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Original Article

The polymorphism (Gln261Arg) of 12-lipoxygenase and cancer risk: a meta-analysis

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Abstract: Background: Many studies suggest that the Gln261Arg polymorphism in 12-lipoxygenase gene is assicated with cancer susceptibility, but the results are inconclusive. This meta-analysis aimed to investigate the overall association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk. Methods: Literature search was performed in Pubmed, Embase and other databases for studies evaluating the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk. Data were extracted and statistical analysis was performed using STATA 12.0 software. Results: A total of eight publications involving 8,379 subjects were included in this meta-analysis. Combined analysis revealed a significant association between this polymorphism and cancer susceptibility with an OR of 1.19 (95% CI: 1.09-1.31, P=0.000 for Gln/Gln vs. Arg/Gln + Arg/Arg). Subgroup analysis by ethnicity showed that the cancer risk associated with the Gln261Arg polymorphism in 12-lipoxygenase gene was significantly elevated among Asians (OR=1.21, 95% CI: 1.10-1.34, P=0.000 for Gln/Gln vs. Arg/Gln + Arg/Arg), but not among Caucasians. Subgroup analysis by cancer type suggested that the Gln261Arg polymorphism in 12-lipoxygenase gene is not a risk factor for colon cancer or rectal cancer. Conclusion: This meta-analysis suggests that the Gln261Arg polymorphism in 12-lipoxygenase gene contributes to cancer susceptibility, specifically in Asian populations. More studies are needed to validate our findings.

Keywords: Cancer, 12-lipoxygenase, polymorphism, meta-analysis

Introduction

Cancer is still a major public health problem around the world, it places a heavy burden on patients because it reduces life quality, work ability and increases disability, in addition, cancer is the leading cause of death worldwide [1, 2]. The etiology of cancer is so complicated and has not been fully elucidated, a complex interaction between an individual's genetic makeup and exposure to environmental risk factors may contribute to cancer [3]. It was reported that genetic variation may contribute individual susceptibility to cancer through interaction with environmental factors [3, 4]. Growing studies aim to identify the host genetic factors for susceptibility to cancer, which would greatly assist the global control and therapeutic strategies of cancer.

12-lipoxygenase is one of the most important enzymes in the arachidonic acid-metabolizing pathway, 12-lipoxygenase-derived bioactive substances play a key role in inducing production of reactive oxygen species and inflammation, which are increasingly implicated in variety of cancers [5]. Studies suggest that overexpression of 12-lipoxygenase has been demonstrated in various types of cancers, including head and neck squamous cell carcinoma, breast, prostate, and renal cancers [6-9]. The Gln261Arg polymorphism in 12-lipoxygenase gene results in amino acid change, from glutamine to arginine at position 261 (Gln261Arg) of the enzyme which is in the lipoxygenase domain, a conserved region. The mutation of such polymorphism may affect 12-lipoxygenase activity and cause aberrations in arachidonic acid metabolism, thus, plays a role in the pathogenesis of cancer [10]. A number of studies have

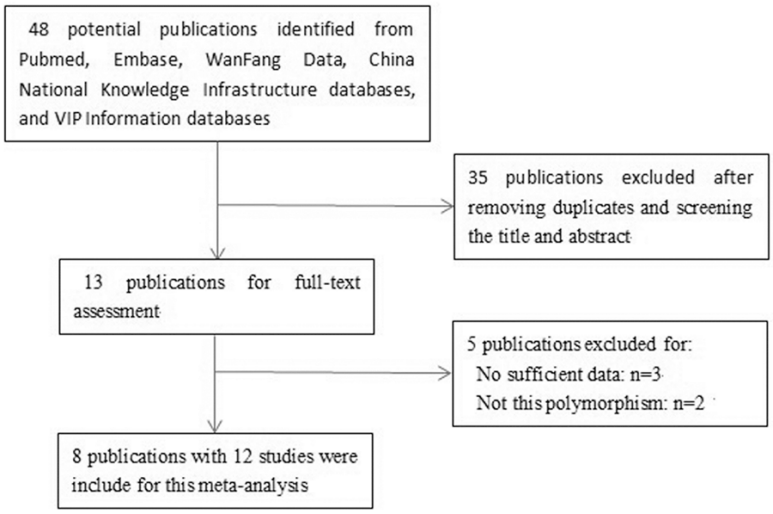

Figure 1. Flow diagram of selection of studies.

investigated whether the Gln261Arg polymorphism in 12-lipoxygenase gene is associated with cancer risk, and the results have been considerable inconsistent and inconclusive. Since pooled estimates based on meta-analysis have proven to be useful in determining the overall risk of certain disease polymorphisms when results of individual studies are inconsistent [11], we decided to perform the present meta-analysis in order to clarify the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk.

