The -607C/A Polymorphisms in Interleukin-18 Gene Promoter Contributes to Cancer Risk: Evidence from A Meta-Analysis of 22 Case-Control Studies

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Abstract

Background: Several observational studies have investigated the association between -607 C/A polymorphism of IL-18 gene and cancer risk; however, the results were inconsistent. Therefore, we performed a meta-analysis to derive a more precise estimation of the association to help us better understand the relationship between -607 C/A polymorphism of IL-18 gene promoter and risk of cancer.

Methods: A literature search was carried out using PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) database between January 1966 and February 2013. Fixed-effect and random-effect models were used to estimate the pooled odds ratio (OR) and the corresponding 95% confidence intervals (CIs).

Results: A total of 22 case-control studies including 4100 cancer cases and 4327 controls contributed to the analysis. Significant association between -607C/A polymorphism in IL-18 gene promoter and cancer risk was observed (CA vs CC: OR = 1.221, 95% CI: 1.096, 1.360; \( P_{\text{heterogeneity}} = 0.219 \); AA/CA vs. CC: OR = 1.203, 95% CI: 1.057, 1.369; \( P_{\text{heterogeneity}} = 0.064 \)). In the subgroup analysis by ethnicity, -607C/A polymorphism significantly increased risk of cancer among Asian population (AA/CA vs. CC: OR = 1.197, 95% CI: 1.023, 1.401; \( P_{\text{heterogeneity}} = 0.088 \)); however, no significant association was found in Caucasian or African population. The -607C/A polymorphism was associated with a significantly increased risk of nasopharyngeal carcinoma (CA vs CC: OR = 1.330, 95% CI: 1.029, 1.719; \( P_{\text{heterogeneity}} = 0.704 \); AA/CA vs. CC: OR = 1.323, 95% CI: 1.037, 1.687; \( P_{\text{heterogeneity}} = 0.823 \)) and esophageal cancer (AA/CA vs. CC: OR = 1.289, 95% CI: 1.002, 1.658; \( P_{\text{heterogeneity}} = 0.700 \)).

Conclusions: The present meta-analysis suggests that the -607C/A polymorphisms in IL-18 gene promoter is associated with a significantly increased risk of cancer, especially for nasopharyngeal carcinoma and esophageal cancer and in Asian population. More studies with larger sample size, well controlled confounding factors are warranted to validate this association.

Introduction

IL-1 family includes ten known members, all of which are characterized by gene structure, predicted three-dimensional fold, processing, receptor, signal transduction pathway and pro-inflammatory properties [1]. IL-18, also known as interferon-gamma inducing factor (IGIF), is a member of the IL-1 super-family [2]. IL-18 is secreted by a wide range of cells, including T and B lymphocytes, and antigen-presenting cells (APCs), including activated monocytes, macrophages, Kupffer cells, Langerhans cells, and NK cells [3-5]. IL-1 beta converting enzyme can convert IL-18 to a mature biologically active 18.3-kDa form through cleavage of the propeptide. IL-18 binds to the cell through a specific receptor, IL-18R, belonging to the toll-like receptor family [6]. IL-18 plays a central role in inflammation and immune response, and is generally acknowledged as a key defense cytokine against infectious agents. Because immune stimulating effects of IL-18 have also antineoplastic properties, it was tempting to propose IL-18 as a novel adjuvant therapy against cancer [7]. A number of single...
nucleotide polymorphisms (SNPs) of IL-18 gene have been identified and investigated [8]. There are three SNPs in the promoter region of IL-18 gene: -137, -607 and -656, relative to the transcriptional start site, which may alter the expression of IL-18 [9]. The C to A substitution at position -607 disrupts a consensus cAMP-responsive element protein-binding site, causing altered transcription factor binding and gene expression [9]. Several observational studies have investigated the association between -607 C/A polymorphism of IL-18 gene promoter and cancer risk; however, the results were inconsistent. For example, some studies found that -607 C/A polymorphism of IL-18 gene promoter was associated with increased risk of nasopharyngeal carcinoma [10] and lung cancer [11]. However, other studies found there was no association between -607 C/A polymorphism of IL-18 gene and risk of breast cancer [12] or head and neck squamous cell carcinoma [13]. Therefore, we performed a meta-analysis to derive a more precise estimation of the association to help us better understand the relationship between -607 C/A polymorphism of IL-18 gene and risk of cancer.

