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# Association of polymorphisms in *interleukin-8* gene with cancer risk: a meta-analysis of 22 case–control studies

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**Abstract:** Interleukin-8 (IL-8) is a kind of chemokine that plays an important role in the development and progression of many human malignancies. Previous studies have uncovered that polymorphisms in *IL-8* is associated with the risk of many cancer types, but the results were inconsistent and inconclusive. In the present study, we aimed to explore the roles of *IL-8* polymorphisms (rs2227307, rs2227306, +678T/C, rs1126647, and +1633C/T) and cancer risk through a systematic review and meta-analysis. Potential source of heterogeneity was sought out through sensitivity analysis. Desirable data were extracted and registered into databases. Finally, a total of ten publications comprising of 22 case–control studies, including 4,259 cases and 7,006 controls were ultimately eligible for the meta-analysis. No significant association was uncovered for all the five polymorphisms and the overall cancer risk. However, in the stratification analysis by cancer type, a significantly decreased risk of hepatocellular carcinoma was identified for rs2227306 polymorphism (T vs C: odds ratio [OR] =0.721, 95% confidence interval [CI] =0.567–0.916, $P_z$=0.007; TT vs CC: OR =0.447, 95% CI =0.274–0.728, $P_z$=0.001; TT vs TC + CC: OR =0.480, 95% CI =0.304–0.760, $P_z$=0.002). In conclusion, our data shows that rs2227306 polymorphism plays a protective role in hepatocellular carcinoma risk. Future well-designed studies with a larger sample size are warranted to verify our findings.

**Keywords:** interleukin-8, polymorphisms, cancer

## Introduction

Interleukin-8 (IL-8) is a member of the CXC chemokine superfamily, which can activate neutrophil and lymphocyte attraction and cause a wide range of proinflammatory chemical reactions, generally by initiating and amplifying the acute inflammatory effects and chronic inflammatory process.[1,2] It is also reported that IL-8 is related to different malignancies due to the involvement of thrombophilia and angiogenesis.[3–5] Increased secretion of IL-8 may contribute to the metastatic ability of hepatocellular carcinoma (HCC),[6] gastric cancer,[7] renal cell carcinoma,[8] colorectal cancer,[9] prostate cancer,[10] melanoma,[11] and bladder neoplasms.[12] These observations indicated that *IL-8* might act as a biomarker for monitoring the clinical course of many tumor types.

The interleukin production is regulated by the polymorphisms of cytokine genes in promoter regions.[13] Thus, *IL-8* is located on chromosome 4q13-21 and contains three introns, four exons, and a proximal promoter region.[14] Five polymorphisms in *IL-8*, +781C/T (rs2227306), +678T/C, 276A/T (rs1126647), +1633C/T, and +396G/T (rs2227307), have been extensively studied.[15] The +781C/T polymorphism is situated in an intron and acts as an important factor in the process of gene transcription and regulation.[16] The +678T/C polymorphism is associated with Behcet's disease

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and ulcerative colitis risk although it does not regulate the transcript of *IL-8*.[17,18]

A large number of investigations were conducted to explore the associations between *IL-8* polymorphisms and risk of human cancers; however, the conclusions were inconsistent.[19–28] Therefore, it is necessary to perform a systematic review and meta-analysis to summarize the current available studies in order to draw a more cohesive conclusion.

# Materials and methods

## Search strategy

A systematic retrieval was performed to identify all eligible studies regarding *IL-8* polymorphisms and cancer risk in PubMed, Web of Science, and Embase databases up until August 1, 2015. The combination of search terms were presented as follows: ("IL8" OR "Interleukin 8" OR "*IL-8*") AND ("polymorphism" OR "variant" OR "SNP" OR "mutation" OR "genotype") AND ("tumor" OR "carcinoma" OR "cancer"). The language of the enrolled studies was restricted to English or Chinese. We also conducted a hand search of the reference lists of the enrolled studies or reviews to identify additional eligible studies.

## Study selection

Studies concerning the association of *IL-8* polymorphisms with cancer risk were included if the following conditions were met: 1) any study described the association between *IL-8* polymorphisms and cancer risk; 2) studies were case–control or cohort type; 3) the genotype frequencies of the cases and controls were available; and 4) each enrolled study should comprise at least one of rs2227306, rs2227307, rs1126647, +678T/C, and +1633C/T polymorphisms. Studies were excluded if: 1) there were no data regarding the associations between *IL-8* polymorphisms and cancer risk; 2) they were duplicate of previous publications (when the same cohort was used in several publications, only the most complete information was included after careful examination); and 3) they were reviews or abstracts.

## Data extraction

The following data from each article were extracted by MZ and TF independently: name of first author, year of publication, ethnicity of the participants (categorized as Caucasians, Asians, etc), source of control, number of controls and cases, genotyping method, and so on. We extracted the data through the following ways: 1) from the articles directly; 2) from the supplementary materials; and 3) by requesting the author through email to send the data.

## Statistical analysis

All the statistical analyses were performed using STATA 12.0 statistical software (StataCorp LP., College Station, TX, USA). A $\chi^2$-based $Q$-test assessed the heterogeneity in each research. If $P<0.05$, it indicated significant heterogeneity, the random-effects model was adopted to estimate the pooled odds ratio (OR);[29] otherwise, the fixed-effects model was performed.[30] Two-sided $P<0.05$ were considered statistically significant. The $\chi^2$ OR and 95% confidence interval (CI) were applied to evaluate the power of associations between *IL-8* gene polymorphisms and cancer risk. Sensitivity analysis was also performed by removing one study at a time to calculate the overall homogeneity and effect size. Publication biases were calculated through Egger's regression test and Begg's funnel plot.[31,32]

# Results

## Identification and characteristics of the included studies

As presented in Figure 1, the systematic literature retrieval identified a total of 574 relevant publications on PubMed, Web of Science, and Embase databases. After the titles and abstracts were checked only 31 articles related to the association between *IL-8* polymorphisms and cancer risk remained. An additional 21 publications were excluded due to the lack of sufficient data, or they were without control groups, or they were related to the survival or treatment. As a result, ten publications comprising of 22 case–control studies were included in the present meta-analysis.

