Association between the -607 C > A polymorphism in interleukin-18 gene promoter with gastrointestinal cancer risk: a meta-analysis

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ABSTRACT. The interleukin-18 (IL-18) gene -607 C/A polymorphism has been reported to be associated with gastrointestinal cancer, but there are conflicting results from previous studies on said topic. Therefore, the aim of this meta-analysis is to derive a more precise estimation of the association between the -607 C/A polymorphism in the IL-18 gene and gastrointestinal cancer risk. Literature searches of PubMed, Google Scholar, and Web of Science databases were carried out in 2015. Five studies were assessed with a total of 1618 cases and 1155 healthy controls. When results from all eligible studies were pooled into the meta-analysis, we found significant association between the IL-18 gene -607 C/A polymorphism

and gastrointestinal cancer risk (CC *vs* AA: OR = 0.93, 95%CI = 0.72-1.20; CC *vs* CA: OR = 0.76, 95%CI = 0.62-0.92; dominant model: OR = 1.25, 95%CI = 1.03-1.50; recessive model: OR = 1.09, 95%CI = 0.87-1.37). In the subgroup analysis, significant associations between the -607 C/A polymorphism and gastrointestinal cancer risk were found in esophageal cancer. However, this polymorphism did not appear to have any influence on gastric cancer and colorectal cancer susceptibility. In conclusion, this meta-analysis suggests that the -607 C/A polymorphism in the IL-18 gene may be associated with susceptibility to esophageal cancer. Further studies with large sample sizes are needed to confirm these conclusions.

Key words: IL-18; -607 C/A polymorphism; Gastrointestinal cancer

INTRODUCTION

Gastrointestinal cancer, especially esophageal, gastric, and colorectal cancer, is a major global health concerns. Recent research has shown that esophageal cancer, gastric cancer and colorectal cancer are the eighth, the third, and the fourth most common cancers in the world (Parkin et al., 2005; Crew and Neugut, 2006; Shridhar et al., 2011). The development of gastrointestinal cancer is a multi-factorial and multi-step process. Traditionally-known factors such as lifestyle and diet account for a significant proportion of digestive system cancer susceptibility, but the is much that remains unknown (Desauw, 2010). With recent developments in molecular biology, researchers provide strong evidence that genetic factors such as the epidermal growth factor gene and phospholipase C epsilon 1 gene are also important in the pathogenesis of gastrointestinal cancer (Piao et al., 2013; Hao et al., 2013).

Interleukin-18 (IL-18), a member of the IL-1 family, is an important proinflammatory cytokine which plays key roles in the inflammatory cascade (Chang et al., 2000). IL-18 is produced by various cells such as monocytes, activated macrophages, and Kupffer cells (Dinarello, 1999). Since the immune stimulating effects of IL-18 also include anti-neoplastic properties, IL-18 was proposed as a novel adjuvant therapy against cancer (Vidal-Vanaclocha et al., 2006). In addition, higher expression of IL-18 was detected in various cancer cells as compared with normal control (Park et al., 2007).

The IL-18 gene is located on chromosome 11q22.2-q22.3, and is composed of six exons and five introns (Nolan et al., 1998). It is polymorphic, and one extensively studied example is the promoter polymorphism at positions -607 C/A (618 A/C, rs1946518). The association of the -607 C > A polymorph with cancer risk has been investigated in several studies. Previous studies have demonstrated that rs1946518 was associated with increased risk of nasopharyngeal carcinoma and lung cancer (Pratesi et al., 2006; Farjadfar et al., 2009). Although still a topic of debate, accumulating evidence also suggests that the -607 C > A polymorphism in the IL-18 gene is also associated with gastrointestinal cancer development.

Meta-analysis can be a useful tool in detecting associations that would otherwise remain masked in individual sample size studies, especially those that evaluate rare allele frequency polymorphisms. In view of the conflicting results and low statistical power from previous studies, we performed a meta-analysis to evaluate the association between the IL-18 gene -607 C/A polymorphism and risk of gastrointestinal cancer.

