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−251 T/A polymorphism of the interleukin-8 gene and cancer risk: a HuGE review and meta-analysis based on 42 case–control studies

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Abstract The −251T/A (rs4073), a single nucleotide polymorphism, has been identified in the promoter region of the interleukin-8 (IL-8) gene. It's presence could influence the production of IL-8 protein by regulating the transcriptional activity of the gene. A large number of studies have been performed to evaluate the role of −251T/A polymorphism on various cancers, with inconsistent results being reported. In this paper, we summarized 13,189 cases and 16,828 controls from 42 case–control studies and attempted to assess the susceptibility of −251T/A polymorphism to cancers by a comprehensive meta-analysis. Pooled odds ratios and 95% confidence intervals were calculated by using the random-effects model. Publication bias, subgroup, and sensitivity analysis were also performed. Results showed that the carriers of the −251A allele had about a 12–21% increased risk for the reviewed cancer, in total. The carriers of −251A had an elevated risk to breast cancer, gastric cancer and nasopharyngeal cancer and a reduced risk to prostate cancer, but no evidence was found to indicate that the −251A allele predisposed its carriers to colorectal and lung cancers. When stratified separately by 'racial descent' and 'study design', it was found that the carriers of the −251A allele among the African group, Asian group and hospital-based case–control study group were at a higher risk for cancer, but not in European group and population-based case–control study. These results show that −251A allele is susceptible in the development of low-penetrance cancers.

Keywords Interleukin-8 · Meta-analysis · Association · Cancer

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Our study indicated that −251A allele of the interleukin-8 gene was emerging as a low-penetrance cancer susceptibility allele for the development of cancers.

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Introduction

Tumorigenesis is a complex, multi-step process that includes cellular neoplastic transformation, resistance to apoptosis, autonomous growth signaling, emergence of a vascular supply, evasion of immunologic surveillance, and the acquisition of invasive/metastatic properties [1]. Soluble factors in the tumoral environment which are derived not only from tumor cells, but also from stroma, inflammatory cells, and endothelial cells, are critical determinants of tumor processes. Direct and indirect evidence strongly

implicates that chemokines, a subset of soluble factors, play a key role in tumorigenesis [2, 3].

As a member of the chemokine family, interleukin-8 (IL-8) is well known for its leukocyte chemotactic properties and its tumorigenic and proangiogenic activities [4, 5]. It is produced by a wide range of normal cells including monocytes, neutrophils, fibroblasts, and endothelial cells [6]. Initially characterized for its leukocyte chemotactic activity, it is mainly involved in the initiation and amplification of acute inflammatory reactions as well as in the maintenance of chronic inflammatory processes [7]. In addition, IL-8 is produced by several types of tumor cells [8] and has been involved in angiogenesis and neovascularization-dependent tumor growth [9, 10]. It is also overexpressed in a variety of human tumors and is involved in tumor invasion and metastasis [11–13]. Therefore, IL-8 may constitute a risk factor in the development and progression of tumors.

IL-8 gene is located on chromosome 4q13-21 and consists of four exons, three introns, and a proximal promoter region. It's gene coding exhibits several functional polymorphisms, fifteen of them have been characterized [14]. Among these, a T/A single nucleotide polymorphism was identified in the promoter region of the *IL-8* gene −251 base pairs upstream of the transcriptional start site and in vitro assays performed show that it influences the production of IL-8 and affects the transcriptional activity of the IL-8 promoter [15, 16]. However, the relationship between the −251T/A polymorphism and *IL-8* gene transcriptional activity has been inconsistent. Most all reports have demonstrated that the −251A allele is directly associated with higher IL-8 transcription activity [16–18]. However, in gastric carcinoma cell line, Lee et al. [19] found that −251T possessed transcription activity 2- to 5-fold stronger than its −251A counterpart.

A large number of molecular epidemiology studies have been preformed to evaluate the role of −251T/A polymorphism on various cancers such as breast, colorectal, gastric, lung, prostate, etc. [15, 18–66]. The frequency of the −251A allele varies in different geographic areas and ethnic populations. Moreover, genetic effects of the polymorphism have been shown to vary from one type of cancer to the other. Even at the same tumor site, the results are conflicting. Consequently, the statistical power of an individual study could be very limited for efficient assessment of the −251A allele. Integration of these data sets may provide improved statistical power to detect the significance.