Methods

Identification of studies

Comprehensive searches were carried out using PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases between January 1966 and February 2013. There were no restriction of origin and languages. Search terms included: "Interleukin-18" or "IL-18" or "rs1946518", in combination with "polymorphism" or "variant" and "cancer" or "neoplasm" or "malignancy". The reference list of each comparative study and previous reviews were manually examined to find additional relevant studies.

Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: (i) case-control studies; (ii) investigating the association between IL-18 rs1946518 (C>A) SNP and cancer risk; (iii)cancers diagnosed by histopathology; (iii) providing detail genotype frequencies. Studies without detail genotype frequencies were excluded. Titles and abstracts of searching results were screened and full text papers were further evaluated to confirm eligibility. Two reviewers (WM and ZXY) independently selected eligible trials. Disagreement between the two reviewers was settled by discussing with the third reviewer(WL).

Data extraction

In the present study, the following characteristics were collected by two reviewers (WM and LY) independently using a purpose-designed form: name of first author, publishing time, country where the study was conducted, ethnicity, cancer types, source of control, number of cases and controls, genotype frequency in cases and controls. Different ethnicity descents were categorized as Asian, Caucasian, and African. Cancer types were classified as prostate cancer, esophageal cancer, nasopharyngeal carcinoma, colorectal cancer, breast cancer, cervical cancer, and other cancers (bladder cancer, renal cell carcinoma, head and neck squamous cell carcinoma, lung cancer, stomach cancer, ovarian cancer, choriocarcinoma, and oral cancer). Eligible studies were defined as hospital-based (HB) and population-based (PB) according to the control source.

Statistical analysis

Chi-square based Q test was used to check the statistical heterogeneity between studies, and the heterogeneity was considered significant when p<0.10 [14]. The fixed-effects model (based on Mantel-Haenszel method) and random-effects model (based on DerSimonian-Laird method) were used to pool the data from different studies. The fixed-effects model was used when there was no significant heterogeneity; otherwise, the random-effects model was applied [15]. The association strength between -607 C/A (rs1946518) polymorphism and cancer risk was measured by odds ratio (OR) with 95% confidence intervals (95% CI). The estimates of pooled ORs were achieved by calculating a weighted average of OR from each study. A 95% CI was used for statistical significance test and a 95% CI without 1 for OR indicating a significant increased or reduced cancer risk. The pooled ORs were calculated for homozygote comparison (AA versus CC), heterozygote comparison (CA versus CC), dominant (CA/AA versus CC) and recessive (AA versus CC/CA) modes, assuming dominant and recessive effects of the variant A allele, respectively. Subgroup analyses were performed according to (i) cancer types, (ii) ethnicities, (iii) source of control, and (iii) sample size, to examine the impact of these factors on the association. To test the robustness of association, sensitivity analysis were carried out by excluding studies one-by-one and analyzing the effect size for all of rest studies. Cumulative meta-analysis was also performed to identify the change in trend of reporting risk over time. In cumulative meta-analysis, studies were chronologically ordered by publication year, then the pooled RRs were obtained at the end of each year. To better investigate the possible sources of between-study heterogeneity, a meta-regression analysis was performed [16]. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test [17,18]. HWE (Hardy-Weinberg equilibrium) was tested by Pearson’s X² test (P<0.05 means deviated from HWE). All analyses were performed using Stata version 11.0 (StataCorp, College Station, TX).

Results

Search results and characteristics of studies included in the meta-analysis

A total of 792 citations were identified during the initial search (shown in Figure 1). On the basis of the title and abstract, we identified 24 papers. After detailed evaluation, one study was excluded for incorrect data, and two studies were excluded for having not presented -607 C/A polymorphisms. In the study reported by Haghshenas MR and colleagues [19], they investigated rs1946518 polymorphisms and colorectal cancer, as well as stomach cancer, and the data was
presented separately, thus both of them were considered as a separate study in this meta-analysis. At last, 22 case-control studies [10-13,19-35], including 4100 cancer cases and 4327 controls, were included in the meta-analysis (Baseline data and other details are shown in Table 1). 16 eligible studies were conducted in Asia [11-13,19,21,23-27,29,30,32,34,35], five in Europe [10,20,28,31,33], and the remaining one in Africa [22]. There were five studies including more than 500 participants and the others had a sample size less than 500 participants. Genotype distribution of controls in all studies was consistent with HWE.
Table 1. Characteristics of studies included in the meta-analysis.

