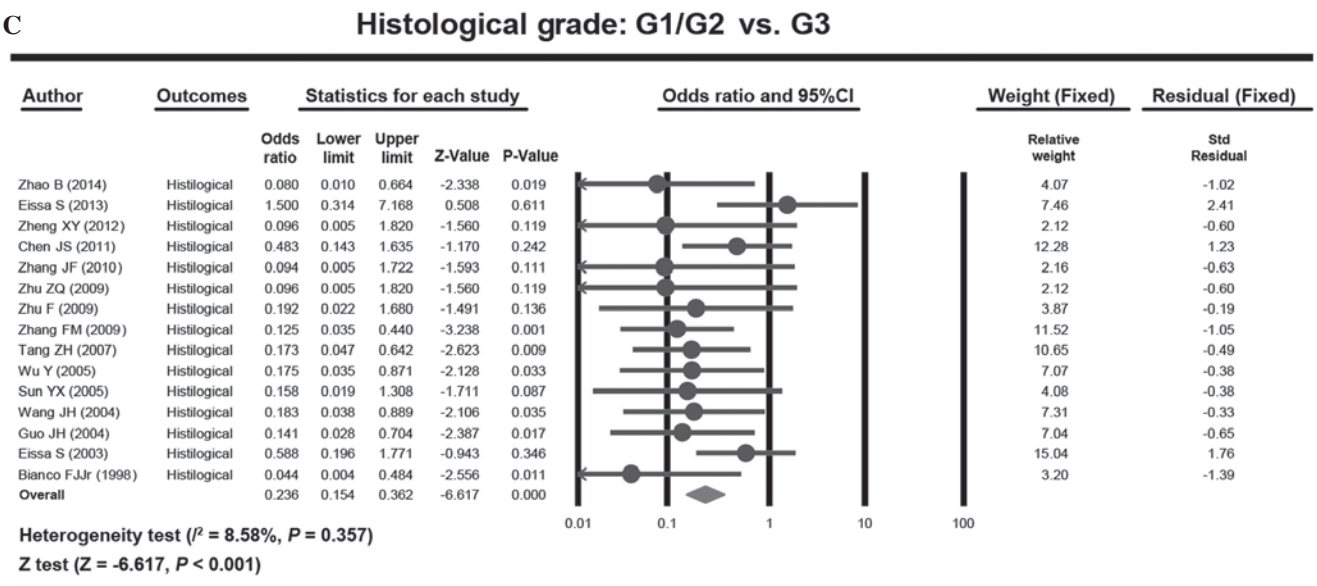


Figure 2. Forest plots of (A) the expression rate and (B) protein levels of MMP-9 in bladder cancer patients and healthy controls, and (C) the expression rate of MMP-9 between patients with histological grade G1/G2 and G3 tumors. MMP-9, matrix metalloproteinase-9; CI, confidence interval.

