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Review

IL-8 –251A/T polymorphism is associated with decreased cancer risk among population-based studies: Evidence from a meta-analysis

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ABSTRACT

Growing evidence suggests that interleukin-8 (IL-8) play pivotal roles in the pathogenesis of cancer through the modulation of tumour immune response or enhanced angiogenesis. A single nucleotide polymorphism, –251A/T, has been identified in the promoter region of the *IL-8* gene and has been shown to influence its production. Results from previous studies on the association of –251A/T polymorphism with different cancer types remained contradictory. To assess the effect of –251A/T of *IL-8* on cancer susceptibility, we conducted a meta-analysis, up to May 2009, of 14,876 cases with different cancer types and 18,465 controls from 45 published case–control studies. Summary odds ratios and corresponding 95% confidence intervals (CIs) for *IL-8* polymorphism and cancer were estimated using fixed- and random-effects models when appropriate. The AA/AT genotypes were associated with a significantly increased risk of nasopharyngeal carcinoma when compared with TT genotype (OR = 1.48; 95% CI, 1.16–1.89). Moreover, significantly elevated risks were observed in 'other cancers', and also in African population when population is concerned. Interestingly, when stratified separately by population-based studies and hospital-based studies, significantly elevated risk was found among hospital-based studies (OR = 1.21, 95% CI, 1.07–1.37), whereas significantly decreased risk was found among population-based studies (OR = 0.90, 95% CI, 0.83–0.97). This meta-analysis shows that *IL-8* –251A/T polymorphism may play a complex role in cancer development.

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1. Introduction

Interleukin-8 (IL-8), a member of the CXC chemokine family, is a chemoattractant of neutrophils and lymphocytes.[1–3] A wide variety of normal and tumour cells could express IL-8, and the principal role of IL-8 is to initiate and amplify acute inflammatory reactions.[4] Additionally, growing evidence has shown that the important roles IL-8 may play in the pathogenesis of cancer, including angiogenesis, tumour growth, and metastasis.[5–9]

The *interleukin-8* (*IL-8*) gene, located on chromosome 4q13–q21 in humans, is composed of four exons, three introns, and a proximal promoter region.[10] A common single nucleotide polymorphism at position –251 of the *IL-8* promoter region was identified in 2000, and consequent evidences demonstrated the *IL-8* –251A/T polymorphism was associated with IL-8 production or protein expression both *in vivo* and *in vitro*.[11–13] For example, some authors reported that mucosal IL-8 levels of the gastric body with A allele were significantly higher than those with T/T genotype.[12,14] Ohyauchi and colleagues reported that the *IL-8* –251A promoter activity stimulated with IL-1β was significantly higher than that of the –251T allele ($P = 0.021$).[13] However, Lee and colleagues reported that the presence of –251T allele exerts a 2–5-fold higher transcriptional activity than that of the –251A counterpart.[15] To date, a number of molecular epidemiological studies have been done to evaluate the association between *IL-8* –251 A/T polymorphism and tumour risk in diverse populations. The tumour types included gastric cancer,[12–26] breast cancer,[27–31] colorectal cancer,[32–37] prostate cancer,[38–41] lung cancer,[42–45] nasopharyngeal carcinoma,[46–48] bladder cancer,[49] tongue cancer,[50] basal cell cancer,[51] oral squamous cell carcinoma,[52] oesophageal squamous cell carcinoma,[26,53] cutaneous malignant melanoma[54] and Kaposi's sarcoma,[55] and so on. However, the results remained contradictory. For instance, Taguchi and colleagues reported that the –251AA genotype of *IL-8* was associated with a significantly increased risk of gastric cancer in a Japanese population[12]; nevertheless, Savage and colleagues did not find any significant association between –251A/T polymorphism of *IL-8* and gastric cancer in a case–control study based on a Polish population.[23]

Because a single study might have been underpowered to detect the overall effects, a quantitative synthesis of the accumulated data from different studies was deemed important to provide evidence on the association of *IL-8* promoter genetic polymorphism with cancer risk. Until recently, only one meta-analysis has been performed to assess the association between *IL-8* –251A/T polymorphism and gastric cancer,[56] but it was limited to a single cancer site. Few studies have been conducted to examine the systematic review of association between *IL-8* promoter polymorphism and overall cancer risk, and the role of IL-8 in the aetiology of cancer is still equivocal.

We carried out a meta-analysis on all published case–control studies to estimate the overall tumour risk of *IL-8* promoter polymorphism and to quantify heterogeneity between the individual studies as well as to investigate the existence of potential publication bias.