The characteristics of the enrolled studies were presented in Table 1. Approximately 14 studies were conducted among Asian descendants[19,20,23–26] and eight studies among Caucasians.[21,22,27,28] In addition, there were eleven studies conducted by polymerase chain reaction-restriction fragment length polymorphism,[19–21,24] four performed by TaqMan,[27,28] and only one used polymerase chain reaction-sequence-specific primer.[25] The control groups were composed of ten population-based studies[22,23,25,27,28] and twelve hospital-based studies.[19–21,24,26] Approximately 19 of them were conformed with Hardy–Weinberg equilibrium,[19,20,23–27] whereas three others were not.[21,22,28] Furthermore, of these included studies, six studies[23,27,28] reported about gastric cancer and five about HCC.[19,24] Oral cancer[20] and ovarian cancer[21] were described by three studies.

## Meta-analysis

Table 2 demonstrated the results of meta-analysis. No significant association was identified between the five polymorphisms in *IL-8* (rs2227306, rs2227307, +678T/C, rs1126647, and +1633C/T) and the overall cancer risk. Table 2 also shows the results of subgroup analyses, and the data suggested

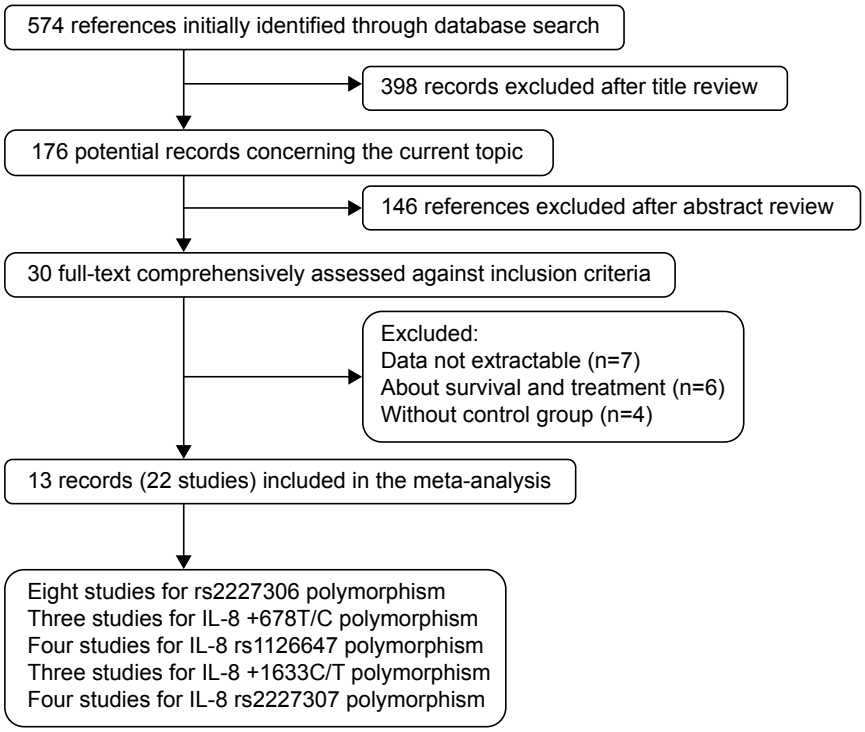



**Figure 1** The flow diagram depicts literature search and study selection.
**Abbreviation:** IL-8, interleukin-8.

**Table 1** Characteristics of the eligible case–control studies enrolled in the meta-analysis

| SNP | First author | Year | Ethnicity | Genotyping method | Source of control | Cancer type | Case | | | Control | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | AA | AB | BB | AA | AB | BB | *P*(HWE) | Y or N |
| rs2227306 | Wang et al[19] | 2014 | Asian | PCR-RFLP | HB | HCC | 80 | 105 | 20 | 76 | 96 | 36 | 0.550 | Y |
| | Liu et al[20] | 2012 | Asian | PCR-RFLP | HB | Oral cancer | 117 | 118 | 35 | 129 | 169 | 52 | 0.781 | Y |
| | Koensgen et al[21] | 2015 | Caucasian | PCR-RFLP | HB | OC | 48 | 150 | 69 | 128 | 226 | 72 | 0.100 | Y |
| | Savage et al[23] | 2004 | Asian | PCR | PB | GC | 28 | 41 | 16 | 167 | 177 | 62 | 0.186 | Y |
| | Savage et al[23] | 2004 | Asian | PCR | PB | ESCC | 53 | 51 | 22 | 167 | 177 | 63 | 0.186 | Y |
| | Chien et al[24] | 2011 | Asian | PCR-RFLP | HB | HCC | 65 | 57 | 9 | 126 | 164 | 50 | 0.776 | Y |
| | Savage et al[27] | 2006 | Caucasian | TaqMan | PB | GC | 80 | 140 | 68 | 133 | 204 | 91 | 0.438 | Y |
| | Kamangar et al[28] | 2006 | Caucasian | TaqMan | PB | GC | 47 | 52 | 11 | 81 | 105 | 22 | 0.158 | Y |
| rs2227307 | Savage et al[23] | 2004 | Asian | PCR | PB | GC | 29 | 33 | 24 | 152 | 181 | 69 | 0.233 | Y |
| | Savage et al[23] | 2004 | Asian | PCR | PB | ESCC | 49 | 50 | 25 | 152 | 181 | 69 | 0.233 | Y |
| | Savage et al[27] | 2006 | Caucasian | TaqMan | PB | GC | 74 | 142 | 71 | 121 | 207 | 102 | 0.464 | Y |
| | Kamangar et al[28] | 2006 | Caucasian | TaqMan | PB | GC | 42 | 55 | 14 | 72 | 112 | 24 | 0.047 | N |
| rs1126647 | Liu et al[20] | 2012 | Asian | PCR-RFLP | HB | Oral cancer | 104 | 123 | 43 | 128 | 161 | 61 | 0.400 | Y |
| | Koensgen et al[21] | 2015 | Caucasian | PCR-RFLP | HB | OC | 87 | 124 | 57 | 137 | 228 | 61 | 0.029 | N |
| | Chien et al[24] | 2011 | Asian | PCR-RFLP | HB | HCC | 60 | 55 | 16 | 125 | 156 | 59 | 0.392 | Y |
| | Hsieh et al[26] | 2007 | Asian | PCR | HB | Leiomyoma | 27 | 71 | 68 | 32 | 65 | 59 | 0.078 | Y |
| +1633C/T | Liu et al[20] | 2012 | Asian | PCR-RFLP | HB | Oral cancer | 100 | 126 | 44 | 125 | 164 | 61 | 0.569 | Y |
| | Koensgen et al[21] | 2015 | Caucasian | PCR-RFLP | HB | OC | 62 | 123 | 61 | 20 | 31 | 11 | 0.865 | Y |
| | Chien et al[24] | 2011 | Asian | PCR-RFLP | HB | HCC | 57 | 58 | 16 | 122 | 159 | 59 | 0.562 | Y |
| +678T/C | Wang et al[19] | 2014 | Asian | PCR-RFLP | HB | HCC | 100 | 78 | 27 | 100 | 82 | 26 | 0.161 | Y |
| | Ahirwar et al[22] | 2010 | Caucasian | PCR | PB | BC | 149 | 32 | 24 | 187 | 61 | 22 | 0 | N |
| | Wei et al[25] | 2007 | Asian | PCR-SSP | PB | NPC | 38 | 104 | 138 | 144 | 111 | 35 | 0.065 | Y |