Methods

Literature search

Two authors independently performed a systematic literature search in Pubmed, Embase, WanFang Data, China National Knowledge Infrastructure databases, and VIP Information databases to identify studies examining the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk before July 2014. The search terms were listed as follows: "cancer *or* carcinoma *or* neoplasm" *in combination with* "12-lipoxygenase *or* 12-LOX" *in combination with* "polymorphism *or* variant *or* mutation". The reference lists of identified studies or review articles were manually searched to identify possible relevant publications.

Study selection

A study was included in this meta-analysis if it met the following inclusion criteria: (1) it evaluated the potential association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk; (2) it was a case-control study; (3) genotype distributions were available for cases and controls in order to estimate an odds ratio (OR) with 95% confidence interval (95% CI). Abstracts, reviews, and studies in which genotype frequencies were not reported were excluded. When publications involved the same or overlapping data sets, only the study with the largest number of participants was included.

Data extraction

Two reviewers independently extracted data from the final set of included studies. The following data were extracted: the name of the first author, publication year, country of origin, ethnicity, sample size, cancer types, genotyping method, and genotype frequencies in cancer cases and controls. For publications containing several cancer types or different ethnicities, each group was treated as a separate study in the meta-analysis.

Statistical analysis

The strength of the association between the 12-lipoxygenase Gln261Arg polymorphism and cancer risk was assessed using ORs and 95% CIs [4]. The significance of the pooled OR was determined using the Z-test and $P<0.05$ was considered statistically significant. First, we evaluated the recessive model (Gln/Gln vs. Gln/Arg + Arg/Arg) and dominant model (Gln/Gln + Gln/Arg vs. Arg/Arg), followed by the additive model (Gln/Gln vs. Arg/Arg). We also estimated the association based on allelic contrast (Gln vs. Arg). To evaluate whether the association showed any ethnicity- or cancer-specific effects, we analyzed the data for separate subgroups defined by ethnicity and cancer type.

Heterogeneity was evaluated using a x^2-based Q statistic and I^2 statistic, with $P<0.10$ considered statistically significant [4]. When $P\geq0.10$, the pooled OR of each study was calculated using a fixed-effects model; otherwise, a random-effects model was used. Publication bias

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Cancer type	Cancer cases	Controls	Genotyping method	HWE
Goodman et al (a)	2004	USA	Caucasian	Colon cancer	175	324	PCR	Y
Goodman et al (b)	2004	USA	African-American	Colon cancer	112	191	PCR	Y
Guo et al	2007	China	Asians	Esophageal squamous cell carcinoma	1026	1270	PCR-RFLP	N
Tan et al (a)	2007	China	Asians	Colon cancer	403	1300	PCR-RFLP	Y
Tan et al (b)	2007	China	Asians	Rectal cancer	597	1300	PCR-RFLP	Y
Prasad et al	2011	India	Asians	Breast cancer	163	111	PCR-RFLP	N
Prasad et al (a)	2012	India	Asians	Colorectal cancer	104	317	PCR-RFLP	N
Prasad et al (b)	2012	India	Asians	Thyroid cancer	101	317	PCR-RFLP	N
Dai et al	2013	China	Asians	Gastric cancer	148	148	PCR-RFLP	Y
Guo et al	2013	China	Asians	Hepatic cancer	278	560	PCR-RFLP	Y
Li et al (a)	2013	China	Asians	Colon cancer	134	631	PCR-RFLP	Y
Li et al (b)	2013	China	Asians	Rectal cancer	286	631	PCR-RFLP	Y

PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: Yes. a, b means two studies in one publication.