2. Materials and methods

2.1. Selection of published studies

We searched the PubMed, Embase and CNKI (China National Knowledge Infrastructure) databases for all articles on the association between *IL-8* polymorphism and cancer risk (last search update 31st May 2009). The following terms were used in this search: 'IL-8 or interleukin-8' and 'cancer' and 'polymorphism or polymorphisms'. Additional eligible studies on this topic were identified by a hand search of references of retrieved articles. Studies testing the association between *IL-8* gene polymorphism and cancer were included if all the following conditions were met: (a) the publication was a case–control study; (b) the study reported odds ratios (ORs) or data for their calculation; and (c) the study was published in English or Chinese. If the studies have the same or overlapping data published by the same researchers,[52,57] we selected the recent one with a larger number of participants. Therefore, the data for this meta-analysis were available from 45 case–control studies, including 14,876 cases with different types of tumour and 18,465 controls.

2.2. Data extraction

Data from these studies were extracted by Gao L.B. and Pan X.M. Publications were read by Jia J. in order to check original data extraction. The following information was recorded for each study: first author, year of publication, country of the first or corresponding author, cancer type, ethnicity, number of cases and controls, genotyping methods, matching variables, A allele frequency in controls, and evidence of Hardy–Weinberg equilibrium (Table 1). Different ethnicity descents were categorised as African, Asian, and European.

2.3. Statistical analysis

ORs were used as a measure of the association between *IL-8* –251A/T polymorphism and risk of cancer. We evaluated the risk of the AA homozygote on cancers compared with the AT or TT genotypes, and then calculated the ORs of AA/AT versus TT and AA versus AT/TT, using dominant and recessive genetic models of the A allele, respectively.

The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics.[58] If there was no obvious heterogeneity, the fixed-effects model (the Mantel–Haenszel method) was used to estimate the summary OR[59]; otherwise, the random-effects model (the DerSimonian and Laird method) was used.[60] To explore sources of heterogeneity across studies, we did stratified and logistic meta-regression analyses. We examined the following study characteristics: cancer types (if one cancer type contains less than three studies, it was merged into the 'other cancers' group), ethnicities, source of controls (hospital-based studies and population-based studies), sex, *Helicobacter pylori* status, smoking status, genotyping methods and sample size ($\leqslant$500 and >500 subjects).

Table 1 – Characteristics of literatures included in the meta-analysis.

Reference	Country	Cancer type	Ethnicity	Sample size (case/control)	Genotyping methods	Matching criteria	A allele frequency in controls	HWE
Ben Nasr et al.[46]	Tunisia	Nasopharyngeal carcinoma	African	160/169	AS-PCR	Age and sex	0.35	Yes
Snoussi et al.[30]	Tunisia	Breast carcinoma	African	308/236	AS-PCR	Residence district	0.46	Yes
Kamali-Sarvestani et al.[27]	Iran	Breast cancer	Asian	257/233	ASO-PCR	–	0.57	Yes
Kang et al.[20]	Korea	Gastric cancer	Asian	334/322	PCR-RFLP	–	0.31	Yes
Ko et al.[21]	Korea	Gastric cancer	Asian	81/308	Snapshot	Age, sex, residence area, year of recruitment	0.32	Yes
Lee et al.[15]	China	Gastric cancer	Asian	470/308	PCR-RFLP	Age and sex	0.43	Yes
Lee et al.[44]	America	Lung cancer	Asian	119/112	Taqman	Sex, age, village and type of fuel currently used for cooking and home heating	0.35	Yes
Liu et al.[28]	China	Breast cancer	Asian	426/647	PCR-RFLP	Age	0.40	Yes
Lu et al.[22]	China	Gastric cancer	Asian	250/300	DHPLC	Gender and age	0.36	Yes
Ohyauchi et al.[13]	Japan	Gastric cancer	Asian	212/244	Direct sequence analysis	–	0.22	Yes
Savage et al.[26]	America	Gastric cancer/oesophageal squamous cell carcinoma	Asian	217/429	Single base extension	Age, smoking and drinking	0.42	Yes
Shimizu et al.[50]	Japan	Tongue cancer	Asian	69/91	PCR-melting curve analysis	–	0.34	Yes
Shirai et al.[24]	Japan	Gastric cancer	Asian	181/468	PCR-RFLP	Sex and smoking status	0.33	Yes
Tai et al.[48]	China	Nasopharyngeal carcinoma	Asian	105/109	PCR-RFLP	–	0.40	Yes
Taguchi et al.[12]	Japan	Gastric cancer	Asian	396/252	PCR-RFLP	Sex and smoking status	0.30	Yes
Wei et al.[47]	China	Nasopharyngeal carcinoma	Asian	280/290	PCR-RFLP	Gender, age, cigarette smoking and alcohol drinking status	0.36	Yes
Ye et al.[14]	Korea	Gastric carcinoma	Asian	153/206	PCR-RFLP	–	0.32	Yes
Zeng et al.[25]	China	Gastric cancer	Asian	206/196	PCR-RDB	Age and sex	0.49	No
Zhang et al.[53]	China	Oesophageal squamous cell car cinoma	Asian	320/404	PCR-RFLP	Age and sex	0.43	Yes
Cacev et al.[37]	Croatia	Colon cancer	European	160/160	Taqman	–	0.44	Yes
Campa et al.[42]	France	Non-small cell lung cancer	European	239/210	Taqman	Age and sex	0.48	Yes
Campa et al.[43]	France	Lung cancer	European	2144/2116	Taqman	–	0.47	Yes
Campa et al.[67]	France	Upper aerodigestive tract cancers	European	769/898	Taqman	Age, sex, and referral or residence area	0.47	Yes
Canedo et al.[16]	Portugal	Gastric cancer	European	333/693	Taqman	–	0.45	Yes
Crusius et al.[17]	Spain	Gastric cancer	European	428/1139	Taqman	Centre, gender, age and date of blood collection	0.47	Yes
Garza-Gonzalez et al.[18]	Mexico	Gastric cancer	European	78/259	ARMS-PCR	Age and sex	0.57	Yes
Howell et al.[54]	United Kingdom	Cutaneous malignant melanoma	European	142/235	ARMS-PCR	–	0.45	Yes