**Notes:** AA, AB, BC, homozygotes for the common allele, heterozygotes, and homozygotes for the rare allele, respectively. N refers to *P*(HWE)≤0.05; Y refers to *P*(HWE)>0.05.
**Abbreviations:** BC, bladder cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HB, hospital-based; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; NPC, nasopharyngeal carcinoma; OC, ovarian cancer; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSP, polymerase chain reaction-sequence-specific primer; PB, population-based; SNP, single nucleotide polymorphism.

**Table 2** Results of meta-analysis for polymorphisms in *IL-8* and cancer susceptibility

| Variables (rs2227306) | Case/control | T vs C | | | TT vs CC | | | TC vs CC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ |
| Total | 1,483/2,772 | 0.992 (0.813–1.211) | 0.000 | 0.939 | 0.988 (0.647–1.509) | 0.000 | 0.955 | 1.016 (0.812–1.272) | 0.022 | 0.888 |
| HCC | 336/548 | **0.721 (0.567–0.916)*** | 0.250 | **0.007** | **0.447 (0.274–0.728)*** | 0.414 | **0.001** | 0.838 (0.548–1.281) | 0.154 | 0.415 |
| GC | 484/1,042 | 1.109 (0.946–1.300) | 0.433 | 0.201 | 1.244 (0.899–1.723) | 0.650 | 0.187 | 1.104 (0.860–1.419) | 0.407 | 0.437 |
| Other cancer | 663/1,183 | 1.098 (0.753–1.600) | 0.001 | 0.629 | 0.886 (0.595–1.320) | 0.001 | 0.507 | 1.071 (0.641–1.789) | 0.022 | 0.794 |
| Genotyping method | | | | | | | | | | |
| PCR-RFLP | 873/1,324 | 0.906 (0.615–1.333) | 0.000 | 0.616 | 0.791 (0.330–1.900) | 0.000 | 0.601 | 0.988 (0.649–1.505) | 0.003 | 0.956 |
| PCR | 211/812 | 1.128 (0.905–1.406) | 0.336 | 0.285 | 1.278 (0.823–1.983) | 0.482 | 0.280 | 1.091 (0.726–1.642) | 0.229 | 0.651 |
| TaqMan | 398/636 | 1.065 (0.889–1.275) | 0.372 | 0.495 | 1.169 (0.807–1.692) | 0.541 | 0.410 | 1.034 (0.777–1.375) | 0.345 | 0.817 |
| Ethnicity | | | | | | | | | | |
| Asian | 817/1,710 | 0.884 (0.716–1.091) | 0.029 | 0.251 | 0.764 (0.481–1.213) | 0.026 | 0.253 | 0.894 (0.716–1.117) | 0.234 | 0.199 |
| Caucasian | 666/1,062 | 1.193 (0.910–1.563) | 0.030 | 0.202 | 1.506 (0.845–2.683) | 0.031 | 0.165 | 1.220 (0.823–1.810) | 0.060 | 0.322 |
| Source of control | | | | | | | | | | |
| HB | 873/1,324 | 0.906 (0.615–1.333) | 0.000 | 0.616 | 0.791 (0.330–1.900) | 0.000 | 0.601 | 0.988 (0.649–1.505) | 0.003 | 0.956 |
| PB | 610/1,448 | 1.090 (0.948–1.253) | 0.598 | 0.229 | 1.213 (0.914–1.610) | 0.811 | 0.186 | 1.052 (0.847–1.308) | 0.498 | 0.639 |
| | **Case/control** | **TT + TC vs CC** | | | **TT vs TC + CC** | | | | | |
| | | **OR (95% CI)** | $P^a$ | $P_z$ | **OR (95% CI)** | $P^a$ | $P_z$ | | | |
| Total | 1,483/2,772 | 1.012 (0.780–1.314) | 0.001 | 0.927 | 0.979 (0.720–1.330) | 0.007 | 0.890 | | | |
| HCC | 336/548 | 0.735 (0.493–1.097) | 0.159 | 0.132 | **0.480 (0.304–0.760)*** | 0.695 | **0.002** | | | |
| GC | 484/1,042 | 1.135 (0.890–1.447) | 0.351 | 0.308 | 1.156 (0.869–1.536) | 0.895 | 0.319 | | | |
| Other cancer | 663/1,183 | 0.836 (0.649–1.076) | 0.381 | 0.685 | 1.220 (0.794–1.874) | 0.067 | 0.365 | | | |
| Genotyping method | | | | | | | | | | |
| PCR-RFLP | 873/1,324 | 0.948 (0.577–1.558) | 0.000 | 0.834 | 0.789 (0.416–1.496) | 0.000 | 0.467 | | | |
| PCR | 211/812 | 1.139 (0.780–1.665) | 0.230 | 0.443 | 1.222 (0.818–1.824) | 0.824 | 0.329 | | | |
| TaqMan | 398/636 | 1.059 (0.802–1.399) | 0.305 | 0.660 | 1.121 (0.813–1.547) | 0.793 | 0.486 | | | |
| Ethnicity | | | | | | | | | | |
| Asian | 817/1,710 | 0.869 (0.676–1.118) | 0.095 | 0.275 | 0.803 (0.543–1.188) | 0.055 | 0.273 | | | |
| Caucasian | 666/1,062 | 1.276 (0.820–1.987) | 0.020 | 0.280 | 1.331 (0.977–1.814) | 0.233 | 0.070 | | | |
| Source of control | | | | | | | | | | |
| HB | 873/1,324 | 0.948 (0.577–1.558) | 0.000 | 0.834 | 0.789 (0.416–1.496) | 0.000 | 0.467 | | | |
| PB | 610/1,448 | 1.089 (0.888–1.335) | 0.463 | 0.404 | 1.160 (0.902–1.490) | 0.973 | 0.251 | | | |
| **Variables (+678T/C)** | **Case/control** | **T vs C** | | | **TT vs CC** | | | **TC vs CC** | | |
| | | **OR (95% CI)** | $P^a$ | $P_z$ | **OR (95% CI)** | $P^a$ | $P_z$ | **OR (95% CI)** | $P^a$ | $P_z$ |
| Total | 690/768 | 1.020 (0.866–1.201) | 0.970 | 0.816 | 1.165 (0.837–1.623) | 0.814 | 0.365 | 0.879 (0.696–1.111) | 0.390 | 0.281 |
| Ethnicity | | | | | | | | | | |
| Asian | 485/498 | 1.025 (0.848–1.239) | 0.822 | 0.799 | 1.092 (0.738–1.617) | 0.830 | 0.659 | 0.966 (0.738–1.266) | 0.922 | 0.804 |
| Source of control | | | | | | | | | | |
| PB | 485/660 | 1.029 (0.845–1.254) | 0.852 | 0.776 | 1.224 (0.824–1.818) | 0.644 | 0.316 | 0.848 (0.638–1.126) | 0.194 | 0.254 |
| HWE | | | | | | | | | | |
| Y | 485/498 | 1.025 (0.848–1.239) | 0.822 | 0.799 | 1.092 (0.738–1.617) | 0.830 | 0.659 | 0.966 (0.738–1.266) | 0.922 | 0.804 |
| | **Case/control** | **TT + TC vs CC** | | | **TT vs TC + CC** | | | | | |
| Total | 690/768 | 0.952 (0.770–1.177) | 0.785 | 0.650 | 1.203 (0.874–1.654) | 0.702 | 0.257 | | | |
| Ethnicity | | | | | | | | | | |
| Asian | 485/498 | 0.997 (0.776–1.280) | 0.868 | 0.980 | 1.109 (0.763–1.612) | 0.847 | 0.589 | | | |
| Source of control | | | | | | | | | | |
| PB | 485/660 | 0.944 (0.732–1.216) | 0.494 | 0.654 | 1.271 (0.867–1.863) | 0.503 | 0.220 | | | |
| HWE | | | | | | | | | | |
| Y | 485/498 | 0.997 (0.776–1.280) | 0.868 | 0.980 | 1.109 (0.763–1.612) | 0.847 | 0.589 | | | |
| **Variables (rs1126647)** | **Case/control** | **T vs A** | | | **TT vs AA** | | | **TA vs AA** | | |
| | | **OR (95% CI)** | $P^a$ | $P_z$ | **OR (95% CI)** | $P^a$ | $P_z$ | **OR (95% CI)** | $P^a$ | $P_z$ |
| Total | 831/1,272 | 0.997 (0.808–1.230) | 0.053 | 0.976 | 1.049 (0.673–1.634) | 0.043 | 0.834 | 0.908 (0.741–1.111) | 0.307 | 0.348 |
| Ethnicity | | | | | | | | | | |
| Asian | 563/932 | 0.944 (0.720–1.237) | 0.062 | 0.674 | 0.917 (0.535–1.572) | 0.073 | 0.753 | 0.935 (0.729–1.200) | 0.178 | 0.598 |

