Association between *IL-27* Gene Polymorphisms and Cancer Susceptibility in Asian Population: A Meta-Analysis

Abdolkarim Moazeni-Roodi\(^1,2\), Mohammad Hashemi\(^3,4\)*, Saeid Ghavami\(^2,5,6\)*

**Abstract**

**Background:** Interleukin 27 (*IL-27*) has potent antitumor activity. Several epidemiological studies have designated that genetic variants of the *IL-27* gene may contribute to various cancer susceptibility, but the data were inconclusive.

**Objective:** The current meta-analysis aimed to address the association between *IL-27* rs153109, rs17855750, and rs181206 polymorphisms and the risk of cancer.

**Data Sources:** Our team has selected eligible studies up to May 1, 2020, from several electronic databases, including Web of Science, PubMed, Scopus, and Google Scholar databases.

**Results:** Our meta-analysis revealed that the carriers rs153109 A>G polymorphism in the *IL-27* gene have higher risks of diseases in the heterozygous (OR=1.26, 95%CI=1.06-1.49, P=0.007, AG vs AA), homozygous (OR=1.18, 95%CI=1.01-1.37, p=0.33, GG vs AA), dominant (OR=1.25, 95%CI=1.07-1.47, P=0.006, AG+GG vs AA), and allele (OR=1.15, 95%CI=1.04-1.27, P=0.008, G vs A) genetic models. Stratified analysis by cancer type indicated that this variant was significantly associated with gastrointestinal cancer, colorectal cancer and breast cancer. The findings did not support an association between rs17855750 T>G, rs181206 T>C polymorphisms of *IL-27* and cancer risk.

**Conclusion:** the current study findings suggest that *IL-27* rs153109 polymorphism significantly increased the risk of cancer susceptibility. Well-designed replication in a larger independent genetic association study with larger sample sizes in diverse ethnicities is required to verify the findings.

**Keywords:** *IL-27*- polymorphism- cancer- meta-analysis

Introduction

Cancer, a major public health concern, remains a leading cause of morbidity and mortality worldwide (Siegel et al., 2015). While the etiologies of cancer is complicated and not fully understood, growing evidences indicating that a complex interaction between genetic and environmental factors involved in cancer development (Lichtenstein et al., 2000).

Interleukin-27 (IL-27), belonging to the IL-12 family, is a heterodimeric cytokine comprising of two subunits, IL-27p28 and the Epstein-Barr virus-induced gene 3 protein (EBI3), and is generally secreted by activated antigen-presenting cells (Devergne et al., 1996; Liu et al., 2008). The human *IL-27* gene (IL-27P28) is located on chromosome 16 (16p11) (Pflanz et al., 2002). It is well-known that IL-27 possesses antitumor activities against a variety of tumor types (Nagai et al., 2010; Di Carlo et al., 2014; Yoshida and Hunter, 2015; Yoshimoto et al., 2015). IL-27 is a polymorphic gene and several studies examined the association between *IL-27* gene polymorphisms and risk of various cancers including, non-small-cell lung cancer (NSCLC) (Ge and Xiao, 2016), acute lymphoblastic leukemia (ALL) (Ghavami et al., 2018), nasopharyngeal carcinoma (NPC) (Wei et al., 2009; Pan et al., 2012), colorectal cancer (CRC) (Guo et al., 2012; Huang et al., 2012; Lyu et al., 2015), prostate cancer (PCa) (Munretnam et al., 2014), papillary thyroid carcinoma (PTC) (Zhang et al., 2015; Nie et al., 2017), hepatocellular carcinoma (HCC) (Peng et al., 2013), renal cell carcinoma (RCC) (Pu et al., 2015), osteosarcoma (Tang et al., 2014), esophageal cancer (Tao et al., 2012), cervical cancer (Wang et al., 2016), endometrial cancer (Yu et al., 2016), ovarian cancer (Zhang et al., 2014b), breast cancer (Zhang et al., 2014a), glioma (Zhao et al., 2009), and bladder cancer (Zhou et al., 2015). However,
the findings of these studies have been controversial. So we conducted the present meta-analysis of eligible published studies to further assess the association between the IL-27 polymorphisms and cancer risk.

Materials and Methods

Identification of Eligible Studies

Two authors independently carried out a systematic literature search in PubMed, Web of Knowledge, and Scopus for all related reports using the key words “IL-27 or IL27 or interleukin 27” and “polymorphism or SNP or variation” and “cancer or tumor or carcinoma or malignancy or neoplasm”. The last search was updated on March 04, 2019.

Inclusion and Exclusion Criteria

Studies were implemented in the current meta-analysis if they met all of the criteria: (1) Assessment of the relationship between IL-27 gene polymorphisms and cancer susceptibility; (2) Case–control studies; (3) Adequate data to estimate pooled ORs with a 95% CIs. The exclusion criteria were: (1) not a case–control study, reviews, case reports, meta-analysis, and comments; (2) duplicate publication; (3) studies with insufficient data.

Data extraction

The data extraction from the eligible studies was achieved independently by two researchers according to the inclusion and exclusion criteria mentioned above. In each study, the following items were collected from each study: first author’s name, publication year, country, ethnicity, cancer type, source of controls, total number of cases and controls, genotype distributions of cases and controls, and Hardy-Weinberg equilibrium (HWE), respectively.

Statistical analysis

All statistical analyses were achieved using Stata, version 14.1 (Stata Corporation, College Station, TX, USA).

The HWE was evaluated for each study by the chi-square test in the control group. Pooled ORs and corresponding 95%CIs were calculated to estimate the strength of association between IL-27 gene polymorphism and cancer risk. The significance of the pooled OR was determined by Z test, in which p-value less than 0.05 was considered statistically significant.