(continued on next page)

Table 1 – (*continued*)

Reference	Country	Cancer type	Ethnicity	Sample size (case/control)	Genotyping methods	Matching criteria	A allele frequency in controls	HWE
Kamangar et al.[19]	America	Gastric cancer	European	112/207	Taqman	Age	0.38	Yes
Kury et al.[32]	France	Colorectal cancer	European	1023/1121	TaqMan	Age and sex	0.44	No
Landi et al.[33]	Spain	Colorectal Cancer	European	352/308	Taqman	Age and sex	0.45	No
Leibovici et al.[49]	America	Bladder cancer	European	463/440	Taqman	Age, sex, and ethnicity	NA	NA
McCarron et al.[38]	United Kingdom	Prostate Cancer	European	238/235	ARMS-PCR	–	0.45	Yes
Michaud et al.[39]	America	Prostate cancer	European	484/613	Taqman	Age, ethnicity, time since initial screening, and date of blood draw	0.50	Yes
Savage et al.[23]	Poland	Gastric cancer	European	287/428	Taqman	–	0.51	Yes
Smith et al.[29]	United Kingdom	Breast cancer	European	119/235	ARMS-PCR	–	0.45	Yes
Theodoropoulos et al.[34]	Greece	Colorectal cancer	European	222/196	ARMS-PCR	Age and sex	0.56	Yes
Vairaktaris et al.[52]	Greece	Oral squamous cell carcinoma	European	158/156	PCR-RFLP	Ethnicity, age, sex and a low-risk working environment	0.23	No
van der Kuyl et al.[55]	Netherlands	AIDS-related Kaposi's sarcoma	European	84/69	Direct sequence analysis	–	0.38	Yes
Vogel et al.[31]	Denmark	Breast cancer	European	361/361	Taqman	Age	0.55	Yes
Vogel et al.[51]	Denmark	Basal cell carcinoma	European	304/315	Taqman	Age and sex	0.49	Yes
Vogel et al.[36]	Denmark	Colorectal cancer	European	355/753	Taqman	Sex	0.54	Yes
Vogel et al.[45]	Denmark	Lung cancer	European	403/744	Taqman	Age and sex	0.54	Yes
Wang et al.[40]	America	Prostate cancer	European	254/252	Taqman	Age at blood donation, ethnicity, date of blood draw, and number of hours between last meal and blood draw	0.48	Yes
Wilkening et al.[35]	Germany	Colorectal cancer	European	300/580	Taqman	Age and gender	0.55	Yes
Yang et al.[41]	America	Prostate cancer	European	520/418	Taqman	Age, intervention group, study clinic, and date of blood draw	0.42	Yes

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; DHPLC, denatured high performance liquid chromatography; PCR-RDB, polymerase chain reaction and reverse dot blot; AS-PCR, allele-specific polymerase chain reaction; ASO-PCR, allele-specific oligonucleotide-polymerase chain reaction; ARMS-PCR, amplification refractory mutation system-polymerase chain reaction; NA, not available; HWE, Hardy–Weinberg equilibrium.