With an aim of addressing inconsistencies in the findings of these studies, we adopted a meta-analysis based on published case–control studies attempting to assess the association between the IL-8-251 T/A polymorphism and cancer susceptibility.

Materials and methods

Primary search strategy

We searched MEDLINE (US National Library of Medicine, Bethesda, MD) for all genetic association studies on the rs4073 polymorphism of IL-8 and the susceptibility of cancer published before November 2010 using the PubMed search engine. The search used the keywords and subject terms "IL-8" or "interleukin-8," "−251T/A" or "rs4073," "polymorphism," or "SNPs," and "cancer and/or carcinoma and/or neoplasm" and was limited to English-language papers. The references of all computer-identified publications were searched. In addition, the PubMed option "Related Articles" and the publications on same topic in the reference lists of the reviewed articles were retrieved to search for potentially relevant publications.

Criteria for inclusion and exclusion

Any human associated study, regardless of sample size, was included if it met the following criteria: (a) the study used an unrelated case–control design; (b) the study investigated the association between −251T/A polymorphisms of IL-8 and the risk of cancer; and (c) the genotype distribution of control population must be in Hardy–Weinberg equilibrium [goodness of fit test, degree of freedom (df) = 1]. For the articles with same population resource or overlapping data sets, the publication reporting the largest or most recent data set was included.

Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. The following information was sought from each article: author, journal and year of publication, country of origin, selection and characteristics of cancer cases and controls, demographics, ethnicity, study design, genotyping methods and genotyping information. For subjects of different ethnicities, data were extracted separately and categorized as European, Asian, and African (Table 1).

Statistical analysis

Firstly, we tested significance of deviation of genotype distribution at the polymorphic site from that expected from Hardy–Weinberg equilibrium in the control sample for each of the selected case–control data sets. The random-effects model was used to calculate the pooled odds ratio to estimate genotype AA, genotype TA, and A-allele carriers (AA + TA) against the TT genotype. In addition to comparisons for total subjects, studies were categorized

Table 1 Characteristics of included studies investigated the association between −251 T/A polymorphisms of IL-8 and cancer risk