(*Continued*)

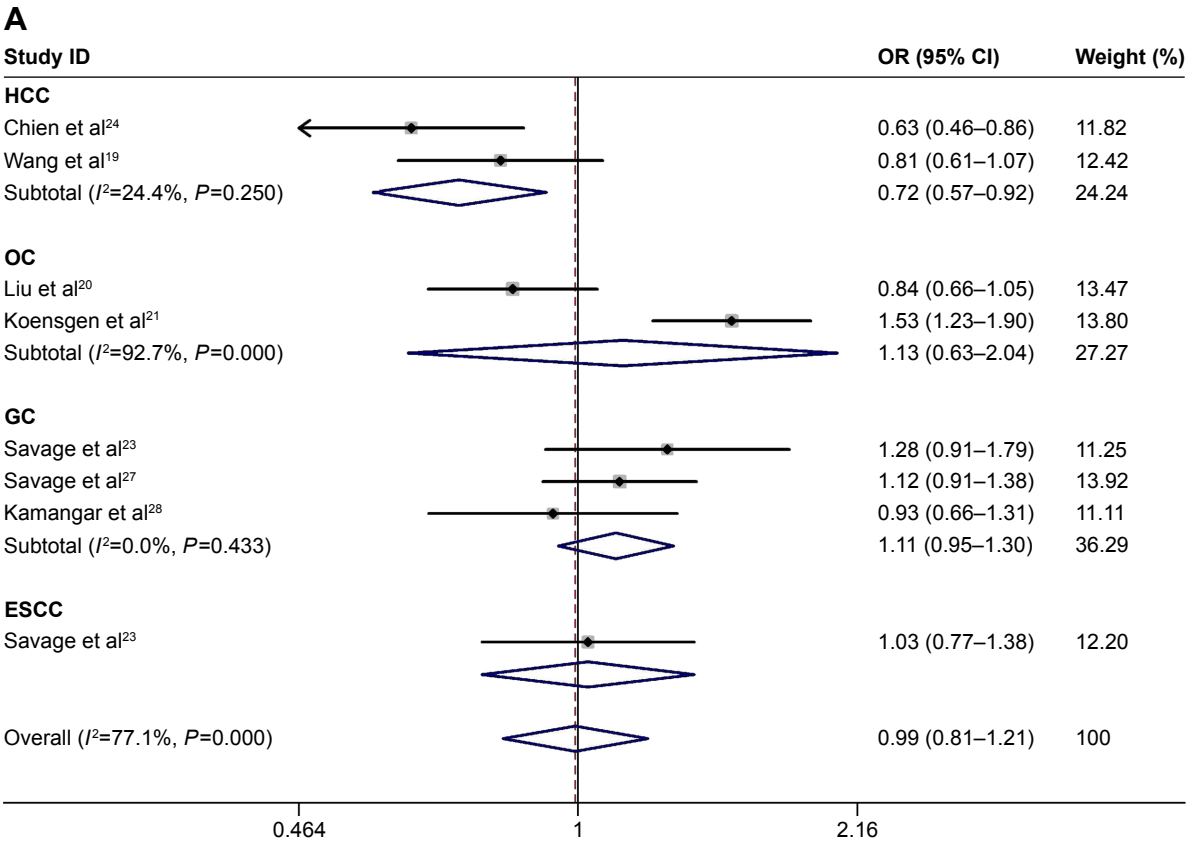
**Table 2** (*Continued*)