Publication bias was evaluated with funnel plot and Egger's regression asymmetry test.[61] All analyses were done using STATA software, version 10.0 (STATA Corp., College Station, TX). All the *P* values were two- sided.

3. Results

3.1. Characteristics of studies

Overall, 45 studies including 14,876 cases and 18,465 controls were available for this analysis. Study characteristics are summarised in Table 1. The sample size in these case–control studies varied considerably (range 153–4260 individuals). There were two studies of African descendents, 17 studies of Asian descendents, and 26 studies of European descendents. Several genotyping methods were used, including TaqMan, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), amplification refractory mutation system-PCR (ARMS-PCR), single base extension, direct sequencing, PCR-melting curve analysis, denatured high performance liquid chromatography (DHPLC), and polymerase chain reaction and reverse dot blot (PCR-RDB). Nevertheless, only 56% (25/45) of these studies included described genotyping quality control measures, such as positive and negative controls, blindness to the case–control status, a different genotyping assay to confirm the data, and/or random repetition of a portion of samples. The genotype distributions among the controls of all studies were consistent with Hardy–Weinberg equilibrium except for four studies.[25,32,33,52]

3.2. Quantitative synthesis

There was a wide variation in the *IL-8* –251A allele frequency among different ethnicities, ranging from 0.22 in an Asian population[13] to 0.57 in another two populations.[18,27] The mean frequency of –251A allele was 0.41 for African, 0.37 for Asian, and 0.47 for European (Fig. 1 and Table 1).

The evaluations of the association of *IL-8* –251A/T with cancer risk are shown in Table 2. The AA/AT genotypes were associated with a significantly increased risk of nasopharyngeal carcinoma when compared with TT genotype (OR = 1.48; 95% confidence intervals (CI), 1.16–1.89). Moreover, significantly elevated risks were observed in 'other cancers' in all comparison models tested except for AA/AT versus TT genotype (AA versus AT: OR = 1.18; 95% CI, 1.01–1.38; AA versus TT: OR = 1.20; 95% CI, 1.01–1.43; and recessive model: OR = 1.19; 95% CI, 1.02–1.38). Similarly, significantly increased risks were observed in the African population (AA versus TT: OR = 1.99; 95% CI, 1.36–2.91; dominant model: OR = 1.71; 95% CI, 1.27–2.30; recessive model: OR = 1.48; 95% CI, 1.07–2.04) but not in the Asian and European populations. Interestingly, after stratified separately by population-based studies and hospital-based studies, significantly elevated risk was found among hospital-based studies (OR = 1.21, 95% CI, 1.07–1.37), whereas significantly decreased risk was found among population-based studies (OR = 0.90, 95% CI, 0.83–0.97) (Figs. 2 and 3). However, no significant association was found in overall analyses or stratified analyses by sex, *H. pylori* and smoking status in any comparison models tested.

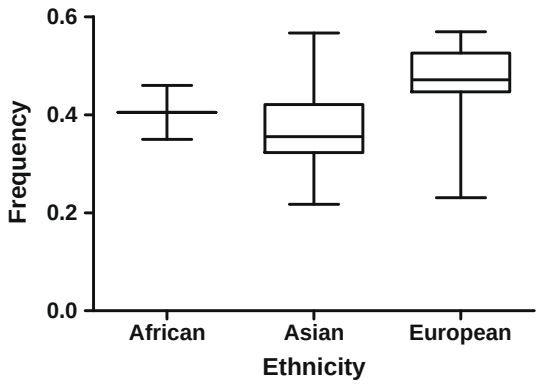

Fig. 1 – Frequencies of the *IL-8* –251A among control subjects stratified by ethnicity.

3.3. Evaluation of heterogeneity

There was heterogeneity among studies in overall comparisons and also subgroup analyses. To explore sources of heterogeneity across studies, we assessed homozygote comparison (AA versus TT) and dominant model comparison (AA/AT versus TT) by source of controls, tumour type, ethnicity, genotyping methods and sample size (⩽500 and >500 subjects).

We found that source of controls (AA/AT versus TT: $P = 0.001$), genotyping methods (AA versus TT: $P = 0.012$; AA/AT versus TT: $P = 0.004$), ethnicity (AA versus TT: $P = 0.012$; AA/AT versus TT: $P = 0.016$), and sample size (AA/AT versus TT: $P = 0.018$) but not tumour type could substantially influence the initial heterogeneity. Additionally, meta-regression analyses revealed that source of controls could explain 35.3% (AA/AT versus TT) of the τ^2, genotyping methods could explain 22.1% (AA versus TT), 20.3% (AA/AT versus TT) of the τ^2, and ethnicity could explain 17.5% (AA versus TT), 11.2% (AA/AT versus TT) of the τ^2, whereas sample size could explain 7.8% (AA/AT versus TT) of the τ^2.

