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ORIGINAL RESEARCH

# Association between the polymorphisms of urokinase plasminogen activation system and cancer risk: a meta-analysis

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**Purpose:** The present study aimed to investigate the potential association between the urokinase plasminogen activation (uPA) system polymorphisms (rs4065, rs2227564, and rs344781) and cancer risk.

**Methods:** An extensive search was performed to identify published case–control studies on the association between the uPA system polymorphisms and cancer risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the relationship between the uPA system polymorphisms and cancer risk.

**Results:** A total of 20 studies comprising 7,037 cancer cases and 10,094 controls were identified and included in the present meta-analysis. Overall, significantly increased cancer risk was associated with the uPA polymorphism rs4065 (T vs C: OR 1.50, 95% CI: 1.19–1.89; TT vs CC: OR 4.63, 95% CI: 3.10–6.91; dominant model: OR 1.93, 95% CI: 1.60–2.33; recessive model: OR 3.02, 95% CI: 1.26–7.25) and the uPA receptor polymorphism rs344781 (T vs C: OR 1.13, 95% CI: 1.04–1.23; TC vs CC: OR 1.26, 95% CI: 1.06–1.49; TT vs CC: OR 1.35, 95% CI: 1.13–1.63; dominant model: OR 1.29, 95% CI: 1.10–1.52). No significant association was found between the uPA polymorphism rs2227564 and cancer risk. Subgroup analysis suggests that the T allele of the rs4065 (T allele vs C allele: OR 1.50, 95% CI: 1.19–1.89) and rs344781 polymorphisms (T allele vs C allele: OR 1.13, 95% CI: 1.04–1.23) was associated with increased cancer risk in Asians.

**Conclusion:** Our results suggest that the uPA polymorphism rs4065 and the uPA receptor polymorphism rs344781 are associated with increased cancer risk.

**Keywords:** uPA system, polymorphisms, cancer, meta-analysis

## Background

The urokinase plasminogen activation (uPA) system, including the ligand uPA, the urokinase plasminogen activation receptor (uPAR), and the plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2), is a serine proteinase system involved in the degradation of extracellular matrix (ECM). The uPA system plays an important role in tumor invasion and metastasis, and is associated with poor prognosis of cancers.[1–4] The uPA ligand binds to the uPAR receptor, a three-domain glycolipid-anchored cell surface protein. The binding of inactive precursor pro-uPA to uPAR-activated surface-bound plasminogen results in the formation of plasmin and matrix metalloproteinase, which enhances the degradation of most components of ECM and the basement membranes.[5–7] It has been reported that the levels of uPA components were associated with poor prognosis and high mortality of a wide range of malignancies[1,2,8–10] due to their roles in metastasis. The effects of uPA/uPAR on plasminogen activation are regulated by their specific inhibitors PAI-1 and PAI-2.[3,11–13]

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Epidemiological studies have evidenced that both environmental carcinogens and genetic factors contributed to cancer susceptibility. Given that single-nucleotide polymorphisms (SNPs) within the promoter or other regulatory regions of the genes encoding the uPA system may affect their expression and activities, SNP identification based on genotyping approaches is useful for investigating the association between these SNPs, cancer risk, and prognosis.[14] In the past few decades, a large number of epidemiological studies have evaluated the association between the genetic variations of genes encoding the uPA system and the risk of breast cancer, prostate cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer, hepatocellular carcinoma, and oral cancer; however, the results of these studies were conflicting.[14–20] Interestingly, a meta-analysis has found an association between the PAI-1 4G/5G polymorphism (rs1799768) and increased cancer risk.[21] In the present study, we conducted a meta-analysis to systemically evaluate the association between the uPA system polymorphisms and cancer risk.

# Methods

## Selection of published studies

Published studies, which have been published no later than November 13, 2014, were identified by searching the PubMed, Embase, and Web of Science databases using the following MeSH terms and keywords: uPA (PLAU), uPAR, urokinase plasminogen activation, urokinase plasminogen activation receptor, polymorphism, cancer, carcinoma, and neoplasms. The reference lists of retrieved studies were also searched to identify relative studies. Studies included in the present meta-analysis were as follows: 1) articles investigating the association between the uPA system polymorphisms rs4065, rs2227564, and rs344781 and cancer risk; 2) case–control studies; 3) studies providing genotype frequency for computing odds ratios (ORs) with 95% confidence intervals (CIs); and 4) studies with full text articles. The exclusion criteria were as follows: 1) only case population studies without comparison outcomes reported or not possible to determine comparison outcomes; 2) duplicated publications; and 3) benign tumors and/or precancerous lesions.

## Data extraction

Two investigators independently screened the manuscript titles, abstracts, and full texts using a standardized extraction form. For conflicting evaluation, an agreement was reached based on consensus and discussion. For each study, the following data were extracted: the first author's name, year of publication, country of origin, ethnicity, genotyping methods, source of control, cancer type, total numbers of cases and controls, and genotype distributions in cases and controls. We did not define a minimum number of patients in each study for the present meta-analysis.

## Evaluation of study quality and validation of study

The quality of studies was assessed by quality scores using a standardized extraction form according to previous studies with minor modification (Table S1).[22,23] The total quality score ranged from 0 (the lowest quality) to 20 (the highest quality). The analyses were stratified according to the study quality.