| Variables (rs1126647) | Case/control | T vs A | | | TT vs AA | | | TA vs AA | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ |
| Genotyping method | | | | | | | | | | |
| PCR-RFLP | 669/1,116 | 0.938 (0.740–1.191) | 0.061 | 0.601 | 0.928 (0.550–1.568) | 0.043 | 0.781 | 0.855 (0.690–1.059) | 0.686 | 0.150 |
| HWE | | | | | | | | | | |
| Y | 563/846 | 0.944 (0.720–1.237) | 0.062 | 0.674 | 0.917 (0.535–1.572) | 0.073 | 0.753 | 0.935 (0.729–1.200) | 0.178 | 0.598 |
| | **Case/control** | **TT + TA vs AA** | | | **TT vs TA + AA** | | | | | |
| Total | 831/1,271 | 0.936 (0.774–1.132) | 0.158 | 0.497 | 1.071 (0.747–1.535) | 0.061 | 0.708 | | | |
| Ethnicity | | | | | | | | | | |
| Asian | 563/932 | 0.912 (0.722–1.152) | 0.081 | 0.789 | 0.928 (0.684–1.259) | 0.297 | 0.595 | | | |
| Genotyping method | | | | | | | | | | |
| PCR-RFLP | 669/1,116 | 0.881 (0.720–1.077) | 0.380 | 0.216 | 1.018 (0.610–1.700) | 0.027 | 0.944 | | | |
| HWE | | | | | | | | | | |
| Y | 563/846 | 0.912 (0.722–1.152) | 0.081 | 0.789 | 0.928 (0.684–1.259) | 0.297 | 0.595 | | | |
| **Variables (+1633C/T)** | **Case/control** | **T vs C** | | | **TT vs CC** | | | **TC vs CC** | | |
| | | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ |
| Total | 608/752 | 0.961 (0.733–1.260) | 0.088 | 0.772 | 0.893 (0.638–1.249) | 0.103 | 0.508 | 0.936 (0.728–1.204) | 0.448 | 0.608 |
| Ethnicity | | | | | | | | | | |
| Asian | 401/690 | 0.869 (0.702–1.075) | 0.247 | 0.146 | 0.768 (0.528–1.116) | 0.274 | 0.166 | 0.885 (0.674–1.163) | 0.468 | 0.382 |
| | **Case/control** | **TT + TC vs CC** | | | **TT vs TC + CC** | | | | | |
| Total | 608/752 | 0.919 (0.725–1.166) | 0.199 | 0.487 | 0.929 (0.685–1.258) | 0.210 | 0.632 | | | |
| Ethnicity | | | | | | | | | | |
| Asian | 401/690 | 0.853 (0.659–1.103) | 0.329 | 0.224 | 0.820 (0.582–1.156) | 0.374 | 0.258 | | | |
| **Variables (rs2227307)** | **Case/control** | **G vs T** | | | **GG vs TT** | | | **GT vs TT** | | |
| | | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ | OR (95% CI) | $P^a$ | $P_z$ |
| Total | 608/1,442 | 1.103 (0.960–1.266) | 0.492 | 0.166 | 1.268 (0.964–1.667) | 0.589 | 0.089 | 0.980 (0.784–1.225) | 0.656 | 0.857 |
| GC | 484/1,040 | 1.126 (0.962–1.318) | 0.348 | 0.140 | 1.317 (0.962–1.804) | 0.432 | 0.086 | 1.024 (0.791–1.325) | 0.558 | 0.859 |
| Ethnicity | | | | | | | | | | |
| Asian | 210/804 | 1.157 (0.931–1.439) | 0.220 | 0.189 | 1.396 (0.926–2.105) | 0.252 | 0.111 | 0.896 (0.634–1.266) | 0.762 | 0.533 |
| Caucasian | 398/638 | 1.068 (0.893–1.276) | 0.444 | 0.474 | 1.177 (0.816–1.697) | 0.632 | 0.384 | 1.044 (0.779–1.400) | 0.297 | 0.772 |
| Genotyping method | | | | | | | | | | |
| PCR | 210/804 | 1.157 (0.931–1.439) | 0.220 | 0.189 | 1.396 (0.926–2.105) | 0.252 | 0.111 | 0.896 (0.634–1.266) | 0.762 | 0.533 |
| TaqMan | 398/638 | 1.068 (0.893–1.276) | 0.444 | 0.474 | 1.177 (0.816–1.697) | 0.632 | 0.384 | 1.044 (0.779–1.400) | 0.297 | 0.772 |
| HWE | | | | | | | | | | |
| Y | 497/1,650 | 1.135 (0.976–1.322) | 0.458 | 0.101 | 1.314 (0.980–1.763) | 0.476 | 0.068 | 1.017 (0.792–1.306) | 0.555 | 0.892 |
| | **Case/control** | **GG + GT vs TT** | | | **GG vs GT + TT** | | | | | |
| Total | 608/1,442 | 1.055 (0.857–1.300) | 0.633 | 0.611 | 1.249 (0.984–1.585) | 0.444 | 0.067 | | | |
| GC | 484/1,040 | 1.101 (0.865–1.401) | 0.536 | 0.433 | 1.257 (0.961–1.646) | 0.265 | 0.095 | | | |
| Ethnicity | | | | | | | | | | |
| Asian | 210/804 | 1.034 (0.754–1.416) | 0.444 | 0.837 | 1.480 (1.023–2.141) | 0.258 | **0.037** | | | |
| Caucasian | 398/638 | 1.073 (0.813–1.415) | 0.294 | 0.620 | 1.115 (0.818–1.520) | 0.981 | 0.491 | | | |
| Genotyping method | | | | | | | | | | |
| PCR | 210/804 | 1.034 (0.754–1.416) | 0.444 | 0.837 | 1.480 (1.023–2.141) | 0.258 | **0.037** | | | |
| TaqMan | 398/638 | 1.073 (0.813–1.415) | 0.294 | 0.620 | 1.115 (0.818–1.520) | 0.981 | 0.491 | | | |
| HWE | | | | | | | | | | |
| Y | 497/1,650 | 1.104 (0.876–1.391) | 0.622 | 0.403 | 1.269 (0.985–1.634) | 0.282 | 0.065 | | | |

**Notes:** *Statistically significant ($P<0.05$). Y refers to $P$(HWE)$>0.05$. Statistically significant figures are shown in bold.