| First Author   | Year | Country | Ethnicity | Control               | No. of Cases | No. of Controls | Cancer Type               | Sample size | Cases | Controls |
|----------------|------|---------|-----------|-----------------------|--------------|------------------|---------------------------|-------------|-------|----------|
| Liu JM         | 2013 | China   | Asian     | Population Based      | 375          | 400              | Prostate Cancer           | Large       | 103   | 172      |
| Babar M        | 2012 | UK      | Caucasian | Population Based      | 1070         | 194              | Esophageal Cancer         | Large       | 178   | 508      |
| Du B           | 2012 | China   | Asian     | Hospital Based        | 150          | 180              | Nasopharyngeal Carcinoma  | Small       | 34    | 80       |
| Guo JY         | 2012 | China   | Asian     | Hospital Based        | 170          | 160              | Colorectal Cancer         | Small       | 49    | 85       |
| Taheri M       | 2012 | Iran    | Asian     | Population Based      | 72           | 93               | Breast Cancer             | Small       | 11    | 32       |
| Saenz-Lopez P  | 2010 | Spain   | Caucasian | Population Based      | 154          | 500              | Other Types               | Large       | 19    | 76       |
| Asefi V        | 2009 | Iran    | Asian     | Hospital Based        | 111          | 212              | Other Types               | Small       | 15    | 53       |
| Farjadfar A    | 2009 | Iran    | Asian     | Hospital Based        | 73           | 97               | Other Types               | Small       | 13    | 45       |
| Haghshenas MR  | 2009 | Iran    | Asian     | Population Based      | 142          | 311              | Colorectal Cancer         | Small       | 15    | 72       |
| Haghshenas MR  | 2009 | Iran    | Asian     | Population Based      | 87           | 311              | Other Types               | Small       | 16    | 40       |
| Khalil-Azad T  | 2009 | Iran    | Asian     | Population Based      | 200          | 206              | Breast Cancer             | Small       | 33    | 103      |
| Nong LG        | 2009 | China   | Asian     | Population Based      | 250          | 270              | Nasopharyngeal Carcinoma  | Large       | 71    | 132      |
| Samsami DA     | 2009 | Iran    | Asian     | Hospital Based        | 85           | 158              | Other Types               | Small       | 12    | 51       |
| Farhat K       | 2008 | Tunisia | African   | Population Based      | 163          | 164              | Nasopharyngeal Carcinoma  | Small       | 28    | 94       |
| Kashef MA      | 2008 | Iran    | Asian     | Population Based      | 19           | 103              | Other Types               | Small       | 3     | 10       |
| Qi T           | 2008 | China   | Asian     | Hospital Based        | 50           | 50               | Cervical Cancer           | Small       | 28    | 17       |
| Liu Y          | 2007 | China   | Asian     | Hospital Based        | 265          | 280              | Prostate Cancer           | Large       | 72    | 143      |
| Nikiteas N     | 2007 | Greece  | Caucasian | Population Based      | 84           | 89               | Colorectal Cancer         | Small       | 18    | 47       |
| Vairaktaris E  | 2007 | Germany | Caucasian | Population Based      | 149          | 89               | Other Types               | Small       | 28    | 66       |
| Wei YS         | 2007 | China   | Asian     | Hospital Based        | 235          | 250              | Esophageal Cancer         | Small       | 64    | 123      |
| Yang HL        | 2007 | China   | Asian     | Population Based      | 107          | 80               | Cervical Cancer           | Small       | 24    | 50       |
| Pratesi C      | 2006 | Italy   | Caucasian | Population Based      | 89           | 130              | Nasopharyngeal Carcinoma  | Small       | 21    | 42       |