3.4. Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable.

3.5. Publication bias

The Egger's test was performed to evaluate the publication bias of literatures on cancer. Fig. 4 displays a funnel plot that examined the *IL-8* –251A/T polymorphism and overall cancer risk included in the meta-analysis in the dominant model. There was a marginal significance for homozygote comparison (AA versus TT) ($P = 0.047$). However, the bias disappeared when we excluded studies[25,32,33,52] that departed from Hardy–Weinberg equilibrium ($P = 0.129$). No evidence of publication bias in other comparison models was observed.

Table 2 – Stratified analyses of the *IL-8* –251A/T polymorphism on cancer risk.

	n[a]	Cases/controls	AA versus AT		AA versus TT		AA/AT versus TT (dominant)		AA versus AT/TT (recessive)	
			OR (95% confidence intervals (CI))	P[b]	OR (95% CI)	P[b]	OR (95% CI)	P[b]	OR (95% CI)	P[b]
Total	45	14876/18465	1.05 (0.96–1.13)[c]	0.010	1.07 (0.96–1.19)[c]	<0.001	1.06 (0.98–1.15)[c]	<0.001	1.05 (0.97–1.15)[c]	<0.001
Cancer types										
Gastric cancer	15	3609/5759	1.07 (0.87–1.32)[c]	0.002	1.15 (0.89–1.48)[c]	<0.001	1.10 (0.94–1.29)[c]	<0.001	1.11 (0.89–1.38)[c]	<0.001
Colorectal cancer	6	2412/3118	1.00 (0.88–1.15)	0.39	1.00 (0.86–1.17)	0.57	1.01 (0.89–1.14)	0.08	1.01 (0.89–1.14)	0.69
Breast cancer	5	1471/1712	0.92 (0.76–1.10)	0.39	0.86 (0.58–1.27)[c]	0.007	0.94 (0.70–1.28)[c]	0.008	0.90 (0.76–1.06)	0.10
Prostate cancer	4	1496/1518	1.14 (0.95–1.37)	0.42	1.01 (0.82–1.24)	0.16	0.95 (0.73–1.24)[c]	0.045	1.08 (0.91–1.29)	0.45
Lung cancer	4	2905/3182	1.03 (0.91–1.17)	0.68	1.02 (0.88–1.18)	0.42	1.00 (0.89–1.12)	0.49	1.03 (0.91–1.16)	0.52
Nasopharyngeal carcinoma	3	545/568	1.15 (0.82–1.61)	0.28	1.49 (0.75–2.98)[c]	0.03	**1.48 (1.16–1.89)**	0.07	1.36 (0.99–1.87)	0.09
Other cancers	9	2438/3037	**1.18 (1.01–1.38)**	0.07	**1.20 (1.01–1.43)**	0.23	1.12 (0.99–1.26)	0.06	**1.19 (1.02–1.38)**	0.14
Ethnicities										
African	2	468/405	1.24 (0.88–1.75)	0.39	**1.99 (1.36–2.91)**	0.41	**1.71 (1.27–2.30)**	0.75	**1.48 (1.07–2.04)**	0.28
Asian	17	4076/4919	1.10 (0.91–1.32)[c]	0.01	1.19 (0.94–1.52)[c]	<0.001	1.12 (0.96–1.31)[c]	<0.001	1.14 (0.93–1.40)[c]	<0.001
European	26	10332/13141	1.03 (0.96–1.10)	0.08	0.99 (0.92–1.07)	0.14	0.99 (0.91–1.07)[c]	0.01	1.01 (0.95–1.08)	0.13
Source of controls										
Hospital-based	25	7099/7680	0.98 (0.85–1.12)[c]	0.01	1.17 (0.97–1.41)[c]	<0.001	**1.21 (1.07–1.37)**[c]	<0.001	1.05 (0.90–1.22)[c]	<0.001
Population-based	19	5633/8240	1.08 (0.99–1.18)	0.13	0.95 (0.86–1.05)	0.10	**0.90 (0.83–0.97)**	0.86	1.03 (0.95–1.12)	0.06
Smokers	5	2883/2403	1.10 (0.93–1.31)	0.53	1.11 (0.92–1.34)	0.46	1.03 (0.91–1.17)	0.98	1.15 (0.99–1.34)	0.13
Non-smokers	5	591/1454	0.77 (0.53–1.12)	0.054	0.71 (0.48–1.07)	0.44	0.87 (0.68–1.12)	0.29	0.93 (0.48–1.81)[c]	0.02
Sex										
Male	4	2216/1990	1.11 (0.95–1.29)	0.10	1.13 (0.65–1.99)[c]	0.002	1.02 (0.73–1.41)[c]	0.03	1.14 (0.74–1.76)[c]	0.01
Female	4	795/813	0.83 (0.64–1.07)	0.35	0.83 (0.63–1.16)	0.10	0.96 (0.77–1.19)	0.20	0.84 (0.66–1.07)	0.20
H. pylori										
Positive	3	692/584	0.94 (0.33–2.68)[c]	0.01	0.91 (0.18–4.49)[c]	<0.001	0.96 (0.43–2.11)[c]	0.01	1.16 (0.50–2.69)[c]	0.001
Negative	3	256/318	0.88 (0.48–1.63)	0.12	0.77 (0.41–1.42)	0.06	1.00 (0.80–1.25)	0.27	1.46 (0.51–4.19)[c]	0.02