MATERIAL AND METHODS

Selection of studies

We searched PubMed, google scholar and Web of Science databases for all articles regarding the role of IL-18 gene -607 C>A polymorphism in gastrointestinal cancer risk (updated to February, 2015). The following terms were used in the search: “gastrointestinal cancer” or “esophageal cancer” or “gastric cancer” or “colorectal cancer”, “interleukin-18” or “IL-18”, “polymorphism” or “allele” or “genetic variant” or “variants”. Reference lists of all retrieved articles were also manually searched for additional studies. All relevant text, tables, and figures were reviewed for data extraction. If necessary, we attempted to contact the corresponding authors of retrieved articles to request additional information.

Inclusion and exclusion criteria

Studies were included in our meta-analysis when the following criteria were met: 1) the study evaluated the association between IL-18 gene -607 C > A polymorphism and gastrointestinal cancer, 2) the studies used case-control design, and 3) the study provided sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). The studies or data were excluded when: 1) the study contained overlapping or incomplete, or unusable data, 2) the number of null and wild genotypes or alleles could not be ascertained, and 3) family members had been studied because their analysis was based on linkage considerations.

Data extraction

Data from all eligible studies were extracted independently by two investigators according to the inclusion criteria listed above. In the case of conflicting evaluations, an agreement was reached following discussions. The following information was recorded for each study: first author, year of publication, ethnicity of the population studied, source of cases and controls, number of cases and controls, sample polymorphisms and genotypes frequency.

Statistical analysis

Pooled ORs with their corresponding 95% CI were used to assess the strength of association between -607 C > A polymorphism and gastrointestinal cancer risk. Different contrast models were utilized including co- dominant models (CC *vs* AA, CC *vs* CA), dominant models (AA + CA vs CC), and recessive models (CC + CA *vs* AA). The I^2 statistics were performed to assess statistical heterogeneity among studies (Higgins and Thompson 2002). When heterogeneity was absent (I^2 < 50%), the fixed-effect model (the Mantel-Haenszel method) was used to estimate the pooled ORs. Otherwise, the random-effect model (the DerSimonian and Laird method) was used. To test for robustness of the summary effects, sensitivity analysis was performed by comparing the random-effect model values with the fixed effect to ensure stability of the findings. Publication bias of all studies was assessed using Begg’s funnel plot, and $P < 0.05$ was considered to be statistically significant (Egger et al., 1997). All statistical analyses were carried out with the STATA software, version 12.0 (STATA Corp., College Station, TX, USA).

RESULTS

Study characteristics

A total of 716 potentially relevant publications were systematically identified through PubMed, google scholar and Web of Science databases. Based on our preliminary search criteria, 712 were excluded as they did not satisfy the inclusion criteria. Finally, five case-control studies from four publications with 1618 cases and 1155 controls were included in the meta-analysis (Nikiteas et al., 2007; Wei et al., 2007; Haghshenas et al., 2009; Babar et al., 2012). All the included journal articles were published between 2007 and 2012.Three of these studies were conducted in Asian populations, and two in Caucasian populations. In this meta-analysis, the role of IL-18 gene -607 C/A polymorphism was derived from one gastric cancer study, two esophageal cancer studies, and two colorectal cancer studies. Study characteristics are summarized below in Figure 1 and Table 1.