First author	Magazine	Country	Racial descent	Study design	Genotyping methods	Case TT/TA/AA	Control TT/TA/AA	HWE *P*-value
Breast cancer								
Snoussi [20]	BMC Cancer	Tunisia	African	PCC	AS-PCR	84/201/124	92/138/71	0.173
Snoussi [21]	Hum Immunol	Tunisia	African	HCC	AS-PCR	65/157/86	72/110/54	0.338
Kamali-Sarvestani [22]	Neoplasma	Iran	Asian	HCC	ASO-PCR	64/114/79	79/106/48	0.261
Vogel [23]	Carcinogenesis	Denmark	European	PCC	Taqman	88/160/113	78/167/116	0.221
Smith [24]	Eur J Immunogenet	England	European	HCC	ARMS-PCR	37/63/19	76/105/54	0.131
Colorectal cancer								
Cacev [25]	Carcinogenesis	Croatia	European	PCC	Taqman	46/75/39	53/73/34	0.346
Wilkening [26]	Carcinogenesis	Germany	European	PCC	Taqman	71/133/96	115/296/169	0.476
Vogel [27]	Mutat Res	Denmark	European	PCC	Taqman	83/178/94	160/367/226	0.627
Gunter [28]	CEBP	America	European	PCC	PCR–RFLP	52/87/66	65/94/32	0.840
Theodoropoulos [29]	World J Gastroenterol	Greece	European	PCC	ARMS-PCR	76/106/40	64/90/42	0.328
Gastric carcinoma								
Bo [30]	J Interferon Cytokine Res	China	Asian	HCC	PCR–RFLP	64/108/36	68/96/26	0.389
Zhang [31]	Mol Biol Rep	China	Asian	PCC	PCR–RFLP	130/261/128	160/251/93	0.754
Song [32]	Comp Funct Genomics	China	Asian	HCC	PCR–RFLP	33/72/20	47/70/23	0.720
Ye [33]	J Clin Gastroenterol	Korea	Asian	HCC	PCR–RFLP	54/82/17	97/86/23	0.553
Ko [34]	Nutr	Korea	Asian	PCC	Snapshot	34/35/12	135/146/27	0.155
Kang [35]	J Clin Gastroenterol	Korea	Asian	PCC	PCR–RFLP	126/159/49	147/148/27	0.226
Shirai [36]	J Gastroenterol Hepatol	Japan	Asian	HCC	PCR–RFLP	83/78/20	211/208/49	0.830
Kamali-Sarvestani [37]	World J Gastroenterol	Iran	Asian	HCC	ASO-PCR	4/6/9	57/74/22	0.798
Taguchi [18]	CEBP	Japan	Asian	HCC	PCR–RFLP	161/191/44	125/105/22	0.994
Lee [19]	Clin Cancer Res	China	Asian	HCC	PCR–RFLP	198/213/59	108/138/62	0.143
Lu [38]	Carcinogenesis	China	Asian	PCC	DHPLC	94/102/54	119/144/37	0.516
Ohyauchi [39]	Gut	Japan	Asian	HCC	Direct sequence analysis	93/106/13	149/84/11	0.847
Savage [40]	CEBP	China	Asian	PCC	Single base extension	26/39/23	147/207/75	0.885
Canedo [15]	Eur J Cancer Prev	Portugal	European	PCC	Taqman	111/169/53	203/353/137	0.460
Crusius [41]	Ann Oncol	Spain	European	PCC	Taqman	142/203/83	315/574/250	0.706
Garza-Gonzalez [42]	BMC Cancer	Mexico	European	HCC	ARMS-PCR	15/47/16	68/97/42	0.492
Kamangar [43]	Cancer Causes Control	Finland	European	PCC	Taqman	42/56/14	72/111/24	0.055
Savage [44]	CEBP	Poland	European	PCC	Taqman	71/140/76	106/205/117	0.391
Lung cancer								
Vogel [45]	Mutat Res	Denmark	European	PCC	Taqman	91/203/109	161/364/219	0.672
Campa [46]	CEBP	France	European	HCC	Taqman	578/1081/485	574/1084/458	0.203
Campa [47]	Carcinogenesis	Norway	European	HCC	Taqman	71/119/49	54/112/44	0.317
Nasopharyngeal carcinoma								
Ben [48]	Hum Immunol	Tunisia	African	HCC	AS-PCR	49/74/37	75/71/23	0.350

Table 1 continued

First author	Magazine	Country	Racial descent	Study design	Genotyping methods	Case TT/TA/AA	Control TT/TA/AA	HWE *P*-value
Wei [49]	Clin Immunol	China	Asian	HCC	PCR–RFLP	89/137/54	126/122/42	0.165
Prostate cancer								
Wang [50]	Prostate	America	European	PCC	Taqman	58/127/69	52/138/62	0.124
Michaud [51]	Cancer Res	America	European	PCC	Taqman	147/225/112	152/310/151	0.777
Yang [52]	Eur J Cancer Prev	Finland	European	PCC	Taqman	181/236/103	135/217/66	0.168
McCarron [53]	Cancer Res	England	European	HCC	ARMS-PCR	57/122/59	76/105/54	0.131
Others								
Shimizu [54]	Auris Nasus Larynx	Japan	Asian	HCC	PCR-melting curve analysis	31/30/8	38/45/8	0.296
Campa [55]	Cancer Causes Control	France	European	HCC	Taqman	213/369/187	241/468/189	0.170
Vogel [56]	Mutat Res	Denmark	European	PCC	Taqman	71/146/87	76/170/69	0.156
Savage [40]	CEBP	China	Asian	PCC	Single base extension	48/55/26	147/207/75	0.885
van der Kuyl [57]	AIDS	Netherlands	European	PCC	Direct sequence analysis	22/43/19	29/27/13	0.151
Howell [58]	Eur J Immunogenet	England	European	HCC	ARMS-PCR	39/74/29	76/105/54	0.131
Deviated from HWE								
Zhang [59]	Cancer Causes Control	America	European	PCC	Time-of-flight mass spectrometry	31/71/60	28/65/80	0.022
Ahirwar [60]	Arch Med Res	Indian	Asian	HCC	AS-PCR	69/65/71	111/107/52	0.006
Kury [61]	BMC Cancer	France	European	HCC	Taqman	307/511/205	375/516/230	0.033
Vairaktaris [62]	Eur J Surg Oncol	Greece	European	HCC	PCR–RFLP	56/88/14	84/72/0	<0.001
Landi [63]	Cancer Res	Spain	European	HCC	Taqman	39/61/28 78/106/40	83/170/55	0.047