**Abbreviations:** CI, confidence interval; GC, gastric cancer; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; $P^a$, $P$ value of $Q$ test for heterogeneity test; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; $P_z$, $P$ value of $Z$ test for significance test; HB, hospital-based; PB, population-based.

that rs2227306 polymorphism in *IL-8* had no significant association with cancer risk in the subgroup analyses sorted by either genotyping method or ethnicity. However, as for the subgroup analysis categorized by cancer type, it demonstrated a decreased risk of HCC (T vs C: OR =0.721, 95% CI =0.567–0.916, $P_z$=0.007, Figure 2A; TT vs CC: OR =0.447, 95% CI =0.274–0.728, $P_z$=0.001, Figure 2B; TT vs TC + CC: OR =0.480, 95% CI =0.304–0.760, $P_z$=0.002, Figure 2C), whereas no evidence showed significant relevance between the *IL-8* rs2227306 polymorphism and gastric cancer



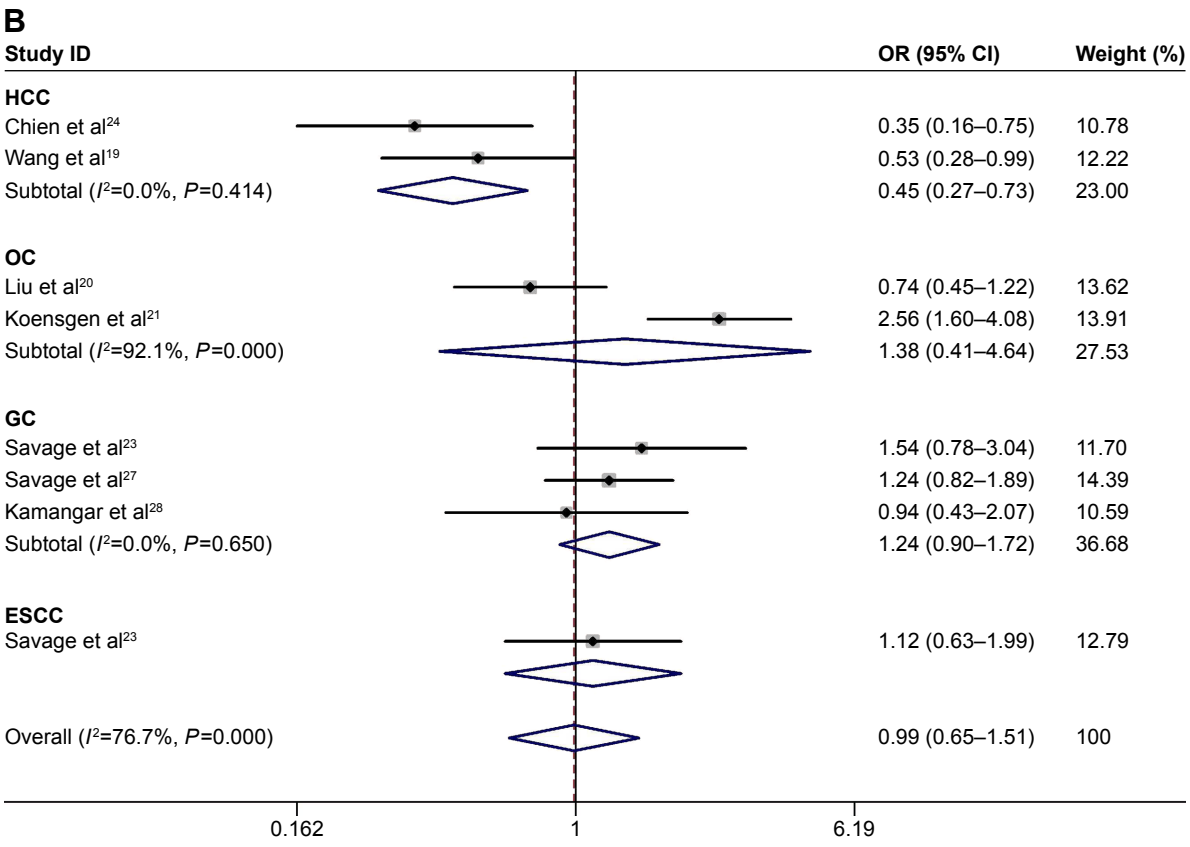




**Figure 2** (*Continued*)

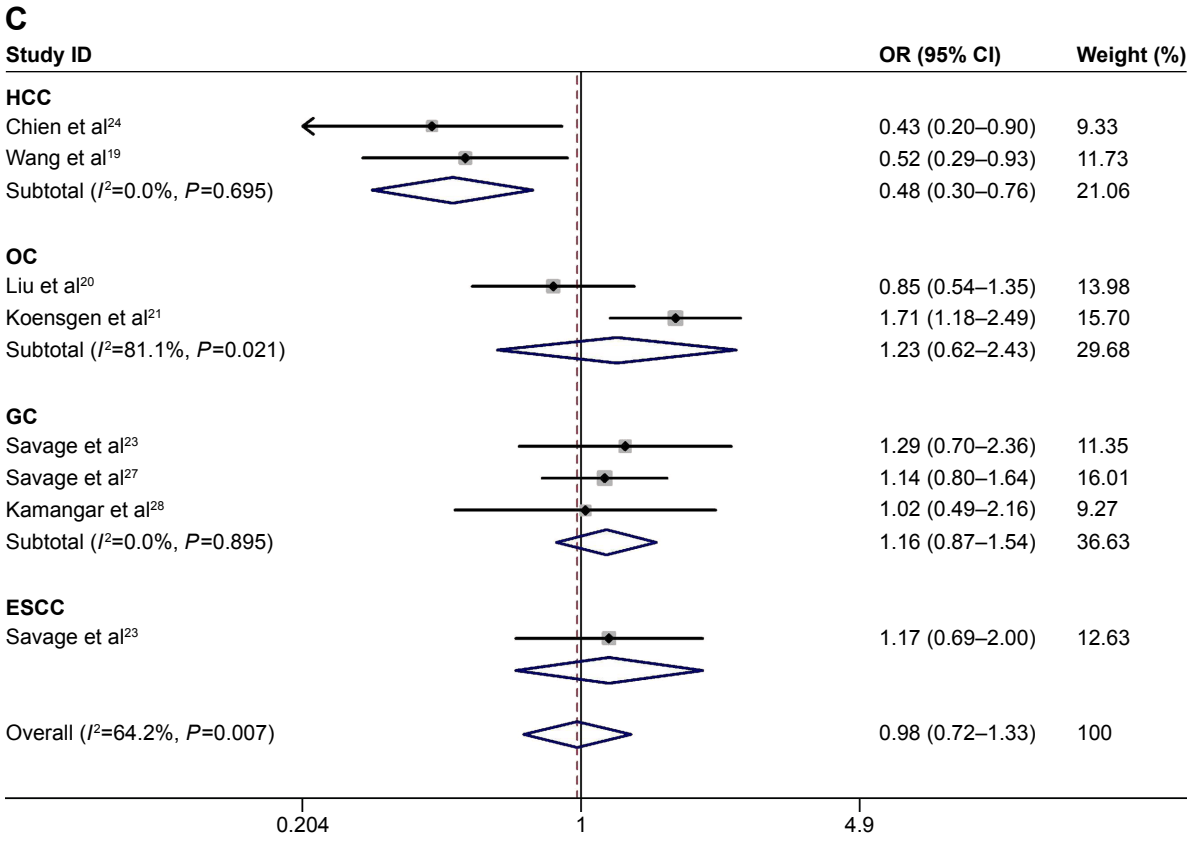



**Figure 2** OR estimates with the corresponding 95% CI for the association of *IL-8* rs2227306 polymorphism with overall cancer risk.
**Notes:** (**A**) T vs C, (**B**) TT vs CC, and (**C**) TT vs TC + CC. The sizes of the squares represent the weighting of the included studies. Weights are from random effects analysis.
**Abbreviations:** CI, confidence interval; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; OC, ovarian cancer; OR, odds ratio.

(T vs C: OR =1.109, 95% CI =0.946–1.300, $P_z$=0.201; TT vs CC: OR =1.244, 95% CI =0.899–1.723, $P_z$=0.187; TC vs CC: OR =1.104, 95% CI =0.860–1.419, $P_z$=0.437; TT + TC vs CC: OR =1.135, 95% CI =0.890–1.447, $P_z$=0.308).

## Sensitivity analysis and publication bias

By deleting one study at a time to evaluate the influence of an individual study on synthetic statistics, we referred this method as a sensitivity analysis. As presented in Figure 3, although each study was removed, the overall results did not alter obviously, which indicated the stability of our eligible statistics. In addition, all the enrolled articles were examined by using Begg's funnel plot and Egger's test in order to find whether publication bias existed, and as shown in Figure 4, no obvious biases were identified. In addition, the study quality was assessed by Newcastle–Ottawa Scale[33] (Table 3).