## Statistical analyses

Statistical analyses were performed using STATA software (Version 11.0; StataCorp LP, College Station, TX, USA), and all tests were two-sided with a significant level of 0.05, unless stated otherwise. The Hardy–Weinberg equilibrium (HWE) in controls was assessed using chi-squared test, and a $P$-value $<0.05$ was considered as significant disequilibrium. If the HWE existed ($P<0.05$) or it was impossible to evaluate the HWE, sensitivity analysis was performed. The strength of the association between the uPA system polymorphisms and cancer risk was evaluated on the basis of ORs with 95% CIs. The Q-statistic was used to test heterogeneities among the studies included in the meta-analysis.[24] When the Q-test $P$-value was not $<0.1$, fixed effect model with Mantel–Haenszel method was used to calculate the pooled ORs.[25] Otherwise, a random effect model with inverse variance method was used. Taking the uPA polymorphism rs4065 as an example, pooled ORs were obtained from the combination of all studies by heterozygote comparison (TC vs CC), homozygote comparison (TT vs CC), dominant and recessive models (TT + TC vs CC and TT vs TC + CC), and allelic comparison (T vs C). Similarly, comparison of the results of other polymorphisms was also obtained. In addition, we also performed stratification analyses according to ethnicity and quality score: high-quality studies (quality score $>15$) vs low-quality studies (quality score $<15$). Begg's and Egger's tests were used to evaluate publication bias.[26,27]

# Results

## Characteristics of the studies

A total of 62 studies were included in this meta-analysis based on the search strategy using different combinations of keywords (Figure 1). Through reviewing the abstracts and

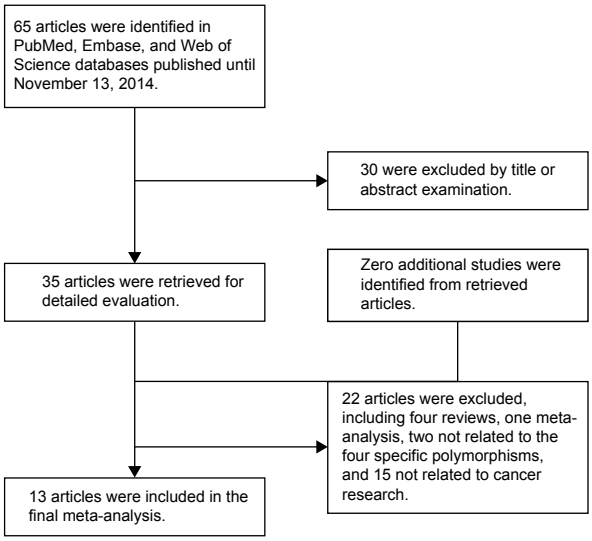


**Figure 1** The inclusion and exclusion criteria used in the selection of published studies on the polymorphisms of uPA system and cancer risk.
**Abbreviation:** uPA, urokinase plasminogen activation.

full texts, 20 case–control studies from 13 articles met our inclusion criteria.[14,17–20,28–35] A total of 7,037 cancer cases and 10,094 controls were included in the 20 case–control studies. The characteristics of these studies are listed in Table 1. Among them, seven studies including 1,233 cancer cases and 1,919 controls investigated the uPA polymorphism rs4065, six studies including 2,343 cancer cases and 2,780 controls studied the uPA polymorphism rs2227564, and seven studies including 2,265 cancer cases and 3,241 controls were about the uPAR polymorphism rs344781. The distribution of genotypes in the controls of all studies was consistent with HWE.

## Meta-analysis

The significance of the association between uPA and uPAR polymorphisms and cancer risk is shown in Table 2. Overall, no significant association was found between the uPA polymorphism rs2227564 and cancer risk based on all genetic models (Table 2), whereas significantly increased cancer risk was associated with the uPA polymorphism rs4065 (T allele vs C allele: OR 1.50, 95% CI: 1.19–1.89; TT vs CC: OR 4.63, 95% CI: 3.10–6.91; dominant model: OR 1.93, 95% CI: 1.60–2.33; recessive model: OR 3.02, 95% CI: 1.26–7.25) (Figure 2) and the uPAR polymorphism rs344781 (T allele vs C allele: OR 1.13, 95% CI: 1.04–1.23; TC vs CC: OR 1.26, 95% CI: 1.06–1.49; TT vs CC: OR 1.35, 95% CI: 1.13–1.63; dominant model: OR 1.29, 95% CI: 1.10–1.52) (Figure 3), which was consistent with the results from studies of high quality (Table 2).

When the cases were stratified according to ethnicity, we found that the uPA polymorphism rs4065 (T allele vs C allele: OR 1.48, 95% CI: 1.11–1.95; TT vs CC: OR 5.52, 95% CI: 3.46–8.81; dominant model: OR 2.02, 95% CI: 1.65–2.47; recessive model: OR 5.53, 95% CI: 3.50–8.75) and the uPAR polymorphism rs344781 (T allele vs C allele: OR 1.16, 95% CI: 1.03–1.29; TC vs CC: OR 1.25, 95% CI: 1.02–1.54; TT vs CC: OR 1.35, 95% CI: 1.08–1.70; dominant model: OR 1.28, 95% CI: 1.06–1.56) were associated with increased cancer risk in Asians, which was consistent with the results of analyses of high quality. No significant association between the uPA polymorphisms rs4065 and rs344781 and cancer risk was found in the Caucasian population.