CEBP Cancer Epidemiol Biomarkers Prev, *HCC* hospital based case–control studies, *PCC* population based case–control studies, *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism, *DHPLC* denatured high performance liquid chromatography, *AS-PCR* allele-specific polymerase chain reaction, *ASO-PCR* allele-specific oligonucleotide-polymerase chain reaction, *ARMS-PCR* amplification refractory mutation system-polymerase chain reaction, *HWE* Hardy–Weinberg equilibrium

into different subgroup analyses according to the ethnicity and tumor site (if a particular tumor type includes only one published study, it was categorized into the "other cancer" group). For each subgroup, we estimated the between-study heterogeneity across the eligible comparisons using the χ^2-based Q test [67] and the heterogeneity was considered significant if $P < 0.05$. We also used the statistic of I^2 to efficiently test for the heterogeneity [68], with $I^2 < 25\%$, 25–75% and >75% to represent low, moderate and high degree of inconsistency, respectively. When heterogeneity was not an issue, fixed effect model with Mantel–Haenszel method was used. Otherwise, a random effect model with Inverse variance method was used.

Publication bias was investigated with funnel plot, which is used as the main graphical method. To supplement the funnel plot approach, the Begg and Mazumdar adjusted rank correlation test [69] and the Egger regression asymmetry test [70] were adopted. To evaluate the stability of the results, we performed a one-way sensitivity analysis. The scope of this analysis reflects the influence of an individual data set by estimating the average odds ratio in the absence of each data set [71]. Statistical tests performed in the present analysis were considered significant whenever the corresponding null-hypothesis probability was $P < 0.05$.

All analyses were done with review manager software (RevMan; version 5.0, The Cochrane Collaboration, Oxford, England) and STATA software (version 10.0, Stata Corporation, College Station, TX). All the P values were two-sided.

Results

Meta-analysis results

A total of 58 published studies investigated the relationship between IL-8-251T/A polymorphism and cancer risk, three

of which were excluded because they did not present detailed genotyping information [64, 65] or they investigated the same population of reported articles [66]. Eight studies were excluded because they were not a case–control study [72–79]. Another five studies were excluded because their genotype distributions in control population significantly deviate from HWE [59–63]. Hence, 42 case–control studies [15, 18–58], including 13,189 cancer cases and 16,828 controls, were used in this analysis, study characteristics were summarized in Table 1.