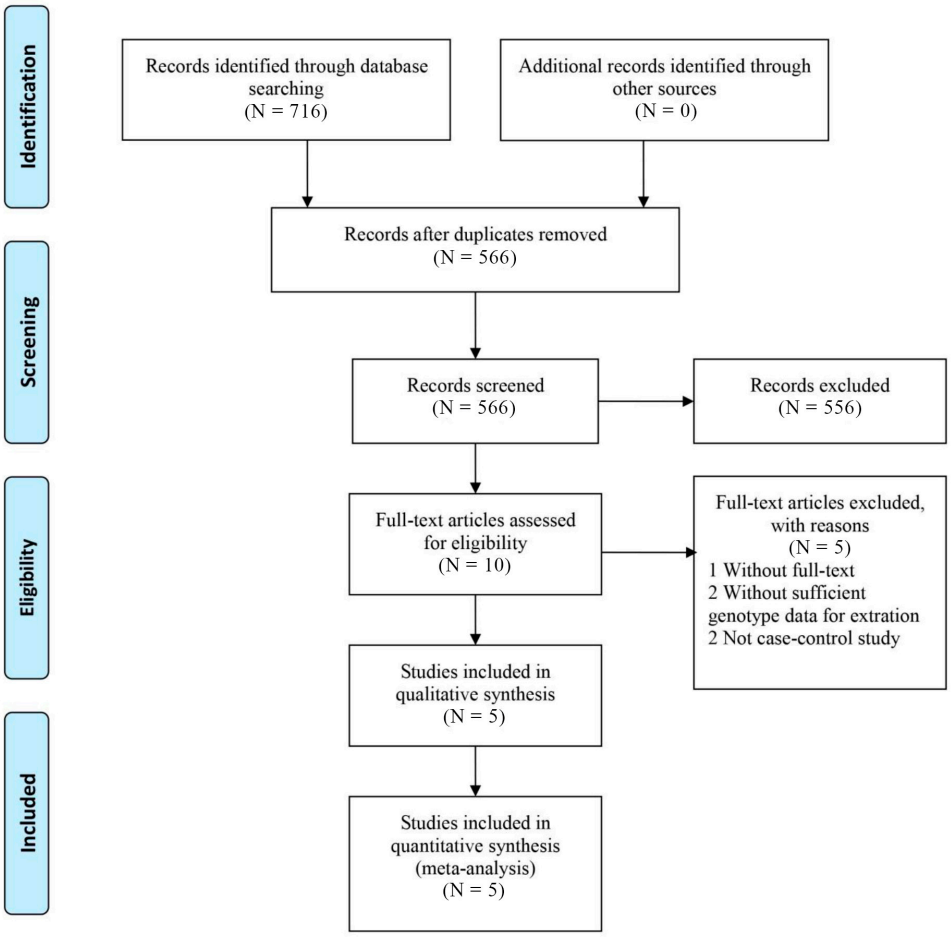

Figure 1. PRISMA flow diagram of the meta-analysis.

Table 1. Characteristics of the studies included for meta-analysis.

Study included	Area	Race	Cancer type	Cases	Controls	Genotypes for cases			Genotypes for controls		
						CC	CA	AA	CC	CA	AA
Nikiteas (2007)	Greece	Caucasians	Colorectal	84	89	19	47	18	35	32	22
Wei (2007)	China	Asians	Esophageal	235	250	48	123	64	59	124	67
Haghshenas (2009)	Iran	Asians	Gastric	87	311	31	40	16	119	144	48
Haghshenas (2009)	Iran	Asians	Colorectal	142	311	55	72	15	119	144	48
Babar (2012)	Ireland	Caucasians	Esophageal	1070	194	384	508	178	83	75	36

Quantitative synthesis

A summary of the meta-analysis findings is shown in Table 2 and Figure 2. The combined results based on all studies showed that -607 C/A polymorphism is associated with increased gastrointestinal cancer risk in different genetic models (CC *vs* AA: OR = 0.93, 95%CI = 0.72-1.20; CC *vs* CA: OR = 0.76, 95%CI = 0.62-0.92; dominant model: OR = 1.25, 95%CI = 1.03-1.50; recessive model: OR = 1.09, 95%CI = 0.87-1.37). In subgroup analysis by ethnicity, the studies included were divided into Asian and Caucasian populations, and no significant association was found between IL-18 gene -607 C/A polymorphism and gastrointestinal cancer. When studies were stratified according to cancer type, the -607 C/A polymorphism was associated with risk of esophageal cancer (CC *vs* AA: OR = 0.90, 95%CI = 0.65-1.25; CC *vs* CA: OR = 0.73, 95%CI = 0.56-0.96; the dominant model: OR = 1.29, 95%CI = 1.00-1.66; the recessive model: OR = 1.06, 95%CI = 0.80-1.40), but not with gastric cancer and colorectal cancer. Sensitivity analyses were conducted by altering the statistic models. No material alteration was detected, which confirmed that results of this meta-analysis were statistically robust.