Table 2. Distribution of Gln261Arg polymorphism in 12-lipoxygenase gene and allele among cancer cases and controls

Author	Year	Cancer cases			Controls			Cancer cases		Controls	
		Arg/Arg	Arg/Gln	Gln/Gln	Arg/Arg	Arg/Gln	Gln/Gln	Gln	Arg	Gln	Arg
Goodman et al (a)	2004	40	71	64	53	151	120	199	151	391	257
Goodman et al (b)	2004	10	48	54	25	87	79	156	68	245	137
Guo et al	2007	231	523	272	324	680	266	1067	985	1212	1328
Tan et al (a)	2007	85	202	116	329	663	308	434	372	1279	1321
Tan et al (b)	2007	137	289	171	329	663	308	631	563	1279	1321
Prasad et al	2011	64	95	4	66	44	1	103	223	46	176
Prasad et al (a)	2012	38	64	2	198	115	4	68	140	123	511
Prasad et al (b)	2012	36	63	2	198	115	4	67	135	123	511
Dai et al	2013	28	75	45	41	79	28	165	131	135	161
Guo et al	2013	53	137	88	136	296	128	313	243	552	568
Li et al (a)	2013	30	74	30	132	337	162	134	134	661	601
Li et al (b)	2013	76	137	73	132	337	162	283	289	661	601

was assessed using Begg's funnel plots and Egger's test [11]. Sensitivity analysis was performed by sequentially excluding individual studies and recalculating the results. All statistical tests were performed using STATA 12.0 software. All the statistics were two-sided, and $P<0.05$ was considered as significant findings.

Results

Characteristics of included studies

After a systematic literature serach and selection, a total of eight publications with 12 studies evaluating the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk were included in the meta-analysis, involving 8,379 subjects (3,527 cancer cases and 4,852 controls) [12-19]. **Figure 1** outlines the process of selecting publications.

There were seven types of cancer, and one publication used PCR to determine gene frequency [12], and the rest all used PCR-RFLP. Except one publication described case-control studies involved Caucasians and African-Americans [12], the rests were all Asians, and five publications were peformed in China [13, 14, 17-19]. The characteristics of each case-control study are summarized in **Table 1**, genotype and allele distributions for each case-control study are listed in **Table 2**.

Quantitative data synthesis

Firstly, we analyzed the recessive model (Gln/Gln vs. Arg/Gln + Arg/Arg) to evaluate the asso-