# Discussion

IL-8 is a kind of chemokine, which has a significant role in tumorigenesis process, particularly for tumor growth, invasion, and angiogenesis.[34] Growing evidence has suggested that abnormal expression of IL-8 may lead to several tumor types, including prostate, breast, lung, and liver cancers.[6,10,11] To illustrate the complicated process of tumorigenesis and improve the theory for preventive interventions, main genes associated with cancer risk should be explored.[35] Genotyping-related polymorphisms were regarded as eligible and valuable methods in predicting cancer risk and prognosis.

The *IL-8* gene, located on chromosome 4q12-21, is 5.2-kb long and is made up of four exons and three introns. A total of five polymorphisms in *IL-8* were reported, such as rs4073, rs2227307, rs2227306, +678T/C, rs1126647, and +1633C/T.[19,20,22–27] However, only rs4073 and rs2227306 polymorphisms are related to the expression alteration of IL-8.[36,37] Rs4073 polymorphism is located at the promoter region of *IL-8*, and a rare allele A of this polymorphism has been identified, which contributed to an increased level of IL-8.[38] In addition, previous studies have confirmed that A allele is associated with an increased risk of many cancer types.[19,20,39] Recently, several meta-analysis have been conducted and have identified that rs4073 polymorphism was related to an increased risk of overall cancers and potentially

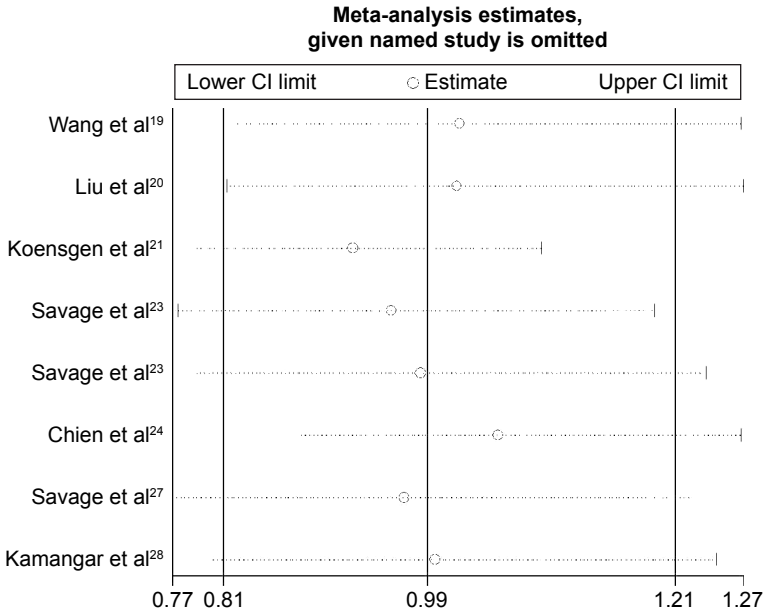



**Figure 3** Sensitivity analysis of overall OR coefficient for *IL-8* rs2227306 polymorphism (T vs C).
**Notes:** Results were calculated by omitting each study in turn. The two ends of the dotted lines represent the 95% CI.
**Abbreviations:** CI, confidence interval; OR, odds ratio.

offered an evidence-based medical certificate to investigate cancer risk.[35,40,41] Considering that a large number of meta-analyses concentrated on *IL-8* rs4073 polymorphism and cancer risk were performed, we focus only on several other polymorphisms in *IL-8* and cancer risk. Rs2227306 polymorphism is located at an intron region of *IL-8* and is involved in the promotion of gene transcription and regulation,[42] while the best strengthening influence on *IL-8* expression was the common haplotype rs4073-rs2227306.[36] Although several other polymorphisms do not influence the expression of *IL-8*, many studies have confirmed the association of those polymorphisms with cancer risk. Wang et al[19] identified that no association of rs4073, rs2227306, −353A/T, and +678T/C polymorphisms in *IL-8* gene and HCC risk was revealed in the Chinese population. Then, Wang et al[39] performed a case–control study enrolling 474 breast cancer patients and