Table 2. Summary ORs and 95%CI of the -607 C/A polymorphism with gastrointestinal cancer risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association	
		Case	Control		I^2 (%)	P	OR	95%CI
Overall	CC *vs* AA	1618	1155	Fixed	0.0	0.58	0.93	0.72-1.20
	CC *vs* CA			Fixed	30.9	0.22	**0.76**	**0.62-0.92**
	The dominant model			Fixed	13.3	0.33	**1.25**	**1.03-1.50**
	The recessive model			Fixed	0.0	0.64	1.09	0.87-1.37
Asians	CC *vs* AA	464	872	Fixed	8.5	0.34	0.98	0.69-1.38
	CC *vs* CA			Fixed	0.0	0.91	0.89	0.68-1.16
	The dominant model			Fixed	0.0	0.79	1.09	0.85-1.41
	The recessive model			Fixed	12.7	0.32	1.05	0.78-1.41
Caucasians	CC *vs* AA	1154	283	Fixed	0.0	0.47	0.87	0.59-1.28
	CC *vs* CA			Random	56.6	0.13	0.55	0.31-0.98
	The dominant model			Fixed	45.4	0.18	1.47	1.11-1.94
	The recessive model			Fixed	0.0	0.90	1.16	0.82-1.63
Colorectal	CC *vs* AA	226	400	Random	53.9	0.14	1.03	0.47-2.26
	CC *vs* CA			Random	78.4	0.03	0.73	0.50-1.04
	The dominant model			Random	76.2	0.04	1.41	0.64-3.13
	The recessive model			Fixed	0.0	0.60	1.39	0.88-2.22
Esophageal	CC *vs* AA	1305	444	Fixed	0.0	0.78	0.90	0.65-1.25
	CC *vs* CA			Fixed	0.0	0.53	**0.73**	**0.56-0.96**
	The dominant model			Fixed	0.0	0.70	**1.29**	**1.00-1.66**
	The recessive model			Fixed	0.0	0.59	1.06	0.80-1.40

Bold values mean significant association.

Publication bias

Funnel plots and Begg tests were performed to assess the publication bias of the studies

included. The shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry in the allele model (Figure 3), which implied that publication bias was low in the present meta-analysis (all P > 0.05).

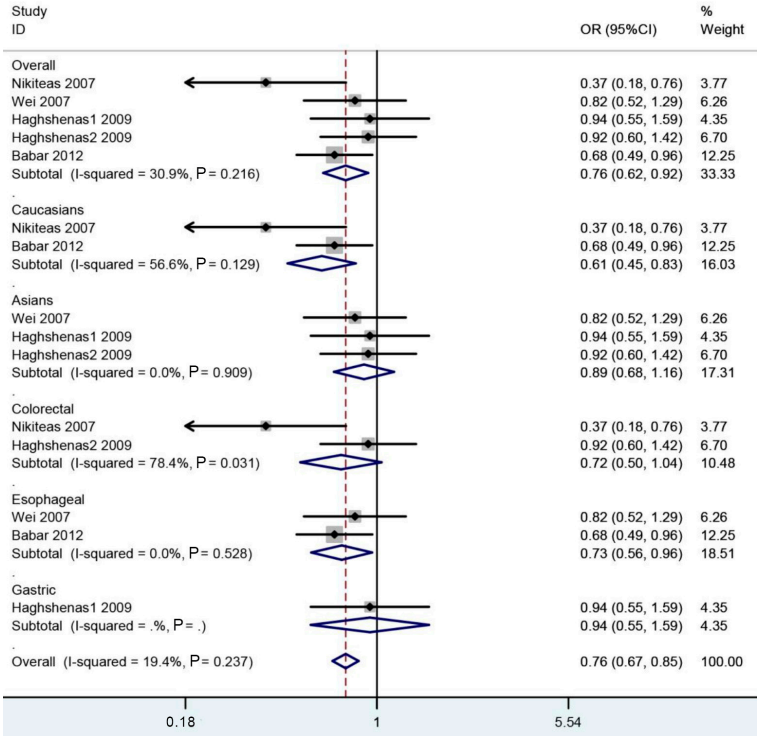

Figure 2. Forest plot of gastrointestinal cancer risk associated with IL-18 gene -607 C/A polymorphism for CC *vs* CA.