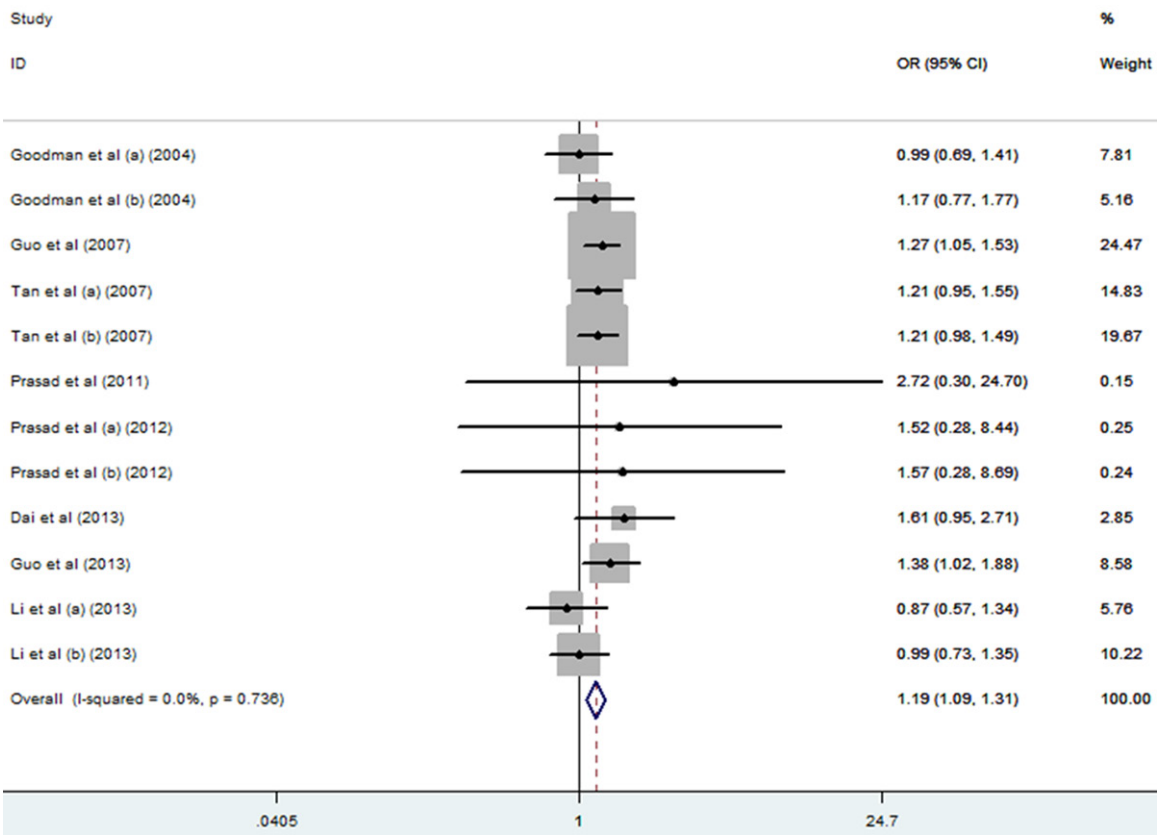

Figure 2. Meta-analysis using a fixed-effects model to evaluate the association between the 12-lipoxygenase Gln261Arg polymorphism and cancer risk (Gln/Gln vs. Arg/Gln+Arg/Arg). The size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.

Table 3. Summary of different comparative results

	Gln/Gln + Arg/Gln vs. Arg/Arg		Gln/Gln vs. Arg/Gln + Arg/Arg		Gln/Gln vs. Arg/Arg		Gln vs. Arg	
	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95%CI)	P*
Total	1.06 (1.00-1.13)	0.057	**1.19 (1.09-1.31)**	**0.000**	**1.14 (1.02-1.26)**	**0.016**	**1.12 (1.03-1.21)**	**0.008**
Subgroup by Ethnicity								
Asian	**1.07 (1.00-1.15)**	**0.038**	**1.21 (1.10-1.34)**	**0.000**	**1.16 (1.04-1.30)**	**0.008**	**1.14 (1.04-1.25)**	**0.005**
Subgroup by Cancer type								
Colon cancer	1.01 (0.90-1.14)	0.808	1.10 (0.93-1.29)	0.281	1.06 (0.88-1.27)	0.533	1.04 (0.94-1.14)	0.458
Rectal cancer	1.00 (0.88-1.13)	0.962	1.14 (0.95-1.35)	0.152	1.06 (0.87-1.28)	0.563	1.03 (0.94-1.14)	0.541

The bold values mean that their association is significant, * *P* value for Z test.

ciation between the 12-lipoxygenase Gln261Arg polymorphism and cancer risk, for heterogeneity examination, across all included studies, χ^2 was 7.74 and P=0.736 for a random-effects model, and I^2, another index of heterogeneity, was 0%. These findings suggested a lack of heterogeneity. Thus, we chose the fixed-effects model to synthesize the data. The pooled OR based on all studies was 1.19 (95% CI: 1.09-1.31), which was associated with a Z value of 3.69 (P=0.000) (**Figure 2**). This suggested that Gln homozygotic carriers have a higher risk of cancer than do Gln and Arg homozygotic individuals. We also chose the fixed-effects model to synthesize the data according to the dominant genetic model. The pooled OR was 1.06 (95% CI: 1.00-1.13) and the associated Z value was 1.91 (P=0.057) (**Figure 2**). These results suggested the possibility that Gln homozygotic carriers and Gln/Arg heterozygotic carriers have higher risk of cancer than do Arg/Arg homozygotic individuals, but the results did not