Subgroup studies were performed according to different cancer types (digestive system cancers and nondigestive system cancers). For digestive system cancers, meta-analyses of all studies and studies of high quality demonstrated a significant association between the uPA polymorphism rs4065 and increased risk of digestive system cancers based on the dominant model (the former: OR 1.60, 95% CI: 1.16–2.22; the latter: OR 1.86, 95% CI: 1.29–2.68). However, no significant association was detected between the uPAR polymorphism rs344781 and increased risk of digestive system cancers. Regarding nondigestive system cancers, we found that the uPA polymorphism rs4065 (TT vs CC: OR 4.61, 95% CI: 3.05–6.96; dominant model: OR 2.12, 95% CI: 1.68–2.67) and the uPAR polymorphism rs344781 (T allele vs C allele: OR 1.17, 95% CI: 1.06–1.30; TT vs CC: OR 1.43, 95% CI: 1.14–1.79; dominant model: OR 1.30, 95% CI: 1.06–1.59; recessive model: OR 1.20, 95% CI: 1.04–1.37) were associated with increased risk of nondigestive system cancers, which was consistent with the results from studies of high quality.

Subgroup studies were also performed according to the source of control. We found that the uPA polymorphism rs4065 (T allele vs C allele: OR 1.50, 95% CI: 1.19–1.89; TT vs CC: OR 4.63, 95% CI: 3.10–6.91; dominant model: OR 1.93, 95% CI: 1.60–2.33; recessive model: OR 3.02, 95% CI: 1.26–7.25) and the uPAR polymorphism rs344781 (T allele vs C allele: OR 1.16, 95% CI: 1.03–1.29; TC vs CC: OR 1.25, 95% CI: 1.02–1.54; TT vs CC: OR 1.35, 95% CI: 1.08–1.70; dominant model: OR 1.28, 95% CI: 1.06–1.56) were associated with increased cancer risk in hospital-based control studies, which was consistent with the results from studies of high quality. No significant association between the uPAR polymorphism rs344781and cancer risk was detected in the studies from population-based control.

**Table 1** Characteristics of the previous studies included in the present meta-analysis

| Author | Year | Country | Ethnicity | Cancer type | Source of control | Genotyping method | Case | Control | Quality score | *P* of HWE |
|---|---|---|---|---|---|---|---|---|---|---|
| uPA rs4065 | | | | | | | | | | |
| Shih et al[17] | 2011 | Republic of China (Taiwan) | Asian | Lung cancer | HB | PCR-RFLP | 375 | 380 | 16 | 0.1230 |
| Su et al[14] | 2011 | Republic of China (Taiwan) | Asian | Endometrial cancer | HB | PCR-RFLP | 134 | 302 | 15.5 | 0.7260 |
| Tee et al[33] | 2012 | Republic of China (Taiwan) | Asian | Cervical neoplasia | HB | PCR-RFLP | 136 | 336 | 15.5 | 0.6114 |
| Weng et al[18] | 2011 | Republic of China (Taiwan) | Asian | Oral cancer | HB | PCR-RFLP | 253 | 344 | 17 | 0.4297 |
| Weng et al[19] | 2010 | Republic of China (Taiwan) | Asian | Hepatocellular carcinoma | HB | PCR-RFLP | 102 | 344 | 17 | 0.4297 |
| Mittal et al[31] | 2005 | India | Others | Prostate cancer | HB | PCR-RFLP | 103 | 107 | 13.5 | 0.0326 |
| Tsai et al[34] | 2004 | Republic of China (Taiwan) | Asian | Oral cancer | HB | PCR sequencing | 130 | 106 | 13.5 | 0.8035 |
| uPA rs2227564 | | | | | | | | | | |
| Forsti et al[29] | 2007 | Sweden | Caucasian | Colorectal cancer | PB | Taqman assay | 303 | 579 | 18 | 0.4022 |
| Przybylowska et al[32] | 2001 | Poland | Caucasian | Colorectal cancer | HB | PCR | 52 | 100 | 12 | 0.0003 |
| Lei et al[30] | 2008 | Germany | Caucasian | Breast cancer | PB | Taqman assay | 957 | 947 | 18 | 0.4670 |
| Wu et al[20] | 2008 | Republic of China (Taiwan) | Asian | Gastric cancer | HB | PCR sequencing | 237 | 242 | 17 | 0.3023 |
| Turkmen et al[35] | 1997 | Germany | Caucasian | Ovarian cancer | HB | PCR-RFLP | 22 | 23 | 12 | 0.8978 |
| Bentov et al[28] | 2009 | Canada | Caucasian | Ovarian cancer | HB | MALDI-TOF | 772 | 889 | 18 | 0.6000 |
| uPAR rs344781 | | | | | | | | | | |
| Shih et al[17] | 2011 | Republic of China (Taiwan) | Asian | Lung cancer | HB | PCR-RFLP | 375 | 380 | 16 | 0.1044 |
| Su et al[14] | 2011 | Republic of China (Taiwan) | Asian | Endometrial cancer | HB | PCR-RFLP | 134 | 302 | 15.5 | 0.2052 |
| Tee et al[33] | 2012 | Republic of China (Taiwan) | Asian | Cervical neoplasia | HB | PCR-RFLP | 136 | 336 | 15.5 | 0.3160 |
| Wenget al[18] | 2011 | Republic of China (Taiwan) | Asian | Oral cancer | HB | PCR-RFLP | 253 | 344 | 17 | 0.8312 |
| Weng et al[19] | 2010 | Republic of China (Taiwan) | Asian | Hepatocellular carcinoma | HB | PCR-RFLP | 102 | 344 | 17 | 0.8312 |
| Lei et al[30] | 2008 | Germany | Caucasian | Breast cancer | PB | Taqman assay | 957 | 951 | 18 | 0.6533 |
| Forsti et al[29] | 2007 | Sweden | Caucasian | Colorectal cancer | PB | Taqman assay | 308 | 584 | 18 | 0.1087 |