[a] Number of comparisons.

[b] *P* value of Q-test for heterogeneity test.

[c] Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used.

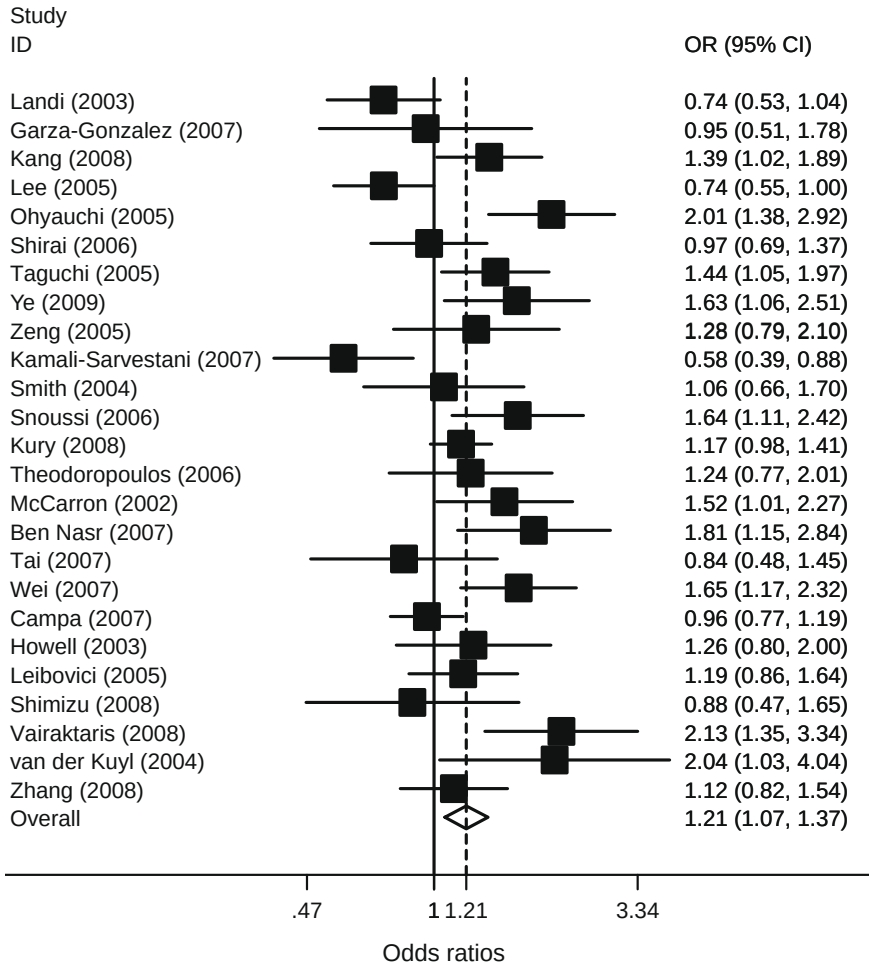

Fig. 2 – Forest plot of cancer risk associated with the AA/AT genotypes compared with the TT genotype in hospital-based studies.

4. Discussion

In this study, we performed a systematic review of association between the *IL-8* –251A/T polymorphism and risk for different types of cancer based on 45 case–control studies for which information was available. Our meta-analysis provided evidence that AA genotype of –251A/T was associated with a significantly increased risk in 'other cancers', and also in African population when population is concerned. Moreover, the AA/AT genotypes were associated with a significantly increased risk among hospital-based studies, whereas the AA/AT genotypes were associated with a significantly decreased risk among population-based studies. Gender and the habit of smoking have nothing to do with the influence of –251A/T polymorphism on cancer risks. These findings indicate that *IL-8* –251A/T polymorphism may play a role, although modest, in cancer development.