Main results

Given that the P value of Q-tests was less than 0.10 under the allelic, homozygous, recessive, and dominant genetic models, the random-effects model was used. By contrast, the P value of Q-tests was more than 0.10 under the heterozygous genetic model (P for heterogeneity = 0.219); thus, the fixed-effects model was adopted. Significant associations between -607C/A polymorphisms in IL-18 gene promoter and cancer risk were observed in the heterozygous model (CA vs CC:OR =1.221, 95% CI: 1.096, 1.360; P_{heterogeneity}=0.219, Figure 2) and the dominant model (AA/CA vs. CC:OR =1.203, 95% CI: 1.057, 1.369; P_{heterogeneity}=0.064, Figure 3) in this meta-analysis. However, no significant association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk was observed under the allelic model (A vs C:OR =1.088, 95% CI: 0.987,1.200; P_{heterogeneity}=0.003), homozygous model (AA vs CC:OR =1.139, 95% CI: 0.948,1.369; P_{heterogeneity}=0.023), and recessive model (AA vs CC/CA: OR =0.995, 95% CI: 0.851, 1.163; P_{heterogeneity}=0.025) (shown in Table 2).

Subgroup analyses, sensitivity analysis and cumulative meta-analysis

In a stratified analysis by specific cancer types, -607C/A polymorphisms in IL-18 gene promoter was significantly associated with an increased risk of nasopharyngeal carcinoma (CA vs CC: OR =1.330, 95% CI: 1.029,1.719; P_{heterogeneity}=0.704; AA/CA vs CC: OR =1.323, 95% CI: 1.037,1.687; P_{heterogeneity}=0.823) and esophageal cancer (CA vs CC: OR =1.371, 95% CI: 1.045,1.800; P_{heterogeneity}=0.528; AA/CA vs CC: OR =1.289, 95% CI: 1.002,1.658; P_{heterogeneity}=0.700) in the heterozygous model and dominant model. No evidence of association was found in any genetic model between -607C/A polymorphisms in IL-18 gene promoter and the risk of prostate cancer, colorectal cancer, breast cancer, cervical cancer, and other cancers (shown in Table 2). According to ethnicity, the polymorphism presented a significantly increased risk of cancer among Asian population in the heterozygous model and dominant model (CA vs CC: OR =1.91, 95% CI: 1.047,1.356; P_{heterogeneity}=0.487; AA/CA vs CC: OR =1.197, 95% CI: 1.023,1.401; P_{heterogeneity}=0.088); however, no significant association was found in Caucasian and African population (shown in Table 2). In the stratified analysis by source of control groups, we found that the -607C/A polymorphisms in...
IL-18 gene promoter was associated with a significantly increased risk in hospital-based controls in the allelic model (A vs C: OR = 1.247, 95% CI: 1.022, 1.523; \( P_{\text{heterogeneity}} = 0.005 \)), heterozygous model (A vs C: OR = 1.353, 95% CI: 1.115, 1.642; \( P_{\text{heterogeneity}} = 0.435 \)), and dominant model (A vs C: OR = 1.362, 95% CI: 1.134, 1.635; \( P_{\text{heterogeneity}} = 0.189 \)). However, among studies with population-based controls, a significant association was only observed in the heterozygous model (A vs C: OR = 1.165, 95% CI: 1.024, 1.327; \( P_{\text{heterogeneity}} = 0.116 \)). When stratifying the sample size, a significant association was observed among studies with small sample size in the heterozygous model and dominant model (CA vs CC: OR = 1.223, 95% CI: 1.036, 1.445; \( P_{\text{heterogeneity}} = 0.085 \); AA/CA vs CC: OR = 1.200, 95% CI: 1.006, 1.430; \( P_{\text{heterogeneity}} = 0.016 \)), but not observed among studies with large sample size in any genetic models. To test the robustness of association, sensitivity analysis was carried out by excluding studies one-by-one and analyzing effect size for all of rest studies. Sensitivity analysis indicated that no significant variation in combined RR by excluding any of the study, confirming the stability of present results. Cumulative meta-analyses were carried out in the heterozygous and dominant genetic models. Between 2006 and 2013, with each accumulation of more studies, the 95% CIs for the pooled ORs became increasingly narrower, indicating that the precision of the estimation was progressively boosted by continually adding more samples (shown in Figure 4).