**Abbreviations:** HB, hospital-based case–control; HWE, Hardy–Weinberg equilibrium; MALDI-TOF, matrix-assisted laser desorption ionisation time-of-flight; PB, population-based case–control study; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-CTPP, PCR with confronting two-pair primers; uPA, urokinase plasminogen activation; uPAR, urokinase plasminogen activation receptor.

**Table 2** Pooled ORs and 95% CIs of stratified meta-analysis

| Variables | N | | VR allele vs WT allele OR (95% CI) | | Ht vs WT Ho OR (95% CI) | | VR Ho vs WT Ho OR (95% CI) | | Dominant model OR (95% CI) | | Recessive model OR (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $N_2$ | All studies | High-quality studies | All studies | High-quality studies | All studies | High-quality studies | All studies | High-quality studies | All studies | High-quality studies |
| uPA rs4065 | | | | | | | | | | | | |
| Total | 7 | 5 | 1.50 (1.19, 1.89) | 1.41 (1.05, 1.90) | 1.17 (0.97, 1.41) | 1.07 (0.87, 1.30) | 4.63 (3.10, 6.91) | 5.52 (3.46, 8.81) | 1.93 (1.60, 2.33) | 2.02 (1.65, 2.47) | 3.02 (1.26, 7.25) | 5.68 (3.61, 8.94) |
| Ethnicity | | | | | | | | | | | | |
| Asian | 6 | 5 | 1.48 (1.11, 1.95) | 1.41 (1.05, 1.90) | 1.11 (0.92, 1.35) | 1.07 (0.87, 1.30) | 5.52 (3.46, 8.81) | 5.52 (3.46, 8.81) | 1.90 (1.56, 2.31) | 2.02 (1.65, 2.47) | 5.53 (3.50, 8.75) | 5.68 (3.61, 8.94) |
| Others | 1 | 0 | 1.55 (1.04, 2.29) | – | 2.52 (1.13, 5.59) | – | 2.61 (1.16, 5.84) | – | 2.41 (1.15, 5.06) | – | 1.35 (0.78, 2.36) | – |
| Cancer type | | | | | | | | | | | | |
| Y | 3 | 2 | 1.50 (1.03, 2.18) | 1.39 (0.99, 1.97) | 1.43 (1.03, 1.98) | 1.30 (0.92, 1.84) | 4.99 (0.90, 27.76) | 4.99 (0.90, 27.76) | 1.60 (1.16, 2.22) | 1.86 (1.29, 2.68) | 4.57 (0.82, 25.65) | 4.77 (0.85, 26.61) |
| Non | 4 | 3 | 1.47 (1.07, 2.03) | 1.41 (0.89, 2.24) | 1.06 (0.84, 1.33) | 0.97 (0.76, 1.24) | 4.61 (3.05, 6.96) | 5.57 (3.43, 9.04) | 2.12 (1.68, 2.67) | 2.09 (1.64, 2.67) | 2.74 (0.95, 7.94) | 5.74 (3.59, 9.20) |
| Source of control | | | | | | | | | | | | |
| PB | 0 | 0 | – | – | – | – | – | – | – | – | – | – |
| HB | 7 | 5 | 1.50 (1.19, 1.89) | 1.41 (1.05, 1.90) | 1.17 (0.97, 1.41) | 1.07 (0.87, 1.30) | 4.63 (3.10, 6.91) | 5.52 (3.46, 8.81) | 1.93 (1.60, 2.33) | 2.02 (1.65, 2.47) | 3.02 (1.26, 7.25) | 5.68 (3.61, 8.94) |
| uPA rs2227564 | | | | | | | | | | | | |
| Total | 6 | 4 | 0.99 (0.91, 1.08) | 0.98 (0.90, 1.07) | 1.04 (0.93, 1.17) | 1.05 (0.93, 1.18) | 0.98 (0.80, 1.21) | 1.00 (0.81, 1.24) | 1.03 (0.92, 1.15) | 1.04 (0.93, 1.17) | 0.97 (0.79, 1.19) | 0.98 (0.80, 1.21) |
| Ethnicity | | | | | | | | | | | | |
| Caucasian | 5 | 3 | 0.98 (0.90, 1.08) | 0.97 (0.89, 1.07) | 1.05 (0.93, 1.19) | 1.06 (0.94, 1.20) | 0.98 (0.77, 1.23) | 1.01 (0.80, 1.26) | 1.04 (0.93, 1.17) | 1.05 (0.93, 1.18) | 0.96 (0.77, 1.19) | 0.98 (0.78, 1.22) |