IL-8, a member of the CXC chemokine family that was initially identified as a neutrophil chemoattractant, is now believed to play critical roles in inflammation as well as in tumour progression and metastasis.[1–9] The gene encoding IL-8 maps to human chromosome 4q13–q21 and consists of four exons and three introns.[10] A common single nucleotide polymorphism (SNP) at –251 upstream from the transcriptional start site has been proved to influence IL-8 production, and an altered transcriptional activity of the *IL-8* promoter has been confirmed by *in vitro* studies.[11,15,16]

To date, a large number of studies have investigated the association between *IL-8* gene polymorphism and human cancers, and all of them have focused on the A/T polymorphism at –251 in the promoter region. However, some of the results were conflicting, even in the same population, and thus a systematic review and meta-analysis of association between *IL-8* –251A/T polymorphism and cancer risk was of great value. In this meta-analysis, we found that individuals carrying the AA genotype were associated with a higher tumour risk in African population but not in Asian and European populations. Although the reason for these discrepancies is not well known, some possibilities should be considered. On the one hand, it may be due to genetic trait differences since *IL-8* –251A/T polymorphism was distinct among different ethnic groups. On the other hand, it may be due to potential reporting bias. Only two studies of *IL-8* –251A/T polymorphism and cancer susceptibility in the African population were published,[30,46] and both were positively associated with increased cancer risk. There may be a high risk of reporting bias for the relationship of the *IL-8* –251A/T polymorphism and cancer development in African population

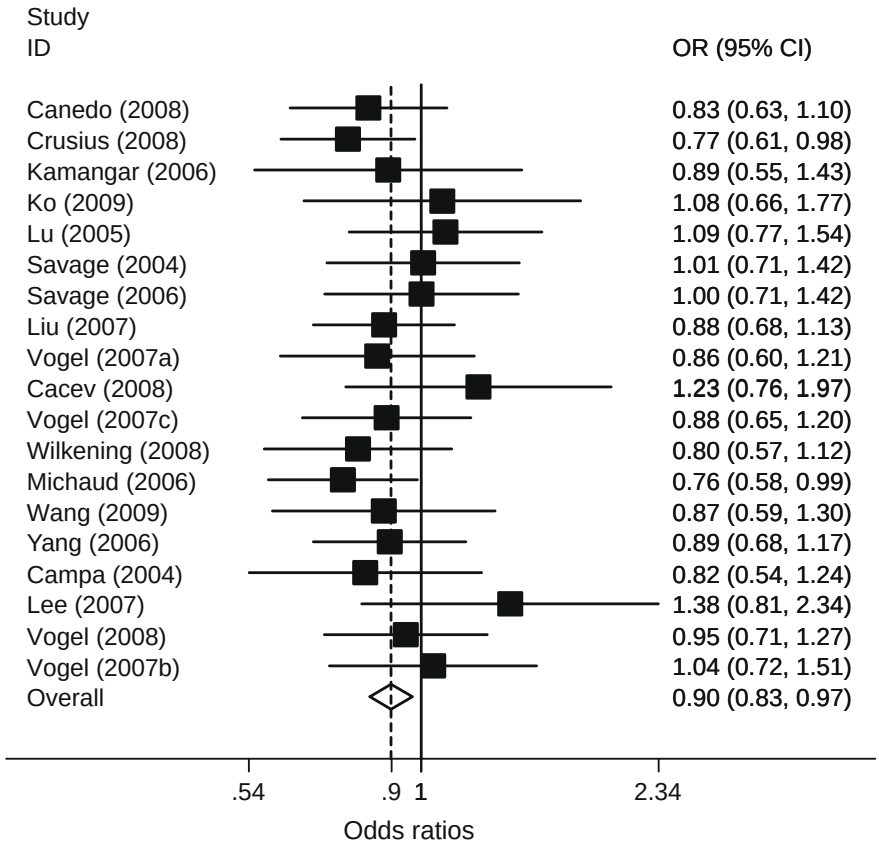

Fig. 3 – Forest plot of cancer risk associated with the AA/AT genotypes compared with the TT genotype in population-based studies.

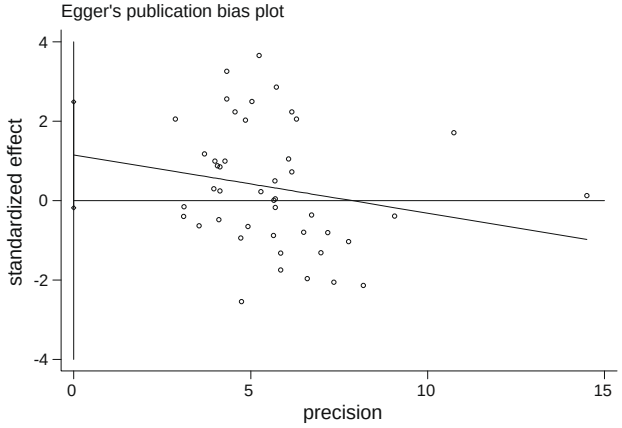

Fig. 4 – Eegger's funnel plot for publication bias test (AA/AT versus TT). Each point represents a separate study for the indicated association.

and thus additional studies with large sample size are necessary to clarify this finding.