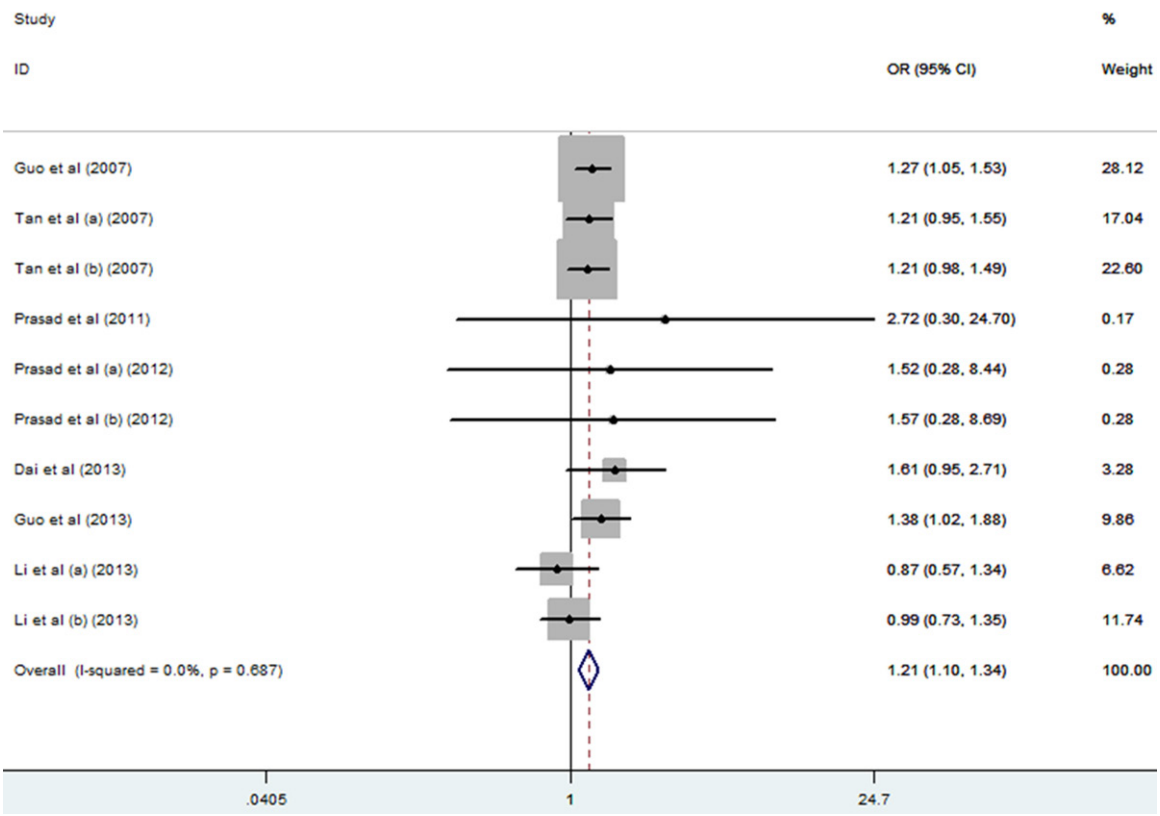

Figure 3. Meta-analysis using a fixed-effects model to evaluate the association between the 12-lipoxygenase Gln261Arg polymorphism and cancer risk in Asians (Gln/Gln vs. Arg/Gln + Arg/Arg). The size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.

achieve statistical significance. Results for these and other genetic comparisons are summarized in **Table 3**.

Subgroup analysis

Subgroup analysis by ethnicity, showed that, among the studies involving Asians [13-19], the Gln261Arg polymorphism in 12-lipoxygenase gene was significantly associated with cancer risk (OR=1.21, 95% CI 1.10-1.34, P=0.000 for Gln/Gln vs. Arg/Gln + Arg/Arg) (**Figure 3**), and this association were confirmed in all the other statistical models (**Table 3**). When cases with colon cancer or rectal cancer were analyzed in separate subgroups, no associations were found between the Gln261Arg polymorphism in 12-lipoxygenase gene and risk of colon cancer or rectal cancer (**Table 3**).

Sensitivity analysis and publication bias

To evaluate the stability of our findings, sensitivity analysis was performed by sequentially excluding each study. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of the results (**Figure 4**). Begg's funnel plot and Egger's test were used to assess publication bias. The shape of the funnel plots seemed symmetrical for the Gln/Gln vs. Arg/Gln + Arg/Arg (**Figure 5A**) or Gln/Gln + Arg/Gln vs. Arg/Arg (**Figure 5B**) comparison genetic model, suggesting the absence of publication bias. Then, Egger's test was performed to provide statistical evidence of funnel plots asymmetry. The results indicated a lack of publication bias of the present meta-analysis (P=0.96 and 0.235 for Gln/Gln vs. Arg/Gln + Arg/Arg and Gln/Gln + Arg/Gln vs. Arg/Arg, respectively).