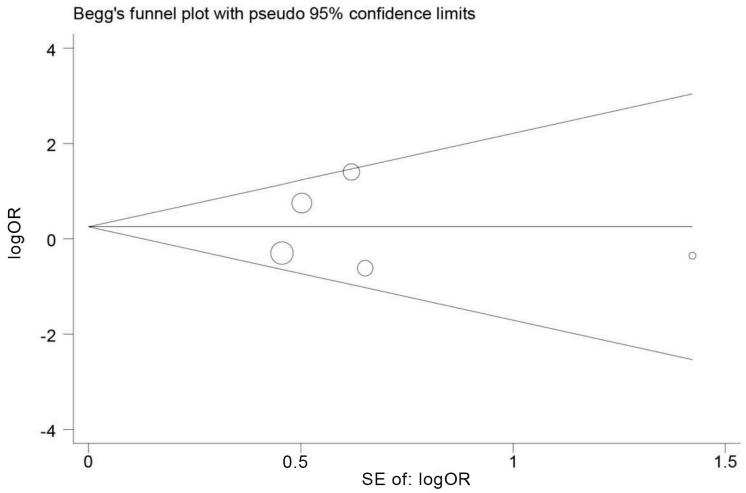

Figure 3. Funnel plot of the IL-18 gene -607 C/A polymorphism and susceptibility of gastrointestinal cancer for CC *vs* CA.

DISCUSSION

Gastrointestinal cancers are the most common cancer worldwide, including esophagus, gastric, hepatocellular, bowels, pancreas, gallbladder and anus. The exact mechanism of carcinogenesis is still not fully understood. During the past few years, increasing evidence suggest that inflammatory molecules and genetic variation of these inflammatory cytokines may take part in the pathogenesis of gastrointestinal cancer (Kato et al., 2001; De et al., 2001). One such candidate cytokine gene implicated in the pathogenesis of cancer is IL-18. Through activation of the immune response, particularly in natural killer cells, IL-18 promotes cell death and tumor regression (Cho et al., 2000). Variations in the IL-18 gene promoter are able to influence IL-18 production and activity. While results are still inconclusive, several emerging studies have reported the associations between -607 C/A polymorphism in the IL-18 gene and gastrointestinal cancer risk (Nikiteas et al., 2007; Wei et al., 2007; Haghshenas et al., 2009; Babar et al., 2012). This controversy may due to several factors, including differences between cancer sites, ethnicity, sample sizes, study designs and assay characteristics. Therefore, we performed this meta-analysis to more conclusively determine whether -607 C/A polymorphism in the IL-18 gene is associated with susceptibility to gastrointestinal cancer.

Our meta-analysis quantitatively assessed the association between -607 C/A polymorphism in IL-18 gene and gastrointestinal cancer risk. Five case-control studies were assessed, encompassing a total of 1618 cancer patients and 1155 healthy controls. We found that -607 C/A polymorphism in the maternal IL-18 gene were significantly associated with the susceptibility of gastrointestinal cancer. To further reduce the influence of potential confounding factors on our results, we also conducted several subgroup analyses. In the stratified analysis sorted by ethnicity, results showed no significant association in both Asians and Caucasians. In the stratified analysis based on cancer types, positive association between IL-18 gene -607 C/A polymorphism and disease susceptibility was found in esophageal cancer, but not in gastric and colorectal cancer. Although the exact mechanism for this cancer-specific difference is not yet clear, one possible reason may be the relatively small sample size in the studies analyzed. Therefore, caution should be exercised when considering this conclusion.

Some limitations of our meta-analysis should be addressed. First, sample size for this meta-analysis is still relatively small, and may not provide sufficient statistical power to estimate the association between IL-18 gene -607 C/A polymorphism and gastrointestinal cancer risk. In addition, due to incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Furthermore, all included studies followed a retrospective case-control design. Thus, owing to the limitations of the case-control designs, we cannot exclude the possibility of undetected bias. Finally, gene-gene and gene-environment interactions were not tested in the present study due to lack of information from the original studies.

In summary, our meta-analysis indicates that IL-18 gene -607 C/A polymorphism might be associated with increased risk of gastrointestinal cancer. Large-scale case-control and population-based association studies are needed to validate the risk identified in the current meta-analysis, and investigate the role of potential gene-gene and gene-environment interactions on gastrointestinal cancer risk.

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