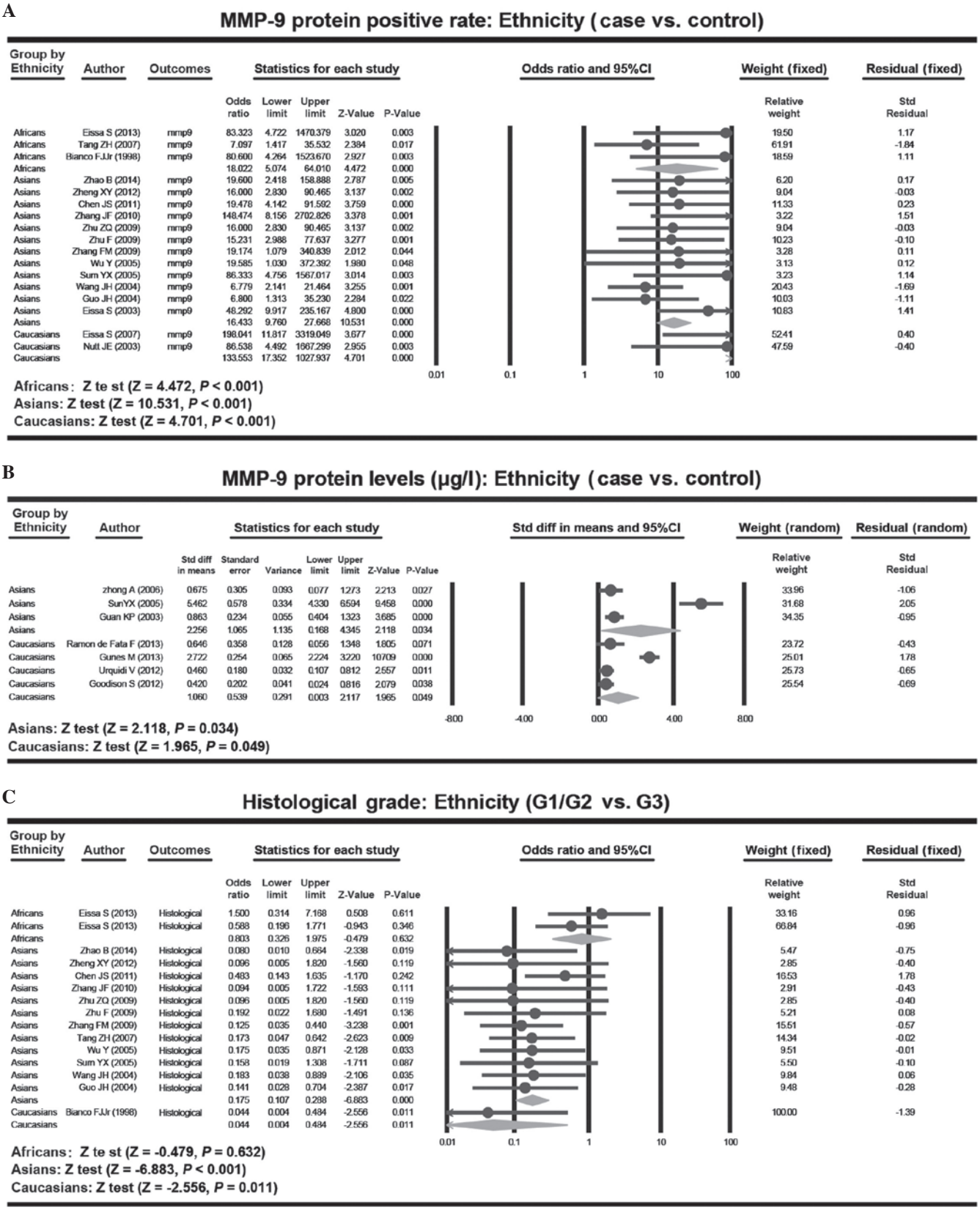


Figure 3. Forest plots of the ethnicity subgroup analyses for (A) the expression rate and (B) protein levels of MMP-9 in bladder cancer patients and healthy controls, and (C) the expression rate of MMP-9 in patients with histological grade G1/G2 and G3 tumors. MMP-9, matrix metalloproteinase-9; CI, confidence interval.

tissue repair (48). However, the degradation of the extracellular matrix has severe adverse consequences in pathological conditions; for instance, the increased expression and activity of MMP-2 have been reported in a variety of pathological cardiovascular conditions, including hypertension (49-51). Previous studies indicate that MMPs may not only be involved in promoting invasion and metastasis, but are vital in the majority of steps leading to cancer development (52-54).