Discussion

12-lipoxygenase is an important inflammation and oxidative stress mediator, and many studies have confirmed that the 12-lipoxygenase may be involved in cancer development and progression [20]. Gene variants may play a role in the pathogenesis of cancer by altering protein function and individual's susceptibility to

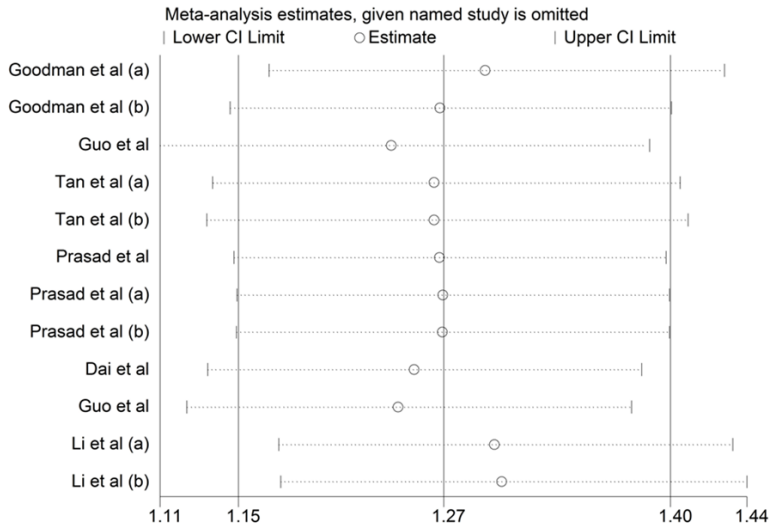

Figure 4. Sensitivity analysis of included studies.

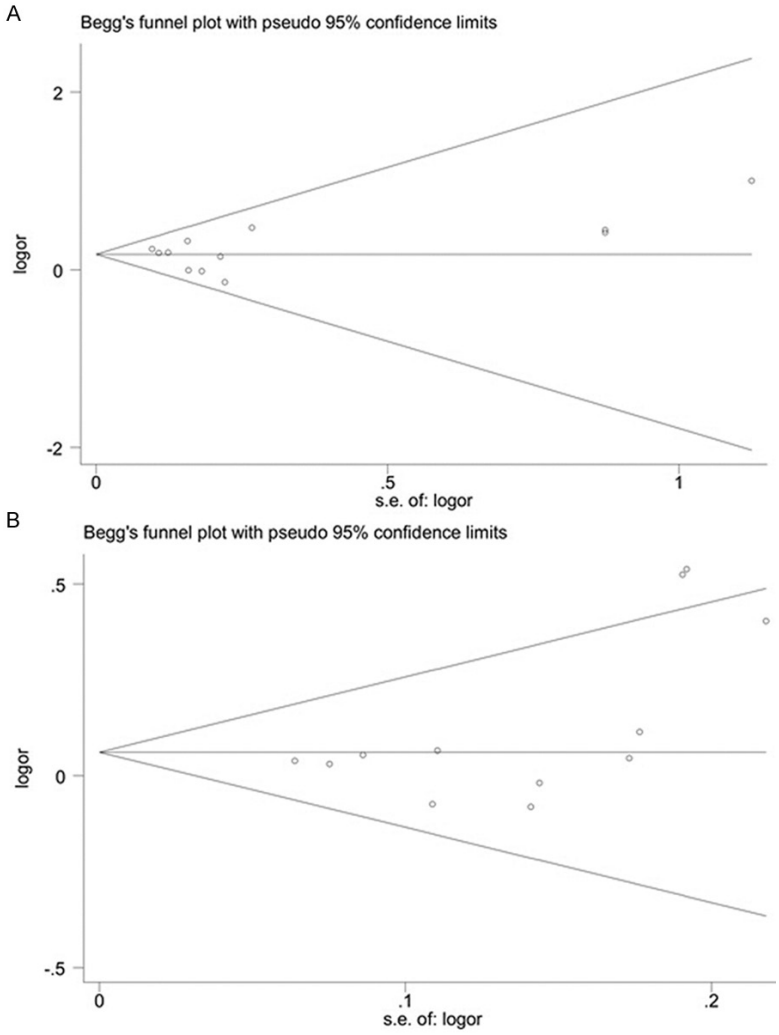

Figure 5. Begg's funnel plot to detect publication bias in studies examining the 12-lipoxygenase Gln261Arg polymorphism. A. Gln/Gln vs. Arg/Gln + Arg/Arg. B. Gln/Gln + Arg/Gln vs. Arg/Arg.

disease and many studies have investigated the potential relationship between the 12-lipoxygenase Gln261Arg polymorphism and cancer risk. However, the results from different published studies were inconsistent. Therefore, we performed this meta-analysis to clarify their relationship, and to our knowledge, it is the first meta-analysis to summarize the overall association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk.