**Meta-regression and Publication bias**

As shown in Table 2, significant heterogeneity was present in all models except for heterozygous model, hence, meta-

![Forest plot of heterozygote comparison for overall comparison (CA vs. CC).](https://doi.org/10.1371/journal.pone.0076915.g002)
regression was conducted to detect the source of heterogeneity. Ethnicity, source of controls, sample size and cancer type, which may be potential sources of heterogeneity, were tested by a meta-regression method. The results showed that, in the dominant model (AA/CA vs. CC) for instance, the heterogeneity could only be explained by cancer type (p=0.014), but not ethnicity, sample size, or the source of controls. The potential publication bias of the literatures was evaluated by funnel plot and Egger’s test. No visual publication bias was found in the funnel plot (Figure 5). And Egger’s test suggested that no publication bias was detected in all the comparison models (P >0.05)

**Discussion**

The present meta-analysis, which included 4100 cancer cases and 4327 controls from 21 publications with 22 case-control studies, explored the relationship between -607C/A polymorphisms in IL-18 gene promoter and cancer risk. For overall comparison of pooled ORs, significantly increased risk was observed in the heterozygous model (CA vs CC) and the dominant model (AA/CA vs. CC). Under the allelic, homozygous and recessive genetic models, there was no significant association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk. For overall comparison of pooled ORs, significantly increased risk was observed in the heterozygous model (CA vs CC) and the dominant model (AA/CA vs. CC). Under the allelic, homozygous and recessive genetic models, there was no significant association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk. Overall, a significant association exists between -607C/A polymorphisms in IL-18 gene promoter and cancer risk. This finding indicates that the genetic variant in IL-18 gene promoter region may crucially modify the susceptibility of cancers. The C to A substitution at position...
Table 2. Stratified analyses of the -607C/A polymorphisms in IL-18 gene promoter with cancer risk.

|                      | A vs. C | AA vs. CC | CA vs. CC | AA vs. CC/CA | AA/CA vs. CC |
|----------------------|---------|-----------|-----------|--------------|--------------|
|                      | Study   | OR(95% CI)| Study     | OR(95% CI)   | Study       | OR(95% CI)| Study     | OR(95% CI) |
| Overall              | 23      | 1.088 (0.987-1.200) | 0.003     | 23 | 1.139 (0.948-1.369) | 0.023 | 23 | 1.221 (1.096-1.360) | 0.219 | 23 | 0.995 (0.851-1.163) | 0.025 | 23 | 1.203 (1.057-1.369) | 0.064 |
| Ethnicity            |         |           |           |              |              |           |           |              |              |           |           |           |              |              |           |
| Asian                | 17      | 1.107 (0.972-1.260) | 0.001     | 17 | 1.196 (0.936-1.530) | 0.007 | 17 | 1.191 (1.047-1.356) | 0.487 | 17 | 1.035 (0.854-1.255) | 0.011 | 17 | 1.197 (1.023-1.401) | 0.088 |
| Caucasian            | 5       | 1.041 (0.909-1.193) | 0.336     | 5  | 1.023 (0.779-1.343) | 0.473 | 5  | 1.294 (0.906-1.848) | 0.041 | 5  | 0.890 (0.686-1.138) | 0.620 | 5  | 1.198 (0.888-1.618) | 0.083 |