Overall data analysis

For all 43 data sets extracted from the 42 case–control studies, −251A allelic frequency in the pooled cases was moderately higher than that in the corresponding controls ($Z = 2.63$, $P = 0.008$). The pooled odds ratio estimate was 1.12 (95% confidence interval (CI) 1.03–1.23), suggesting that carriers of the −251A allele would have a moderately higher risk of being predisposed to developing cancer (Table 2). Both Cochran's Q test ($Q = 105.82$ with 42 df, $P < 0.00001$) and the estimate of I^2 (60%) revealed a significant heterogeneity among the constituent studies (Table 3). To assess the cause of heterogeneity, we carried out subgroup analyses for 'cancer type', 'racial descent' and 'study design'. Table 2 summarizes the odds ratio estimates and the corresponding 95% CIs for the subgroups. Table 3 summarizes Q tests and I^2 estimates for the subgroups. When stratified separately by 'racial descent', we found that −251A homozygote, heterozygote and −251A allele carriers increased cancer risk among the African and Asian group but not the European group. Subgroup analysis of 'study design' indicated that significantly increased risks were found among hospital-based case–control studies but not in population-based case–control studies. Because of the existence of heterogeneity, we carried out one-way sensitivity analyses and found that the results in odds ratio estimates were consistent with previous results when heterogeneity was removed, which confirmed the stability of the odds ratio estimates. The analyses for each type of cancer are detailed later in this text. The P values for the Begg and Mazumdar test and the Egger test were all higher than 0.05 for −251A homozygote, heterozygote and −251A allele carriers (Table S1, on-line supplementary data), both suggesting a negligible publication bias. In addition, to explore sources of heterogeneity, we carried out meta-regression analysis by covariate 'cancer type', 'racial descent', 'genotyping methods' and 'study design'. Results indicated that covariates 'racial descent', 'genotyping methods' and 'study design' could explain 54% (AA vs. TT), 100% (AT vs. TT) and 83.29% ((AA + AT) vs. TT) of heterogeneity (Table S2, on-line supplementary data).

Table 2 Estimates of odds ratios and the corresponding 95% CIs for AA, TA genotypes and A allele carriers versus the TT genotype analyzed by a random-effects model, up to November 2010

Type	No. of data sets	No. of cases	No. of controls	AA vs. TT		TA vs. TT		(AA + TA) vs. TT	
				OR	95% CI	OR	95% CI	OR	95% CI
Overall	43	13,189	16,828	1.21*	1.08–1.36	1.08	0.99–1.17	1.12*	1.03–1.23
Cancer type									
Breast	5	1,454	1,366	1.36	0.91–2.06	1.28*	1.00–1.64	1.32	0.99–1.75
Colorectal	5	1,242	1,880	1.12	0.75–1.66	0.94	0.79–1.13	1.00	0.81–1.25
Gastric									
Asian	13	3,036	3,824	1.48*	1.13–1.95	1.20*	1.04–1.40	1.27*	1.08–1.48
European	5	1,238	2,674	0.85	0.67–1.08	0.96	0.75–1.24	0.94	0.74–1.19
Group total	18	4,274	6,498	1.28*	1.02–1.62	1.13	0.98–1.30	1.17*	1.01–1.36
Lung	3	2,786	3,070	1.00	0.86–1.16	0.97	0.86–1.10	0.98	0.87–1.10
Nasopharyngeal	2	440	459	2.04*	1.38–2.99	1.59*	1.19–2.13	1.70*	1.30–2.24
Prostate	4	1,496	1,518	1.03	0.78–1.36	0.91	0.68–1.22	0.95	0.72–1.25
Others	6	1,497	2,037	1.18	0.97–1.43	1.00	0.80–1.24	1.04	0.87–1.23
Racial descent									
African	3	877	706	1.95*	1.48–2.59	1.59*	1.25–2.02	1.71*	1.36–2.14
Asian	17	3,771	4,867	1.49*	1.20–1.85	1.19*	1.04–1.36	1.26*	1.10–1.45
European	23	8,541	11,255	1.00	0.89–1.12	0.95	0.87–1.04	0.97	0.89–1.05
Study design									
Hospital-based	20	6,567	7,116	1.30*	1.08–1.56	1.25*	1.09–1.43	1.27*	1.11–1.46
Population-based	23	6,622	9,712	1.16	0.98–1.36	0.96	0.88–1.05	1.02	0.92–1.13

*$P < 0.05$

Table 3 Heterogeneity test for studies of each genotype (up to November 2010) with Cochran's Q test and the quantity I^2