Interestingly, when stratified separately by population-based studies and hospital-based studies, inverse results were observed, that is, AA/AT genotypes increased cancer risk among hospital-based studies, whereas AA/AT genotypes decreased cancer risk among population-based studies. Inconsistent results in our population-based studies and hospital-based studies suggest that a selection bias is a major problem for studies of the genetic cause of cancer. Hospital-based studies have a high risk of producing unreliable results because hospital-based controls may not always be truly representative of the general population, especially when the genotypes under investigation were expected to affect the disease conditions that the hospital-based controls may have. Therefore, a methodologically preferable design, such as using non-related subjects that are recruited from the same source population as controls, is crucial to avoid selection bias.

After subgroup analyses according to cancer types, we found that there was an increased cancer risk for nasopharyngeal carcinoma in the dominant model. The same result was observed in 'other cancers' in the heterozygote comparison (AA versus AT), homozygote comparison (AA versus TT), as well as in the recessive model. However, we failed to find any significant association between *IL-8* –251A/T polymorphism and gastric cancer, breast cancer, colorectal cancer, prostate cancer and lung cancer in any comparison models. Moreover, gender was taken into the analysis to see if *IL-8* –251A/T polymorphism was more frequent in one gender than in another affected with cancers. The results demonstrated that there was no association between *IL-8* –251A/T polymorphism and cancer risk in different genders.*H. pylori* is thought to be an aetiologic agent for human cancer, especially for gastric cancer.[62,63] In view of the important role in the aetiology

of cancer, the impact of *H. pylori* status on the development of gastric cancer has been characterised in several studies.[15,20,22] Therefore, it is necessary to combine the results when the effects of *IL-8* –251A/T polymorphism on tumours are explored. However, no evidence of an interaction between the *IL-8* –251A/T polymorphism and *H. pylori* infection was observed, probably because of the insufficient statistical power with only 948 cases and 902 controls eligible in this study.

Tobacco smoking is a common carcinogenic exposure leading to smoking-related cancers, in particular, lung cancer, and influences the production of cytokines.[64–66] Thus, smoking may interact with *IL-8* –251A/T polymorphism to initiate and promote tumourigenesis and metastasis. Nevertheless, our results were inconsistent with our hypothesis, and we found no significant association between *IL-8* –251A/T polymorphism and smoking status. The null result may be due to the limited number of studies with only three studies available in this meta-analysis.[22,43,53]

One of the major concerns in a sound meta-analysis is publication bias due to selective publication of reports. In the current study, funnel plot and Egger's test were done to assess this problem. Although there was a publication bias for homozygote comparison (AA versus TT), the bias disappeared when we rejected studies[25,32,33,52] with departures from the Hardy–Weinberg equilibrium. Another important issue for any meta-analysis is the degree of heterogeneity that exists between the component studies because non-homogeneous data isare liable to result in misleading results. In the present study, the Q-test and I^2 statistics were carried out to test the significance of heterogeneity. Obvious heterogeneity between studies was observed in overall comparisons and also some subgroup analyses, and then meta-regression analysis was used to explore sources of heterogeneity. We found that source of controls, genotyping methods, ethnicity and sample size did contribute to potential heterogeneity. Additionally, if the studied polymorphism is a T/A or C/G transversion, there is a danger that the two alleles have been mixed up in some of the studies in meta-analysis since a T or C will be an A or G when read from the other strand. We have checked the primer and/or probe in the included studies carefully, and found A allele in three literatures[18,27,34] was T in other published studies. Although it is very simple, the error is frequently occurring, which may hamper genetic epidemiology. Therefore, the investigators should make attempt to check that the included studies have chosen the same allele as a reference to avoid the careless error.

In conclusion, this meta-analysis indicates that the AA/AT genotypes are associated with a significantly decreased risk among population-based studies. Well-designed, unbiased prospective studies with larger sample size should be conducted to confirm these results. Moreover, further studies estimating the effect of gene–gene and gene–environment interactions may eventually provide a better, comprehensive understanding of the association between the *IL-8* –251A/T polymorphism and cancer risk.

Conflict of interest statement

None declared.

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