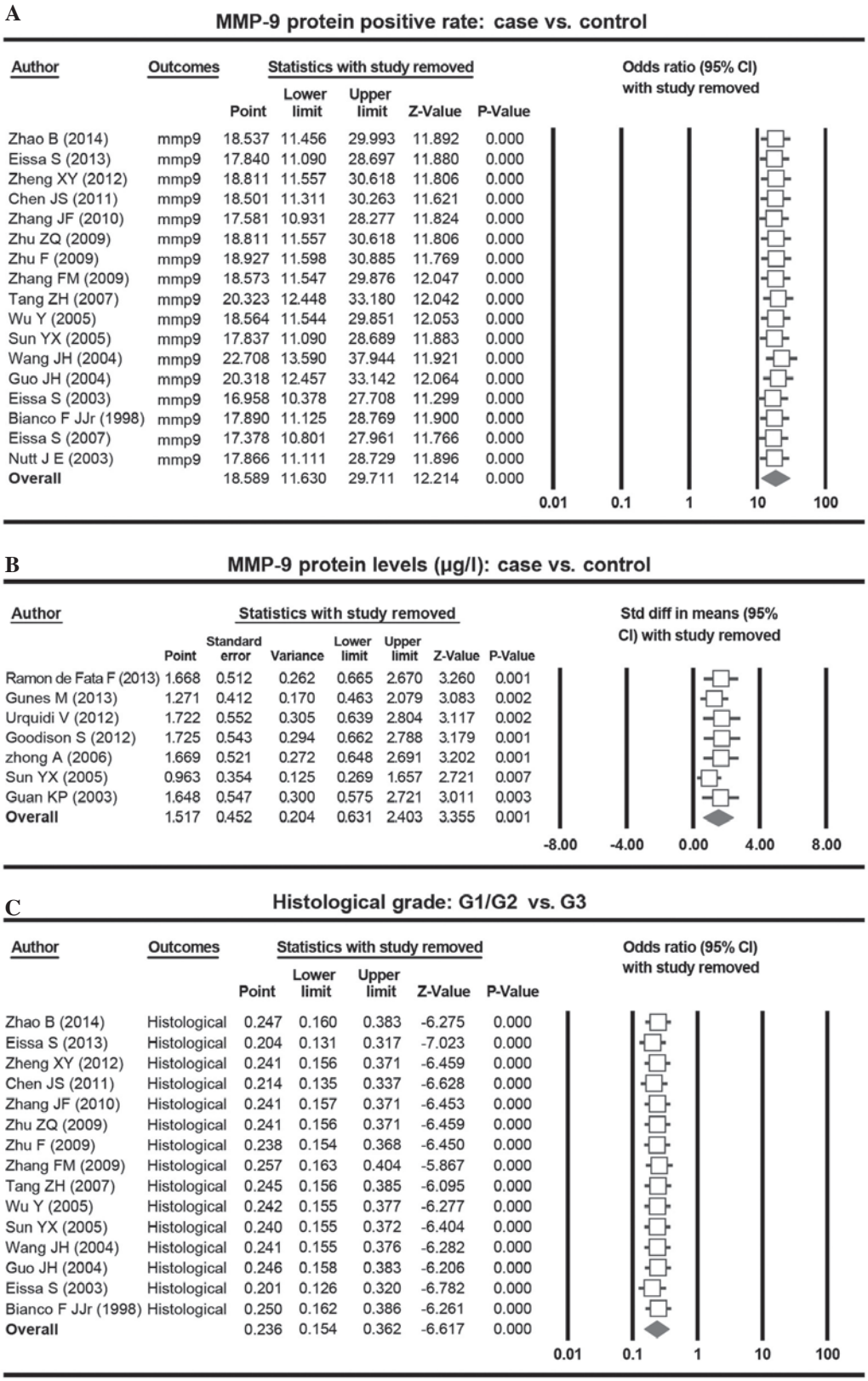


Figure 4. Sensitivity analysis of the differences in the (A) expression rate and (B) protein levels of MMP-9 in bladder cancer patients and healthy controls, and (C) the expression rate of MMP-9 in patients with histological grade G1/G2 and G3 tumors. MMP-9, matrix metalloproteinase-9; CI, confidence interval.

Tumor cells overproduce MMP-9, leading to the degradation of type IV collagen and the basement membrane, which disrupts tissue architecture and function (55). The present findings are consistent with previous studies, which suggested that MMP-9 plays a role in bladder cancer (56,57). The present study identified that the expression rates of MMP-9 in bladder cancer patients was significantly increased compared with healthy control individuals (6,9).