Type	AA vs. TT			TA vs. TT			(AA + TA) vs. TT			No. of data sets
	Q value	P value	I^2 (%)	Q value	P value	I^2 (%)	Q value	P value	I^2 (%)	
Overall	109.47	<0.00001	62	86.09	0.0002	51	105.82	<0.00001	60	43
Cancer type										
Breast	14.84	0.005	73	7.05	0.13	43	10.78	0.03	63	5
Colorectal	14.05	0.007	72	3.55	0.47	0	6.72	0.15	40	5
Gastric										
Asian	32.84	0.001	63	20.72	0.05	42	25.43	0.01	53	13
European	5.14	0.27	22	8.65	0.07	54	8.79	0.07	55	5
Group total	54.22	<0.00001	69	37.39	0.003	55	48.17	<0.0001	65	18
Lung	1.21	0.54	0	0.76	0.68	0	0.94	0.62	0	3
Nasopharyngeal	0.55	0.46	0	0.00	0.99	0	0.10	0.75	0	2
Prostate	5.18	0.16	42	8.19	0.04	63	8.06	0.04	63	4
Others	1.93	0.86	0	7.65	0.18	35	5.88	0.32	15	6
Racial descent										
African	0.70	0.71	0	0.00	1.00	0	0.10	0.95	0	3
Asian	36.99	0.002	57	27.49	0.04	42	33.10	0.007	52	17
European	34.73	0.04	37	30.86	0.10	29	33.20	0.06	34	23
Study design										
Hospital-based	46.09	0.00	59	44.19	0.00	57	52.56	0.00	64	20
Population-based	61.89	0.00	64	30.63	0.10	28	44.27	0.00	50	23

Breast cancer

Five studies investigated the susceptibility of −251A carriers to breast cancer, comprising 1,454 patients and 1,366 normal controls [20–24]. Overall meta-analysis showed that the −251A heterozygotes had a moderately increased risk of developing breast cancer (OR 1.28, 95% CI 1. 00–1.64). However, statistical tests showed a significant heterogeneity among these studies ($Q = 10.78$ with 4 df, $P = 0.03$; $I^2 = 63\%$). To evaluate the stability of the results, we performed a one-way sensitivity analysis. The heterogeneity was effectively removed ($Q = 2.80$ with 3 df, $P = 0.42$; $I^2 = 0\%$) after exclusion of the data of Vogel et al. [23], and the results were consistent with our previous results without omission. The OR estimates for −251A heterozygotes and −251A alleles were 1.45 (95% CI 1.18–1.79) and 1.52 (95% CI 1.25–1.85), respectively. So, our meta-analysis result provided evidence that IL-8 −251A carriers are associated with an increased risk of breast cancer.

Colorectal cancer

Five studies investigated the susceptibility of −251A carriers to colorectal cancer in Europeans, comprising 1,242 patients and 1,880 normal controls [25–29]. When these data sets were analyzed together, there was no significant heterogeneity ($Q = 6.72$ with 4 df, $P = 0.15$; $I^2 = 40\%$). The odds ratio for the risk of cancer for the −251A carriers was estimated as 1.00 (95% CI 0.81–1.25), and it showed no significant association of the −251A allele with progression of colorectal cancer.

Gastric cancer

Eighteen studies investigated −251T/A polymorphism in relation to gastric cancer [15, 18, 19, 30–44], which involved 4,274 cases and 6,498 controls. Meta-analysis showed that the −251A alleles had a significantly increased risk of developing gastric cancer (OR 1.17, 95% CI 1. 01–1.36). The odds ratio estimates for −251A homozygote and heterozygote were 1.28 (95% CI 1. 02–1.62) and 1.13 (95% CI 0.98–1.30), respectively. However, statistical tests showed a significant heterogeneity among these studies ($Q = 48.17$ with 17 df, $P < 0.0001$; $I^2 = 65\%$). To avoid the influence of the genetic heterogeneity on the association analysis, we separated the meta-analysis according to Asian and European groups. Significantly elevated risks were observed in all comparison models in the Asian group but not in the European group (Table 2). However, heterogeneity in the Asian group was still high ($P = 0.01$), which could be directly attributed to the data set from Lee et al. [19]. After exclusion of this data set, the heterogeneity was effectively

removed ($Q = 12.05$ with 11 df, $P = 0.36$; $I^2 = 9\%$). Sensitivity analysis got similar results in odds ratio estimates after excluding this data set [Compared with TT genotype, OR for AA, AT genotypes and A allele carriers were 1.65 (1.39–1.95), 1.26 (1.09–1.45) and 1.34 (1.19–1.51), respectively], indicating that our results were statistically reliable. These results demonstrated that the −251A allele was an ethnicity-dependent risk factor for gastric cancer.