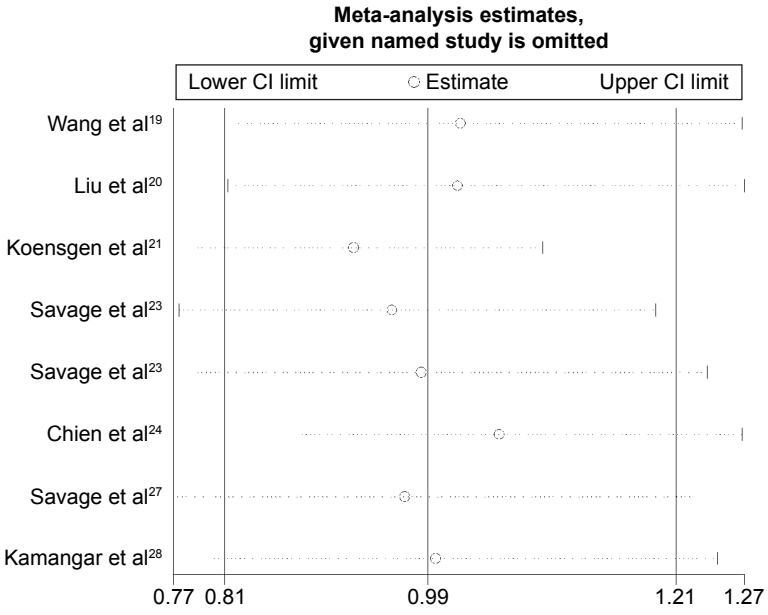



**Figure 4** Publication bias in studies of the association between the *IL-8* rs2227306 polymorphism and cancer susceptibility assessed by Begg's funnel plot.
**Abbreviation:** CI, confidence interval.

**Table 3** Methodological quality of the included studies according to the Newcastle–Ottawa Scale

| Polymorphism | Author | Ethnicity | Adequacy of case definition | Representativeness of the cases | Selection of controls | Definition of controls | Comparability cases/controls | Ascertainment of exposure | Same method of ascertainment | Nonresponse rate |
|---|---|---|---|---|---|---|---|---|---|---|
| rs2227306 | Wang et al[19] | Asian | * | * | NA | * | ** | * | * | * |
| | Liu et al[20] | Asian | * | * | NA | * | ** | * | * | * |
| | Koensgen et al[21] | Caucasian | * | * | NA | * | ** | * | * | * |
| | Savage et al[23] | Asian | * | * | * | * | ** | * | * | * |
| | Savage et al[27] | Asian | * | * | * | * | ** | * | * | * |
| | Chien et al[24] | Asian | * | * | NA | * | ** | * | * | * |
| | Savage et al[23] | Caucasian | * | * | * | NA | ** | * | * | * |
| | Kamangar et al[28] | Caucasian | * | * | * | NA | ** | * | * | * |
| rs1126647 | Liu et al[20] | Asian | * | * | NA | * | ** | * | * | * |
| | Koensgen et al[21] | Caucasian | * | * | NA | * | ** | * | * | * |
| | Chien et al[24] | Asian | * | * | NA | * | ** | * | * | * |
| | Hsieh et al[26] | Asian | * | * | NA | * | ** | * | * | * |
| rs2227307 | Savage et al[23] | Asian | * | * | * | * | ** | * | * | * |
| | Savage et al[27] | Asian | * | * | * | * | ** | * | * | * |
| | Savage et al[23] | Caucasian | * | * | * | NA | ** | * | * | * |
| | Kamangar et al[28] | Caucasian | * | * | * | NA | ** | * | * | * |
| 678T/C | Wang et al[19] | Asian | * | * | NA | * | ** | * | * | * |
| | Ahirwar et al[22] | Caucasian | * | * | * | * | ** | * | * | * |
| | Wei et al[25] | Asian | * | * | * | * | ** | * | * | * |
| 1633C/T | Liu et al[20] | Asian | * | * | NA | * | ** | * | * | * |
| | Koensgen et al[21] | Caucasian | * | * | NA | * | ** | * | * | * |
| | Chien et al[24] | Asian | * | * | NA | * | ** | * | * | * |

**Notes:** This table identifies "high-quality" choices with a "star (*)". A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars (**) can be given for comparability as per the Newcastle-Ottawa Scale.[33] *Represents "yes".

**Abbreviation:** NA, not applicable.

501 female nontumor controls and identified that TT genotype of *IL-8* rs4073 polymorphism has a significantly reduced risk of breast cancer (TT: OR =0.48, 95% CI =0.33–0.72, $P<0.001$). In another study, Liu et al[20] enrolled 270 patients with oral squamous cell carcinoma and 350 healthy controls, and their results demonstrated that four polymorphisms (rs4073, rs2227306, +1633C/T, and +276A/T) were not related to the risk of oral cancer or clinic pathological characteristics.

Currently, the relationship between *IL-8* polymorphisms and cancer risk has been widely reported, but the conclusions remained controversial. Meta-analysis has been regarded as a crucial method to evaluate the influence of chosen genetic polymorphisms on cancer risk. To the very best of our knowledge, this is the first comprehensive meta-analysis of genetics studies on the relevance between *IL-8* gene polymorphisms and cancer risk. We indicated a significantly decreased risk of HCC for rs2227306 polymorphism in allele contrast, recessive, and homozygous models.

## Limitations

Although we have conducted a general retrieval for all eligible studies, there are several drawbacks that should be mentioned. First, the results may lack statistical power because of the limited sample size and limited number of studies enrolled. Second, only publications indexed in PubMed, Web of Science, and Embase databases were retrieved, while some relevant studies might have been ignored in other databases. Finally, unadjusted estimates were obtained in this work, and a more accurate analysis should be conducted on the basis of specific details such as sex, age, alcohol status, and environmental conditions.

## Conclusion

Our meta-analysis suggests that there is no significant relationship between polymorphisms in *IL-8* (rs2227307, rs2227306, +678T/C, rs1126647, and +1633C/T) and overall cancer risk. However, in the subgroup analysis by cancer type, a decreased risk of HCC was found for rs2227306 polymorphism. Well-designed studies are needed to further explicit the actual relevance between *IL-8* polymorphisms and cancer risk.

## Disclosure

The authors report no conflicts of interest in this work.

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