| Asian | 1 | 1 | 1.02 (0.79, 1.33) | 1.02 (0.79, 1.33) | 0.94 (0.64, 1.38) | 0.94 (0.64, 1.38) | 0.99 (0.55, 1.78) | 0.99 (0.55, 1.78) | 0.95 (0.66, 1.37) | 0.95 (0.66, 1.37) | 1.02 (0.59, 1.77) | 1.02 (0.59, 1.77) |
| Cancer type | | | | | | | | | | | | |
| Y | 3 | 2 | 1.01 (0.86, 1.18) | 0.98 (0.83, 1.16) | 1.04 (0.83, 1.30) | 1.07 (0.85, 1.35) | 0.93 (0.64, 1.35) | 0.97 (0.66, 1.42) | 1.02 (0.83, 1.26) | 1.05 (0.84, 1.31) | 0.92 (0.64, 1.31) | 0.95 (0.66, 1.37) |
| Non | 3 | 2 | 0.98 (0.88, 1.09) | 0.98 (0.88, 1.09) | 1.04 (0.91, 1.19) | 1.04 (0.91, 1.19) | 1.01 (0.78, 1.31) | 1.02 (0.79, 1.32) | 1.04 (0.91, 1.18) | 1.04 (0.91, 1.18) | 0.99 (0.77, 1.27) | 1.00 (0.78, 1.28) |
| Source of control | | | | | | | | | | | | |
| PB | 2 | 2 | 0.96 (0.86, 1.08) | 0.96 (0.86, 1.08) | 1.08 (0.92, 1.27) | 1.08 (0.92, 1.27) | 1.01 (0.77, 1.33) | 1.01 (0.77, 1.33) | 1.07 (0.92, 1.24) | 1.07 (0.92, 1.24) | 0.98 (0.75, 1.27) | 0.98 (0.75, 1.27) |
| HB | 4 | 2 | 1.02 (0.89, 1.16) | 1.00 (0.87, 1.14) | 0.99 (0.83, 1.18) | 1.01 (0.84, 1.20) | 0.94 (0.68, 1.31) | 0.99 (0.70, 1.39) | 0.99 (0.84, 1.16) | 1.00 (0.85, 1.19) | 0.95 (0.69, 1.31) | 0.99 (0.72, 1.38) |
| uPAR rs344781 | | | | | | | | | | | | |
| Total | 7 | 7 | 1.13 (1.04, 1.23) | 1.13 (1.04, 1.23) | 1.26 (1.06, 1.49) | 1.26 (1.06, 1.49) | 1.35 (1.13, 1.63) | 1.35 (1.13, 1.63) | 1.29 (1.10, 1.52) | 1.29 (1.10, 1.52) | 1.12 (1.00, 1.26) | 1.12 (1.00, 1.26) |
| Ethnicity | | | | | | | | | | | | |
| Caucasian | 2 | 2 | 1.11 (0.99, 1.25) | 1.11 (0.99, 1.25) | 1.28 (0.94, 1.74) | 1.28 (0.94, 1.74) | 1.35 (1.00, 1.83) | 1.35 (1.00, 1.83) | 1.32 (0.98, 1.78) | 1.32 (0.98, 1.78) | 1.10 (0.94, 1.28) | 1.10 (0.94, 1.28) |
| Asian | 5 | 5 | 1.16 (1.03, 1.29) | 1.16 (1.03, 1.29) | 1.25 (1.02, 1.54) | 1.25 (1.02, 1.54) | 1.35 (1.08, 1.70) | 1.35 (1.08, 1.70) | 1.28 (1.06, 1.56) | 1.28 (1.06, 1.56) | 1.16 (0.97, 1.38) | 1.16 (0.97, 1.38) |
| Cancer type | | | | | | | | | | | | |
| Y | 3 | 3 | 1.06 (0.92, 1.22) | 1.06 (0.92, 1.22) | 1.34 (1.00, 1.79) | 1.34 (1.00, 1.79) | 1.22 (0.89, 1.67) | 1.22 (0.89, 1.67) | 1.28 (0.98, 1.68) | 1.28 (0.98, 1.68) | 0.98 (0.80, 1.20) | 0.98 (0.80, 1.20) |
| Non | 4 | 4 | 1.17 (1.06, 1.30) | 1.17 (1.06, 1.30) | 1.21 (0.98, 1.50) | 1.21 (0.98, 1.50) | 1.43 (1.14, 1.79) | 1.43 (1.14, 1.79) | 1.30 (1.06, 1.59) | 1.30 (1.06, 1.59) | 1.20 (1.04, 1.37) | 1.20 (1.04, 1.37) |
| Source of control | | | | | | | | | | | | |
| PB | 2 | 2 | 1.11 (0.99, 1.25) | 1.11 (0.99, 1.25) | 1.28 (0.94, 1.74) | 1.28 (0.94, 1.74) | 1.35 (1.00, 1.83) | 1.35 (1.00, 1.83) | 1.32 (0.98, 1.78) | 1.32 (0.98, 1.78) | 1.10 (0.94, 1.28) | 1.10 (0.94, 1.28) |
| HB | 5 | 5 | 1.16 (1.03, 1.29) | 1.16 (1.03, 1.29) | 1.25 (1.02, 1.54) | 1.25 (1.02, 1.54) | 1.35 (1.08, 1.70) | 1.35 (1.08, 1.70) | 1.28 (1.06, 1.56) | 1.28 (1.06, 1.56) | 1.16 (0.97, 1.38) | 1.16 (0.97, 1.38) |