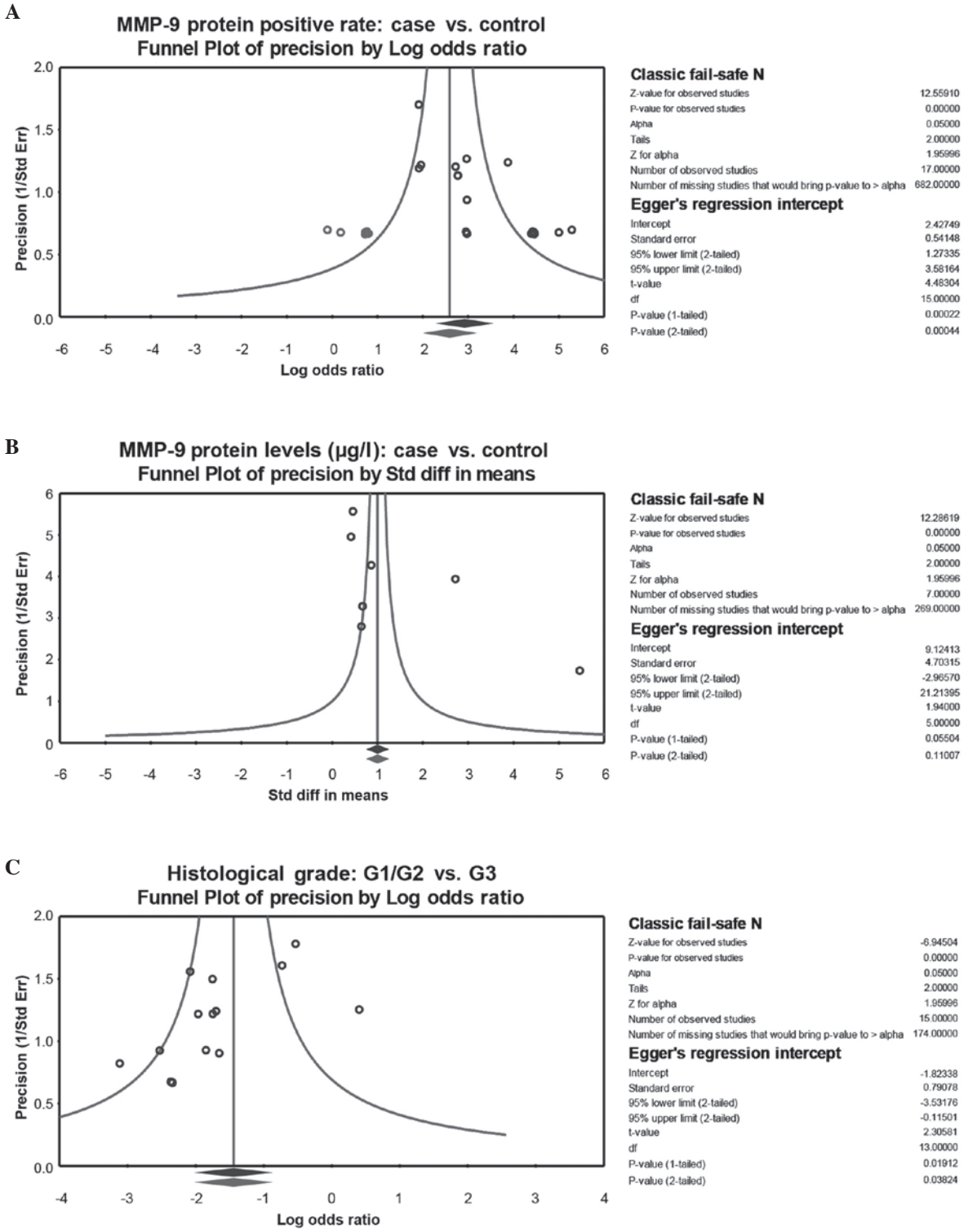


Figure 5. Funnel plot of publication biases on (A) the expression rate and (B) protein levels of MMP-9 in bladder cancer patients and healthy control individuals, and (C) the expression rate of MMP-9 in patients with histological grade G1/G2 and G3 tumors. Std diff, standard deviation; Std Err, standard error; df, degrees of freedom; MMP-9, matrix metalloproteinase-9.

The role of MMPs in tumor progression, angiogenesis and in various inflammatory diseases is well documented (54,58). MMP-9 is mainly expressed by macrophages, neutrophils and mast cells (41). The inflammatory response is often associated with advanced neoplasia, which may also induce the overproduction of MMP-9 (59). The present results suggest that the serum MMP-9 level is an important molecular biomarker, which may identify the initiation and predict the progression of bladder cancer. In addition to the elevated MMP-9 levels identified in bladder cancer tissue, the present study observed that the MMP-9 levels were significantly increased in patients with higher grade tumors. Therefore, MMP-9 is associated with the clinicopathological features of bladder cancer.

The present study also conducted subgroup analysis based on ethnicity. The present results revealed that the rate of MMP-9 protein expression between bladder cancer patients and healthy control individuals was significantly different in African, Asian and Caucasian patients. However, the MMP-9 protein levels in bladder cancer patients and healthy control individuals were significantly different between Asian and Caucasian study subjects, but not between Asian or Caucasian and African study subjects. The expression rate of MMP-9 between G1/G2 and G3 grade tumors was similar, which may be due to the small sample size in the present meta-analysis.

There are limitations in the present meta-analysis that should be acknowledged. First, the sample size was relatively small; therefore the present results lacked sufficient statistical power to fully investigate the association between MMP-9 expression and the pathogenesis of bladder cancer. Second, of the 23 eligible studies, the majority of studies (n=14) were performed using the Chinese population, therefore indicating selection bias. Additional studies using a larger sample size are required to provide a more accurate statistical analysis that is representative of the world population.

In conclusion, the results of the present meta-analysis demonstrated that MMP-9 is associated with the clinicopathological features of bladder cancer, suggesting that MMP-9 may be used in combination with other tumor-specific markers, which may improve the sensitivity of diagnosis and treatment of bladder cancer.

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