| African              | 1       | 1.076 (0.790-1.464) | NA        | 1  | 1.065 (0.558-2.030) | NA   | 1  | 1.578 (0.951-2.620) | NA   | 1  | 0.793 (0.455-1.382) | NA   | 1  | 1.421 (0.877-2.301) | NA   |
| Source of controls   |         |           |           |              |              |           |           |              |              |           |           |           |              |              |           |
| Hospital based       | 9       | 1.247 (1.022-1.523) | 0.005     | 9  | 1.329 (0.924-1.912) | 0.009 | 9  | 1.353 (1.115-1.642) | 0.435 | 9  | 1.135 (0.871-1.479) | 0.044 | 9  | 1.362 (1.134-1.635) | 0.116 |
| Population based     | 14      | 1.021 (0.941-1.107) | 0.124     | 14 | 1.012 (0.832-1.231) | 0.196 | 14 | 1.165 (1.024-1.327) | 0.189 | 14 | 0.911 (0.764-1.087) | 0.154 | 14 | 1.114 (0.986-1.258) | 0.190 |
| Sample size          |         |           |           |              |              |           |           |              |              |           |           |           |              |              |           |
| Small                | 18      | 1.092 (0.955-1.249) | <0.001    | 18 | 1.149 (0.896-1.472) | 0.008 | 18 | 1.223 (1.036-1.445) | 0.085 | 18 | 1.006 (0.813-1.246) | 0.008 | 18 | 1.200 (1.006-1.430) | 0.016 |
| Large                | 5       | 1.032 (0.918-1.161) | 0.269     | 5  | 1.051 (0.830-1.320) | 0.313 | 5  | 1.134 (0.863-1.490) | 0.042 | 5  | 0.980 (0.824-1.164) | 0.810 | 5  | 1.107 (0.862-1.421) | 0.052 |
| Cancer types         |         |           |           |              |              |           |           |              |              |           |           |           |              |              |           |
| Prostate cancer      | 2       | 0.993 (0.852-1.157) | 0.385     | 2  | 0.993 (0.732-1.346) | 0.331 | 2  | 1.039 (0.639-1.690) | 0.081 | 2  | 0.985 (0.773-1.254) | 0.896 | 2  | 1.027 (0.675-1.565) | 0.109 |
| Esophageal cancer    | 2       | 1.095 (0.926-1.293) | 0.852     | 2  | 1.111 (0.799-1.544) | 0.783 | 2  | 1.371 (1.045-1.800) | 0.528 | 2  | 0.945 (0.713-1.253) | 0.591 | 2  | 1.289 (1.002-1.658) | 0.700 |
| Nasopharyngeal cancer| 4       | 1.144 (0.985-1.328) | 0.845     | 4  | 1.305 (0.961-1.772) | 0.759 | 4  | 1.330 (1.029-1.719) | 0.704 | 4  | 1.082 (0.842-1.391) | 0.547 | 4  | 1.323 (1.037-1.687) | 0.823 |
| Colorectal cancer    | 3       | 1.066 (0.883-1.286) | 0.262     | 3  | 1.092 (0.664-1.795) | 0.213 | 3  | 1.460 (0.898-2.371) | 0.973 | 3  | 0.896 (0.638-1.259) | 0.359 | 3  | 1.337 (0.865-2.068) | 0.118 |
| Breast cancer        | 2       | 1.147 (0.904-1.456) | 0.726     | 2  | 1.332 (0.800-2.216) | 0.438 | 2  | 1.169 (0.814-1.678) | 0.532 | 2  | 1.225 (0.716-2.096) | 0.274 | 2  | 1.204 (0.854-1.696) | 0.784 |
| Cervical cancer      | 2       | 1.396 (0.208-9.382) | <0.001    | 2  | 1.890 (0.089-51.901) | <0.001 | 2  | 1.397 (0.644-3.031) | 0.241 | 2  | 1.403 (0.090-21.882) | <0.001 | 2  | 1.653 (0.241-11.339) | 0.003 |
| Other cancers        | 8       | 1.044 (0.910-1.196) | 0.200     | 8  | 0.978 (0.717-1.334) | 0.223 | 8  | 1.100 (0.803-1.507) | 0.014 | 8  | 0.935 (0.738-1.183) | 0.804 | 8  | 1.075 (0.795-1.454) | 0.012 |