**Notes:** Random model was chosen for data pooling when *P*-value <0.10 and/or $I^2$>50%; otherwise fixed model was used.

**Abbreviations:** CI, confidence interval; HB, hospital-based case–control; Ht, heterozygote; N, numbers of involved studies; Non, nondigestive system cancer studies; OR, odds ratio; PB, population-based case–control study; uPA, urokinase plasminogen activation; uPAR, urokinase plasminogen activation receptor; VR, variant; VR Ho, variant homozygote; WT, wild-type; WT Ho, wide-type homozygote; Y, digestive system cancer studies.

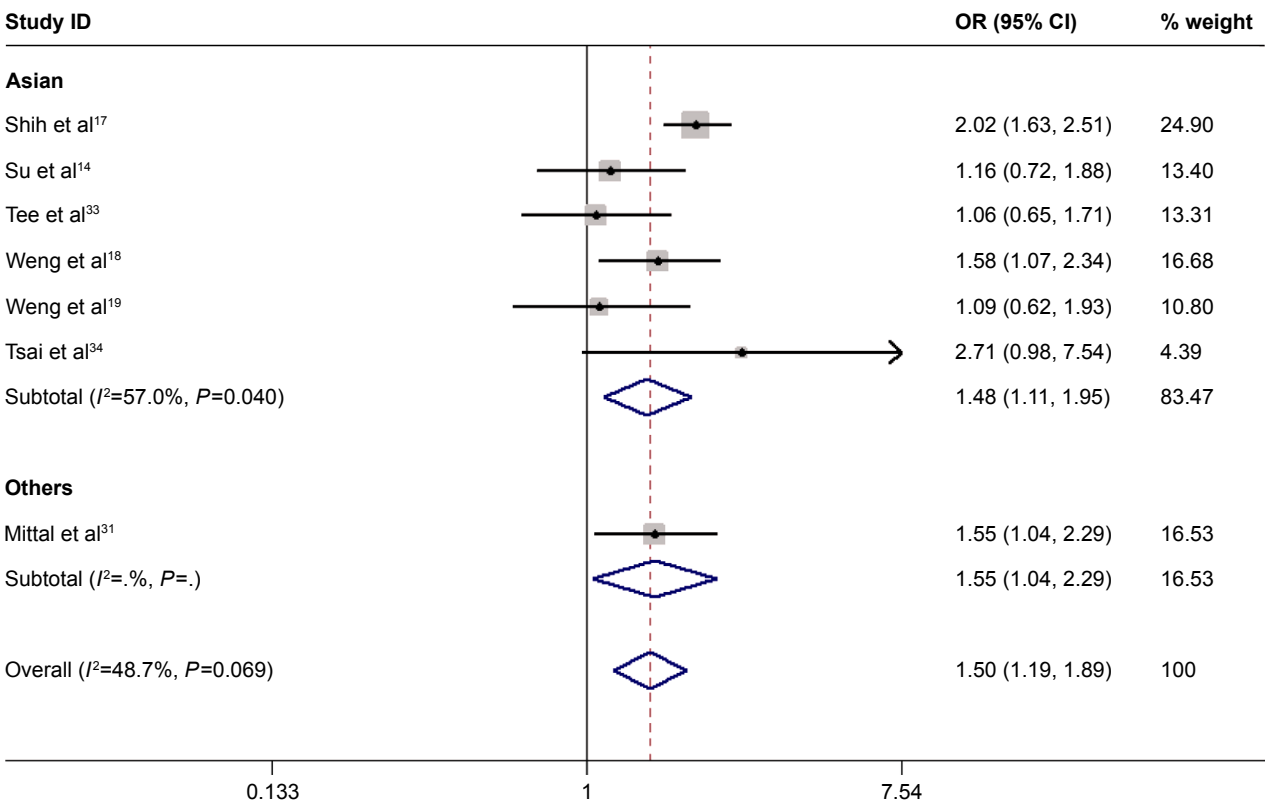


**Figure 2** Forest plot of ORs of the uPA polymorphism rs4065 (T allele vs C allele) associated with cancers stratified by ethnicity.
**Note:** Weights are from random effects analysis.
**Abbreviations:** CI, confidence interval; OR, odd ratio; uPA, urokinase plasminogen activation.