Lung cancer

Three studies addressed the relationship of the −251T/A polymorphism to lung cancer in Europeans [45–47], which involved 2,786 cases and 3,070 controls. The heterogeneity tests were not statistically significant ($Q = 0.94$ with 2 df, $P = 0.62$; $I^2 = 0\%$). The odds ratio estimate from the pooled data sets for the −251A carriers was 0.98 (95% CI 0.87–1.10). There were no significant difference in allelic and genotypic frequency distribution between patients and controls, suggesting that the −251A allele carriers were not susceptible to lung cancer.

Nasopharyngeal cancer

Two studies involving 440 patients and 459 controls detected the −251T/A polymorphism in nasopharyngeal cancer patients in Tunisia [48] and China [49]. The heterogeneity tests showed no statistical significance ($Q = 0.10$ with 1 df, $P = 0.75$; $I^2 = 0\%$). The odds ratio estimate from the pooled data sets was 2.04 (95% CI 1.38–2.99) for −251A homozygote, 1.59 (95% CI 1.19–2.13) for −251A heterozygote, and 1.70 (95% CI 1.30–2.24) for the −251A carriers, respectively. This showed that IL-8 −251A allele carriers have an increased risk to nasopharyngeal cancer.

Prostate cancer

Four studies focused on the association between the −251A allele and prostate cancer in Europeans, with 1,496 patients and 1,518 controls [50–53]. The odds ratio estimate for the −251A allele carriers showed no significance (odds ratio (OR) 0.95, 95% CI 0.72–1.25). However, statistical tests indicated a significant heterogeneity among these studies ($Q = 8.06$ with 3 df, $P = 0.04$; $I^2 = 63\%$). This finding can be attributed to the data set from McCarron et al. [53], in which gender and age were statistically significant in patients and controls. The heterogeneity was effectively removed after exclusion of this data set ($Q = 0.82$ with 2 df, $P = 0.66$; $I^2 = 0\%$). Sensitivity analysis detected significant changes in the pooled odds ratio estimates after excluding this data set. The pooled odds ratio estimates for −251A allele carriers were 0.83 (95% CI 0.70–0.99), which indicated that IL-8 −251A allele carriers have a decreased risk to prostate cancer.

Other cancers

Six studies [40, 54–58] involving 1,497 patients and 2,037 controls had detected the −251T/A polymorphism in cancer patients, including; cutaneous malignant melanoma, esophageal squamous cell carcinoma, tongue cancer etc. The results of the heterogeneity tests showed no statistically significant difference ($Q = 5.88$ with 5 df, $P = 0.32$; $I^2 = 15\%$). The odds ratio estimate from the pooled data sets for the −251A carriers was 1.04 (95% CI 0.87–1.23). No significant difference was detected in allelic and genotypic frequency distribution between patients and controls, implying that the −251A allele bears no susceptibility to these six cancers.

Discussion

Our meta-analysis, based on 42 case–control studies with 13,189 cases and 16,828 controls, showed that the carriers of −251A allele had about a 12–21% increased risk for the reviewed cancer in total. The carriers of −251A had a higher risk to breast cancer, gastric cancer and nasopharyngeal cancer and lower risk to prostate cancer. When stratified separately by 'racial descent' and 'study design', it was found that carriers of the −251A allele demonstrated an increased risk to cancer among the African group, the Asian group and hospital-based case–control group.

Three meta-analyses [80–82] on the association of IL-8 −251T/A polymorphism with various cancers was published in 2010, two of which [80, 81] were based on roughly the same published data from 10 to 12 individual case–control studies [15, 18, 19, 33, 35, 36, 38–40, 42–44] and were restricted to gastric cancer risk. The meta-analysis of Wang et al. [80] analyzed 10 case–control studies with 2,195 cases and 3,505 controls and concluded that −251A homozygote has a significant association with the risk of gastric cancer. Subgroup analysis of 'racial descent' indicated that significantly increased risks were found among the Asian group but not the European group. These results were consistent with ours but were inconsistent with the results of Liu et al., which concluded that the carriers of −251A allele were not associated with the risk of gastric cancer.