In our study, a total of eight publications with 12 case-control studies were included. Our findings support the notion that, the Gln261Arg polymorphism in 12-lipoxygenase gene plays a role in the susceptibility of cancer, and this association may be cancer type and ethnicity specific. Our data indicate a ethnic bias in the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and risk of cancer. We found this polymorphism may be a risk factor for cancer among Asians, while among Caucasians and African-American, we failed to find such association. Since this meta-analysis didn't find studies performed in Lations and other ethnicities, more studies in different ethnicities should be performed to clarify this assciaotion. We also identified a cancer-specific bias in the association, and we did not find any evidence of an association between the 12-lipoxygenase Gln261Arg gene polymorphism and risk of colon or recetal cancer. Both findings suggested that the associations between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk are ethnicity and

cancer-type specific. Therefore, the present meta-analysis extends our appreciation of the complex etiology and genetic risk factors of cancer and provides an opportunity to explore more cancer-associated mechanisms.

Based on our findings, further research is needed to examine not only the role of 12-lipoxygenase Gln261Arg polymorphism on cancer risk, but the environmental risk factors as well [21]. Based on current available evidences, we cannot exclude the possibility that environmental risk factors explain at least part of the ethnic bias observed here in the association between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk. Therefore further work is essential to tease apart the relative contributions of genes and environment. In addition, to take consideration of population differences will be particularly informative, susceptibility genes identified in cancer patients with different ethnicities provide an opportunity to explore new mechanisms of disease that are specific in different population [22]. What's more, a number of studies strongly suggesting that inhibition of 12-lipoxygenase incudecs cancer cell proliferation and apoptosis, which strongly suggests that targeting 12-lipoxygenase may be effective for treating cancer [23, 24]. Thus, comprehensive understanding of genetic, environmental, and clinical factors may not only improve our understanding of the mechanisms of cancer, but also lead to more effective prevention and treatment.

There are several limitiations that should be addressed in present meta-analysis. First of all, our meta-analysis only included eight publications and such a small number of studies and subjects may reduce the statistical power for identifying possible associations between the Gln261Arg polymorphism in 12-lipoxygenase gene and cancer risk, which should be verified in larger-scale studies. Second, the included publications were limited to Asian, so future work should examine other populations, such as Latinos and Caucasian populations, especially given substantial evidence of ethnic bias in the Gln261Arg polymorphism in 12-lipoxygenase gene. Third, although we did not set any language restrictions during our literature searching, we included only English and Chinese-language publications in the meta-analysis. It is possible that our results would be different if they included the findings of studies published in other languages or other unpublished studies.

ased on current available evidences, Gln261Arg polymorphism in 12-lipoxygenase gene may be a risk factor for cancer in Asians but not in Caucasians. Large well-designed, multi-center epidemiological studies should be carried out in these and other ethnic populations to confirm our findings.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.
[2] DeVita VT Jr, Rosenberg SA. Two hundred years of cancer research. N Engl J Med 2012; 366: 2207-14.
[3] Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. JAMA 2008; 299: 2423-36.
[4] Wang Y, Jia L, Shen Y, Guo S, Wan C, Yang T, An J, Chen L, Wang T, Wen F. ICAM-1 + 469 A/G polymorphism and cancer risk: a meta-analysis involving 9375 subjects. Int J Clin Exp Med 2014; 7: 84-92.
[5] Brash AR. Lipoxygenases: occurrence, functions, catalysis, and acquisition of substrate. J Biol Chem 1999; 274: 23679-82.
[6] Celenk F, Bayramoglu I, Yilmaz A, Menevse A, Bayazit Y. Expression of cyclooxygenase-2, 12-lipoxygenase, and inducible nitric oxide synthase in head and neck squamous cell carcinoma. J Craniofac Surg 2013; 24: 1114-7.

[7] Mohammad AM, Abdel HA, Abdel W, Ahmed AM, Wael T, Eiman G. Expression of cyclooxygenase-2 and 12-lipoxygenase in human breast cancer and their relationship with HER-2/neu and hormonal receptors: impact on prognosis and therapy. Indian J Cancer 2006; 43: 163-8.