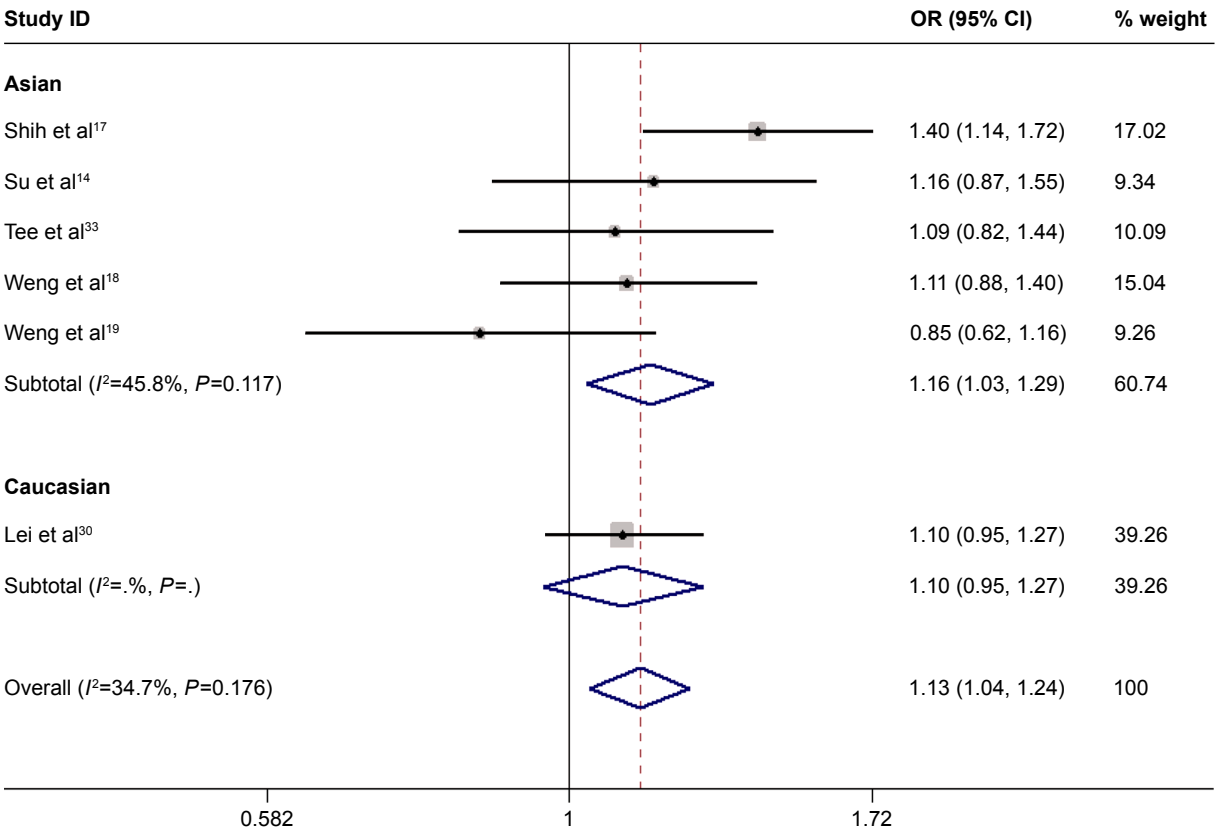


**Figure 3** Forest plot of ORs of the uPAR polymorphism rs344781 (T vs C).
**Abbreviations:** CI, confidence interval; OR, odd ratio; uPAR, urokinase plasminogen activation receptor.

**Table 3** Evaluation of publication bias based on Begg's and Egger's tests

| Polymorphism | Begg's test | | Egger's test | |
|---|---|---|---|---|
| | *P* (all studies) | *P* (high-quality studies) | *P* (all studies) | *P* (high-quality studies) |
| uPA rs4065 | | | | |
| T/C | 1.000 | 0.086 | 0.797 | 0.053 |
| uPA rs2227564 | | | | |
| C/T | 0.133 | 1.000 | 0.074 | 0.711 |
| uPAR rs344781 | | | | |
| T/C | 1.000 | 1.000 | 0.738 | 0.738 |

**Abbreviations:** uPA, urokinase plasminogen activation; uPAR, urokinase plasminogen activation receptor.

## Sensitivity analyses and publication bias

When examining the genotype frequencies in the controls, no significant deviation from HWE was detected, suggesting that the final results of this meta-analysis were reliable and stable. Both Begg's and Egger's tests were conducted to assess the publication bias of literatures. No evidence of publication bias was observed in the allele genetic model in the present meta-analysis (Table 3).[36] Similar results were also observed in analyses restricted to other genetic models (data not shown).

# Discussion

The uPA system plays an essential role in the degradation and regeneration of basement membrane and ECM, as well as cancer metastasis.[11,12] The biological function of the uPA system may be impaired by SNPs within genes encoding the uPA system, resulting in altered susceptibility to cancers. The effects of genetic variations of the uPA system in cancer development have been recognized in recent years; however, the results are contradictory.[14,17–20] In the present study, we provided a comprehensive meta-analysis to evaluate the association of the uPA system polymorphisms and cancer risk. To the best of our knowledge, this is the first systematic meta-analysis addressing the association between the uPA system polymorphisms (not the PAI-1) and cancer risk.