OR: odds ratio; CI: confidence intervals; Phet: P value for heterogeneity; * OR with statistical significance
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−607 disrupts a consensus cAMP-responsive element protein-binding site, causing altered transcription factor binding and gene expression [9]. IL-18 serum levels have been reported to be elevated in a variety of cancers compared with control groups [19,36-39]. Hence, the -607C/A polymorphisms in IL-18 gene promoter may modify the susceptibility of cancers through changing the expression of IL-18 gene. The mechanism needs further investigation.

When identifying eligible studies by reading full text, the study conducted by Jaiswal PK and colleagues [40] was excluded for incorrect data. The OR and 95% CI under heterozygous genetic model (OR =0.59, 95% CI: 0.39, 0.92) we got based on the genotype frequency in cases and controls (CC: 81, CA: 89 in cases; CC: 61, CA: 113 in controls) were totally opposed to that they got(OR =1.59, 95% CI: 1.01-2.95). Hence, we excluded this study for its unbelievable result.

In the stratified analysis based on ethnicity, a significant increased risk of cancer was found in Asian population, but not in Caucasian or African population. One probable reason is that different environment they live in and different genetic backgrounds may account for these differences. As we know, different populations carry different genotype and/or allele frequencies of this locus polymorphism and may lead to

### Table 1. Meta-analysis of association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk under the heterozygous model (CA vs. CC).

| Study ID | OR (95% CI) |
|----------|-------------|
| Pratesi C (2006) | 1.09 (0.58, 2.02) |
| Liu Y (2007) | 1.26 (0.88, 1.80) |
| Nikiteas N (2007) | 1.47 (1.07, 2.02) |
| Vairaktaris E (2007) | 1.43 (1.08, 1.90) |
| Wei YS (2007) | 1.37 (1.08, 1.74) |
| Yang HL (2007) | 1.34 (1.07, 1.68) |
| Farhat K (2008) | 1.38 (1.12, 1.69) |
| Kashef MA (2008) | 1.36 (1.11, 1.67) |
| Qi T (2008) | 1.39 (1.13, 1.69) |
| Asef V (2009) | 1.32 (1.10, 1.59) |
| Farjadfar A (2009) | 1.38 (1.16, 1.66) |
| Haghshenas MR (2009) | 1.33 (1.13, 1.57) |
| Haghshenas MR (2009) | 1.31 (1.12, 1.53) |
| Khalili–Azad T (2009) | 1.30 (1.12, 1.51) |
| Nong LG (2009) | 1.32 (1.14, 1.52) |
| Samsami DA (2009) | 1.34 (1.17, 1.53) |
| Saenz–Lopez P (2010) | 1.27 (1.11, 1.44) |
| Babar M (2012) | 1.29 (1.14, 1.46) |
| Du B (2012) | 1.28 (1.14, 1.44) |
| Guo JY (2012) | 1.28 (1.14, 1.44) |
| Taheri M (2012) | 1.27 (1.14, 1.43) |
| Liu JM (2013) | 1.22 (1.10, 1.36) |

![Figure 4. Cumulative meta-analysis of association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk under the heterozygous model (CA vs. CC).](https://doi.org/10.1371/journal.pone.0076915.g004)
various degrees of cancer susceptibility [41]. And different ethnic groups live with multiple life styles and environmental factors and thus yield diverse gene-environment interactions [42]. In addition, there are only one study and five studies investigating the association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk among African and Caucasian population, respectively. Insufficient number of patients limited us to detect stable effects in these two populations. Additional studies are warranted to further validate ethnic difference in the effect of -607C/A polymorphisms in IL-18 gene promoter on cancer risk, especially in Africans. During sub-group analyses, we found that the source of controls also affected the association between -607C/A polymorphisms in IL-18 gene promoter and cancer risk. A significant association was observed in hospital-based controls under allelic and dominant genetic models, but not the population-based controls. The reason may be that the hospital-based studies have some inherent selection biases as such controls may just represent a sample of ill-defined reference population and may not be very representative of the study population or the general population. In stratified analysis by cancer site, we found that -607C/A polymorphisms in IL-18 gene promoter was statistically related with an increased risk of esophageal cancer and nasopharyngeal carcinoma. However, no evidence of association was found in any genetic model between-607C/A polymorphisms in IL-18 gene promoter and the risk of prostate cancer, colorectal cancer, breast cancer, cervical cancer, or other cancers. One possible reason is that carcinogenic mechanism underlying the etiology may differ by different tumor sites and that the -607C/A polymorphisms in IL-18 gene promoter may play a different role in different cancers. Futher, the number of studies which investigated the association between -607C/A polymorphisms in IL-18 gene promoter and risk of different types of cancer was too small(≤3), which limited us to detect stable effects on different cancer types. So, more studies focusing on different cancer types are need in the future.

The strength of the present analysis lies in inclusion of 22 studies, reporting data of 4100 cancer cases and 4327 controls. Publication bias, which, due to the tendency of not publishing small studies with null results, was not found in our meta-analysis. Furthermore, our findings were stable and robust in sensitivity analyses. Cumulative meta-analyses showed that, with each accumulation of more studies, the 95%
In conclusion, the present meta-analysis suggests that the -607C/A polymorphisms in IL-18 gene promoter is associated with a significantly increased risk of cancer, especially for nasopharyngeal carcinoma and esophageal cancer and in Asian population. More studies with larger sample size, well controlled confounding factors are warranted to further evaluate the association in different ethnicities and different cancer types in the future.

Supporting Information

Checklist S1. PRISMA checklist. (DOC)

Author Contributions

Conceived and designed the experiments: MW XYZ LW YL. Performed the experiments: MW XYZ LW YL. Analyzed the data: MW XZY. Contributed reagents/materials/analysis tools: MW XYZ LW YL. Wrote the manuscript: MW XYZ LW YL.
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