[8] Matsuyama M, Yoshimura R, Mitsuhashi M, Hase T, Tsuchida K, Takemoto Y, Kawahito Y, Sano H, Nakatani T. Expression of lipoxygenase in human prostate cancer and growth reduction by its inhibitors. Int J Oncol 2004; 24:821-7.

[9] Yoshimura R, Inoue K, Kawahito Y, Mitsuhashi M, Tsuchida K, Matsuyama M, Sano H, Nakatani T. Expression of 12-lipoxygenase in human renal cell carcinoma and growth prevention by its inhibitor. Int J Mol Med 2004; 13: 41-6.

[10] Wisastra R, Dekker FJ. Inflammation, Cancer and Oxidative Lipoxygenase Activity are Intimately Linked. Cancers Basel 2014; 6: 1500-21.

[11] Shen Y, Guo S, Yang T, Jia L, Chen L, An J, Wang T, Wen F. The -173 G/C Polymorphism of the MIF Gene and Inflammatory Bowel Disease Risk: A Meta-Analysis. Int J Mol Sci 2013; 14: 11392-401.

[12] Goodman JE, Bowman ED, Chanock SJ, Alberg AJ, Harris CC. Arachidonate lipoxygenase (ALOX) and cyclooxygenase (COX) polymorphisms and colon cancer risk. Carcinogenesis 2004; 25: 2467-72.

[13] Guo Y, Zhang X, Tan W, Miao X, Sun T, Zhao D, Lin D. Platelet 12-lipoxygenase Arg261Gln polymorphism: functional characterization and association with risk of esophageal squamous cell carcinoma in combination with COX-2 polymorphisms. Pharmacogenet Genomics 2007; 17: 197-205.

[14] Tan W, Wu J, Zhang X, Guo Y, Liu J, Sun T, Zhang B, Zhao D, Yang M, Yu D, Lin D. Associations of functional polymorphisms in cyclooxygenase-2 and platelet 12-lipoxygenase with risk of occurrence and advanced disease status of colorectal cancer. Carcinogenesis 2007; 28: 1197-201.

[15] Prasad VV, Kolli P, Moganti D. Association of a functional polymorphism (GIn261Arg) in 12-lipoxygenase with breast cancer. Exp Ther Med 2011; 2: 317-323.

[16] Prasad VV, Padma K. Non-synonymous polymorphism (GIn261Arg) of 12-lipoxygenase in colorectal and thyroid cancers. Fam Cancer 2012; 11: 615-21.

[17] Dai L, Cao L. Relationship between genetic variation in encoding region of 12-lopoxygenase gene and risk of stomach cancer. Chin J Gen Surg 2013; 22: 170-173.

[18] Guo W, Dai L, Pu J, Zhang X, Zhang G, Xu W. Association of genetic variant in 12-lipoxygenase and risk of hepatic carcinoma. Nati Med J China 2013; 93: 3685-87.

[19] Li S, Zhao X, Wu Z, Li Y, Zhu L, Cui B, Dong X, Tian S, Hu F, Zhao Y. Polymorphisms in arachidonic acid metabolism-related genes and the risk and prognosis of colorectal cancer. Fam Cancer 2013; 12: 755-65.

[20] Pidgeon GP, Lysaght J, Krishnamoorthy S, Reynolds JV, O'Byrne K, Nie D, Honn KV. Lipoxygenase metabolism: roles in tumor progression and survival. Cancer Metastasis Rev 2007; 26: 503-24.

[21] Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M; Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005; 366: 1784-93.

[22] Ramírez AS, Rutten LJ, Oh A, Vengoechea BL, Moser RP, Vanderpool RC, Hesse BW. Perceptions of cancer controllability and cancer risk knowledge: the moderating role of race, ethnicity, and acculturation. J Cancer Educ 2013; 28: 254-61.

[23] Xu XM, Yuan GJ, Deng JJ, Guo HT, Xiang M, Yang F, Ge W, Chen SY. Inhibition of 12-lipoxygenase reduces proliferation and induces apoptosis of hepatocellular carcinoma cells in vitro and in vivo. Hepatobiliary Pancreat Dis Int 2012; 11: 193-202.

[24] Guo AM, Liu X, Al-Wahab Z, Maddippati KR, Ali-Fehmi R, Scicli AG, Munkarah AR. Role of 12-lipoxygenase in regulation of ovarian cancer cell proliferation and survival. Cancer Chemother Pharmacol 2011; 68: 1273-83.