Yoshimoto et al[37] reported that the CC genotype exhibited the strongest uPA affinity for substrates and inhibitors, resulting in the formation of uPA/uPAR and uPA/PAI-1 complexes and the activation of the uPA system. Our meta-analysis suggests that the T allele in the uPA polymorphism rs4065 was associated with a high incidence of cancers. Therefore, we speculate that the activation of the uPA system may be interrupted by the lower affinity of the rs4065 variant with its substrates and inhibitors. Based on stratified analysis of ethnicity, significant association between uPA polymorphism rs4065 and cancer risk was found in Asians. However, lack of case–control studies limited our evaluation on the association between the uPA polymorphism rs4065 and cancer risk among other ethnicities. In the subgroup analysis of cancer types, a significant association was identified between the polymorphism rs4065 and increased risk of both digestive and nondigestive system cancers based on a dominant model, which was consistent with the results from high-quality studies.

Regarding the general analysis of the uPAR polymorphism, we showed that the presence of minor alleles significantly increased the risk of cancers than major alleles, suggesting that genetic variations significantly modify the host susceptibility to cancers. In the subgroup analysis of ethnicity, significant association was identified between the polymorphism rs344781 and increased cancer risk in Asians rather than Caucasians. The inconsistent results between these two ethnicities may be explained by distinct lifestyles and environmental factors of these two ethnic groups. In the subgroup analysis of cancer types, we detected an association between the polymorphism rs344781 and the risk of nondigestive system cancers, but not the digestive system cancers. This difference between digestive and nondigestive system cancers may be explained by the differential expression, function, and regulatory mechanisms of the uPA and uPAR systems in various tissues and tumors.[38–42]

General analysis of the uPA polymorphism rs2227564 showed no significant association between the uPA polymorphism rs2227564 and cancer risk. However, case–control studies of large scale are necessary to ascertain the accurate effects of the rs2227564 polymorphism on cancer development.

A number of limitations in the present meta-analysis should be addressed. First, lack of original data of the reviewed studies limited our evaluation of the potential effects of gene–gene and gene–environment interactions. Second, all case–control studies were from People's Republic of China, Taiwan, Europe, the US, and India. These results may be applicable only to the relative ethnicities. Third, the meta-analysis study should provide a more accurate evaluation on the association between the uPA polymorphisms and cancer risk by considering classic cancer risk factors,

such as smoking, age, sex, and diabetes. At last, future studies should evaluate the association between the PAI-1 and PAI-2 polymorphisms and cancer risk when the original data are available.

In summary, the present meta-analysis study suggests that the uPA polymorphism rs4065 and the uPAR polymorphism rs344781 were associated with increased cancer risk in Asian population. In addition, subgroup analysis of cancer types suggests that the uPAR polymorphism rs344781 was associated with increased risk of nondigestive system cancers, but not the digestive system cancers. However, it is important to include larger samples with detailed clinical data, standardized unbiased genotyping methods, homogeneous cancer patients, and well-matched controls to further understand the association between the uPA polymorphisms and cancer risk in the future.

## Conclusion

This meta-analysis found that the uPA polymorphism rs4065 and the uPAR polymorphism rs344781, not the uPA polymorphism rs2227564, are associated with increased cancer risk. However, well-designed case–control studies with larger sample size and more ethnicities are necessary to validate our findings in the future.

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## Disclosure

The authors report no conflicts of interest in this work.

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# Supplementary material

**Table S1** Methodological quality assessment used in the present meta-analysis

| Criteria | Score |
|---|---|
| Representativeness of cases | |
| Selected from cancer registry or multiple cancer centers | 2 |
| Selected from oncology departments or cancer institutes | 1 |
| Not described | 0 |
| Source of controls | |
| Population or community-based | 3 |
| Blood donors | 2 |
| Hospital-based (cancer-free controls) | 1.5 |
| Healthy volunteers without total description | 1 |
| Cancer-free controls with other diseases | 0.5 |
| Not described | 0 |
| Ascertainment of relevant cancers | |
| Histopathological confirmation | 2 |
| Medical record of patients | 1 |
| Not described | 0 |
| Sample size (n) | |
| >1,000 | 2 |
| 200–1,000 | 1 |
| <200 | 0 |
| Genotyping examination | |
| Blinded | 1 |
| Unblinded/not mentioned | 0 |
| Inclusion-exclusion criteria | |
| Described in cases and controls | 2 |
| Only in cases/controls, exclusion was not described | 1 |
| Not mentioned | 0 |
| Genotyping case–controls | |
| In equal ways | 2 |
| Not in equal ways | 0 |
| Statistics reported | |
| OR, CI, *P*-values | 2 |
| Frequency | 0.5 |
| None above, not mentioned | 0 |
| Quality control of genotyping methods | |
| Taqman/DNA sequencing/RFLP/pyrosequencing | 2 |
| Others | 0.5 |
| Not described | 0 |
| HWE among controls | |
| Correctly reported | 2 |
| Wrongly reported | 0 |
| Not described | 0 |

**Abbreviations:** CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odd ratio; RFLP, restriction fragment length polymorphism.