The meta-analysis by Gao et al. [82] analyzed 14,876 cases with different cancer types and 18,465 controls from 45 case–control studies, 36 of them met our inclusion criteria and were included in our meta-analysis. When compared, the results of the two meta-analysis showed that

the carriers of −251A exhibited high risk among the African group and the hospital-based case–control study to nasopharyngeal cancer. However, there were also inconsistent between the analyses. Our results showed that the carriers of −251A had a higher risk to breast cancer and gastric cancer and lower risk to prostate cancer, but Gao et al. found no significant risks to these three cancers. Also, Gao et al. reported that the −251A allele decreased cancer risk among population-based studies with no significant risks being observed in all comparison models for the Asian group only, whereas, our results indicated that there were no significant cancer risks among population-based studies but significantly increased risk in all comparison models for the Asian group. Maybe these differences were mainly caused by the inclusion criteria of the two articles. Firstly, the studies published in English (41 articles) or Chinese (4 articles) were all included in meta-analysis by Gao et al., whereas, only English-language papers were included in ours. Secondly, five studies which did not present detailed genotyping information [64, 65] or which genotype distributions in control population significantly deviate from HWE [61–63] were excluded in our meta-analysis but included in meta-analysis by Gao et al. Thirdly, the data from six newly published papers [20, 28, 30–32, 37] were included in our meta-analysis but not in meta-analysis of Gao et al.

One of the major concerns in meta-analysis is heterogeneity between the component studies. Lack of attention to this commonly occurring problem may cause a misleading statistical inference. To test the significance of heterogeneity, we carried out Cochran's Q test and calculated the quantity I^2 that describes the magnitude of heterogeneity across the constituent studies. To explore the sources of heterogeneity, we carried out meta-regression analysis and found that covariates 'racial descent', 'genotyping methods' and 'study design' could explain about 54–100% of heterogeneities in all comparison models. For (AA vs. TT) model and [(AA + AT) vs. TT] model, not all the heterogeneity could be explained by the covariates, which is common in a meta-regression analysis but the data was permitted. Thus, we also carried out subgroup analyses for 'racial descent' and observed significantly elevated risks in all comparison models among the African group and the Asian group, but not in the European group, which may indicate that the −251A allele is an ethnicity-dependent risk factor for cancer. In a subgroup analysis of 'study design', we observed significantly increased risk among hospital-based case–control studies but not in the population-based case–control studies. Because hospital-based controls were less representative of the general population than population-based controls, there maybe exist a selection bias and we must draw a conclusion carefully.

Another crucial question for meta-analysis is publication bias. To assess this problem, we presented the relation between the odds ratio estimates in a logarithmic scale and their corresponding standard errors across all constituent data sets. The results showed that no obvious publication bias was detected in this analysis. In fact, both the Begg and Mazumdar adjusted rank correlation analysis and the Egger regression asymmetry test revealed no correlation between the estimate of odds ratio and sample size.

It is well established that environmental factors including tobacco use, alcohol consumption and dietary habits are associated with cancer risks [83]. In addition, virus infections such as helicobacter pylori and hepatitis B virus play a key role in gastric cancer risk and hepatocellular carcinoma risk [84, 85]. Furthermore, several studies suggested a possible interaction between −251A and family history on cancer risk [51], and the effect of IL-8 was perhaps best represented by its haplotypes [49]. However, the lack of original data from of the meta-analysis limited our further evaluation of potential gene-to-gene and gene-to-environment interactions. In spite of this, our meta-analysis holds some key benefits in two aspects. Firstly, large numbers of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Secondly, the quality of case–control studies included in our meta-analysis was good. In fact, all included studies were embodied by SCI (Science Citation Index) magazine.

In conclusion, our meta-analysis supports growing evidence that the −251A allele in the promoter region of the IL-8 gene is emerging as a low-penetrance cancer susceptibility allele in the development of cancers. To further evaluate the interactions on −251T/A polymorphisms and cancer risks, a single larger study with thousands of subjects and tissue-specific biochemical and biological characterizations is required.

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