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Review

Interleukin (*IL*)-4 -590C>T polymorphism is not associated with the susceptibility of gastric cancer: An updated meta-analysis

Tie Wang [a], Lining Tian [b], Meizhuo Gao [c], Hongjiang Song [a], Yuzhe Wei [a], Yingwei Xue [a, *]

[a] Department of Gastrointestinal Surgery, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province, China
[b] Department of Medical Education, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China
[c] Department of General Surgery, The Forth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China

HIGHLIGHTS

- Gastric cancer (GC) is a malignant disease with a poor outcome in which genetic background plays roles during pathogenesis.
- The polymorphism of *IL-4 -590C>T* may not be related with the susceptibility of GC.
- Further investigations on the relationship of *IL-4 -590C>T* and subtypes of GC are needed.

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ABSTRACT

Gastric cancer (GC) is a common cancer affecting patients around the world. The pathogenesis of gastric cancer has not been understood completely. Genetic mutations and the inflammation induced by *Helicobacter pylori* (HP) seem to play important roles. The cytokine Interleukin-4 (IL-4) has effects in inflammation, allergies and cancer including GC. The association of *IL-4 -590 C>T* polymorphism and gastric cancer has been studied in different populations with inconsistent results. Here, we report this meta-analysis showing that the polymorphism of *IL-4 -590C>T* might not be associated with the GC susceptibility in both Asian and Caucasian populations.

Contents

* Corresponding author.
E-mail address: medwang@163.com (Y. Xue).

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1. Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, and the third leading cause of cancer related death [1,2]. Although the incidences and mortality of GC are declining, countries in Eastern Asia including China, Korea and Japan still have the highest prevalence in the world, where half of new cases occur.

The outcome of GC is poor since almost half of surgical patients with GC will suffer recurrence even after adjuvant therapies [3]. The reason for this unfavorable outcome is the etiology of GC is complex and remains incompletely understood. The pathogenesis of GC is a multifactorial and multistep process among which chronic *Helicobacter pylori* (HP) infection, environmental toxins, personal diet habits and genetics background [4] are the key components. Chronic and persistent presence of HP infection, which induces long-term inflammation in the stomach, plays an important role in several sequential steps of the pathogenesis of GC [5].

Since GC is a pathogen-induced carcinoma, the inflammatory microenvironment of GC has gained great interest from researchers. Among interleukins (IL) which mediate many effects in inflammation, IL-4 is the major IL for T helper (Th)-2 mediated inflammation and important in maintaining Th1/Th2 balance [6]. IL-4 has the potential to activate alternatively activated macrophages (AAMs) and inhibits the secretion of proinflammatory cytokines including IL-1, IL-6, interferon-γ and tumor necrosis factor-α to promote tumor cells [6]. IL-4 has been reported to be upregulated in GC patients [7]. However, the role of IL-4 in the pathogenesis of GC needs further investigation.

The gene encoding IL-4 is located on chromosome 5 (5q31.1), along with other genes for Th2 cytokines. The *IL-4* gene has about 10 Kb of base pairs which contains 4 exons [8]. The polymorphism *-590C>T* (rs2243250) in the *IL-4* gene promoter region is the most commonly reported variation of this gene, and it has multiple functions in cancer and allergic diseases [9]. Several published papers demonstrated conflicting and inconsistent results regarding the correlation of IL-4 polymorphism *-590C>T* and the prevalence of GC. Although, a good systemic review [10] has been published to show the association between *IL-4 -590C>T* polymorphism and GC susceptibility, it is important to correct a minor flaw in that paper (discussed later) and update the results with a newly published paper [11].

2. Methods

2.1. Literature search

Candidate papers were searched by using the combination of key words: (1) IL-4 or IL4, (2) "gastric cancer" or "gastric carcinoma", and (3) polymorphism or variant or mutation or genotype in the databases: PubMed, Embase, the Cochrane Library, and Google Scholar. The cut-off date was December 25th, 2015. The relevant literature were evaluated by the first and second authors independently to retrieve eligible publications. All eligible papers were subsequently agreed upon by both the first and second authors.

2.2. Inclusion and exclusion criteria

The studies involved in this meta-analysis are limited to original reports and papers that were published in a peer-reviewed journal. The diagnosis of GC in each literature fits the histological criteria. The inclusion studies are all case-control ones that included GC patients and healthy controls. The involved studies must have sufficient data to calculate odds ratios (ORs) and confidence intervals (CI) for carriage of the mutant allele(s). If the same team published more than one publication using the same case series, only the paper with the largest cohort was selected for this analysis. The exclusion criteria include: (1) no healthy control population; (2) repeated papers; (3) the study subject was not human; (4) data were not able to be extracted; and (5) the allele frequency in the control group deviated from the Hardy-Weinberge equilibrium ($p \leq 0.05$).

2.3. Data extraction

A designed data extraction form was used to abstract the data from each included publication. The following information was involved: the name of the first author; the year of publication; the country where the study occurred; the ethnicity of study participants; the age range of the study subjects (if possible); the allele frequencies; ORs and CIs; the sample size; and the clinical characteristics (if possible). All data were extracted independently by the first and second authors. The results were compared and agreed upon by all the authors.

2.4. Statistical analysis

The meta-analysis of the polled data was estimated by a fixed-effect model comparing the incidence of the *IL-4 -590T* allele (either homozygous or heterozygous) with the wild-type genotype as the reference group. Heterogeneity between studies was tested by Q and I^2 statistics. The Q test uses a X^2 distribution under the null hypothesis that there is no heterogeneity between studies ($p < 0.05$ is considered significant). The I^2 test was interpreted as the proportion of the total variation contributed by the between-study heterogeneity. A random-effects model was used for recombined data if heterogeneity exited. The deviation of published data was determined by the Hardy-Weinberg equilibrium using an online program (https://www.easycalculation.com/health/hardy-weinberg-equilibrium-calculator.php). A visual inspection of the funnel plot was used to analyze publication bias. All the processes for this meta-analysis were performed by Review Manager 5.3 software (downloaded from http://tech.cochrane.org/revman/download, 64-bit windows version).

3. Results

3.1. Publications on IL-4 -590C>T

Nine eligible publications [11–19] were identified and used for the meta-analysis. A total of 1972 cases of GC and 3226 healthy controls were involved in this analysis. All the included papers were published in English. Of these publications, 5 were based on the Asian population [11–13,17,19] and the remaining 4 studies used Caucasians as the study population [14–16,18].