The Q statistic test was used to check the heterogeneity among studies included in the meta-analysis. A p<0.10 indicated a lack of heterogeneity among studies, consequently the fixed effect model was used to calculate pooled OR. Otherwise, a random effects model was utilized.

Publication bias was evaluated by Begg’s funnel plot qualitatively, and Begg’s and Egger’s tests quantitatively. P-value less than 0.05 considered significant publication bias.

Sensitivity analysis was done by removing each study in turn to measure the results stability.

Results

Study Characteristics

In the current study, according to the inclusion and exclusion criteria, ultimately 20 case-control studies included in the meta-analysis. For rs153109, 21 studies containing 6,331 cases and 7,287 controls for were included in the quantitative analysis. Regarding rs17855750 variant, 4,023 cases and 4,671 controls from 14 studies and for rs181206 polymorphism, 2,078 cases and 2,242 controls from were 7 studies were included in the meta-analysis. The characteristics of the included studies are summarized in Table 1, Table 2 and Table 3.

Association between IL-27 polymorphisms and cancer risk

The frequency distribution of genotype and allele of the IL-27 polymorphisms in cases and controls are indicated in Table 1, Table 2 and Table 3. Table 4 shows the main findings of our meta-analysis. Regarding rs153109 A>G variant, 21 independent studies were pooled and a random effect was applied due to the presence of significant heterogeneity. The finding revealed that rs153109 variant significantly increased the risk of cancer in heterozygous (OR=1.26, 95%CI=1.06-1.49, P=0.007, AG vs AA), homozygous (OR=1.18, 95%CI=1.01-1.37, p=0.33, GG vs AA), dominant (OR=1.25, 95%CI=1.07-1.47, P=0.006, AG+GG vs AA), and allele (OR=1.15, 95%CI=1.04-1.27, P=0.008, G vs A) genetic models (Figure 1 and Table 4). Stratified analysis by cancer type (Table 5) revealed that rs153109 significantly increased the risk of gastrointestinal (GI) cancer in homozygous (OR=1.35, 95%CI=1.11-1.65, p=0.003), dominant (OR=1.28, 95%CI=1.02-1.59, p=0.030) and allele (OR=1.18, 95%CI=1.07-1.30, p=0.007) genetic models. Besides, the variant was significantly associated with colorectal cancer (CRC) and breast cancer susceptibility in all genetic model tested (Table 5).

The findings showed that rs17855750 T>G, and rs181206 T>C variants were not associated with cancer risk (Table 4).

Heterogeneity and publication bias

Heterogeneity among studies involved in the meta-analysis is presented in Table 4. The findings indicated that heterogeneity exist among studies and random-effects was used to estimate the pooled OR and 95% CI (Figure 2 and Table 4).

Begg’s funnel plot, Begg’s test, and Egger’s test (Figure 3, and Table 4) indicated no evidence of significant publication bias.

Sensitivity analysis

After doing the sensitivity analyses, the pooled ORs showed no statistically significant changes in heterozygous, dominant, recessive, and allele representing that our findings are stable and reliable in overall analysis (Figure 4).

Discussion

Several studies examined the association between
| Year | Country | Ethnicity | Cancer type | Source of controls | Genotype tested | Genotype | Country | Ethnicity | Cancer type | Source of controls | Genotype tested | Genotype |
|------|---------|-----------|-------------|-------------------|-----------------|-----------|---------|-----------|-------------|-------------------|-----------------|-----------|
| 2012 | China   | Asian     | Breast cancer | Hospital-based | GGC             | AG        | China   | Asian     | Breast cancer | Hospital-based | GGC             | AG        |
| 2012 | Iran    | Persian   | Breast cancer | Hospital-based | GG/CC           | AA/AG     | Iran    | Persian   | Breast cancer | Hospital-based | GG/CC           | AA/AG     |
| 2012 | China   | Asian     | Prostate cancer | Hospital-based | GA              | GG        | China   | Asian     | Prostate cancer | Hospital-based | GA              | GG        |
| 2012 | China   | Asian     | Lung cancer   | Hospital-based | GG              | AA        | China   | Asian     | Lung cancer   | Hospital-based | GG              | AA        |
| 2012 | Iran    | Persian   | Lung cancer   | Hospital-based | GG              | AA        | Iran    | Persian   | Lung cancer   | Hospital-based | GG              | AA        |
| 2012 | China   | Asian     | Hepatocellular carcinoma | Hospital-based | GG/GG           | AA/AA     | China   | Asian     | Hepatocellular carcinoma | Hospital-based | GG/GG           | AA/AA     |
| 2012 | China   | Asian     | Non-Hodgkin lymphoma | Hospital-based | GG/GG           | AA/AA     | China   | Asian     | Non-Hodgkin lymphoma | Hospital-based | GG/GG           | AA/AA     |

Table 1. Characteristics of all studies included in the meta-analysis for IL-27 rs153909 polymorphism.
IL-27 polymorphisms and the risk of various cancer (Wei et al., 2009; Zhao et al., 2009; Guo et al., 2012; Huang et al., 2012; Pan et al., 2012; Tao et al., 2012; Peng et al., 2013; Munretnam et al., 2014; Tang et al., 2014; Zhang et al., 2014a; Zhang et al., 2014b; Lyu et al., 2015; Pu et al., 2015; Zhang et al., 2015; Zhou et al., 2015; Ge and Xiao, 2016; Wang et al., 2016; Yu et al., 2016; Nie et al., 2017; Ghavami et al., 2018). The findings were controversial, though it is difficult to clarify the inconsistent findings. In this study, we conducted a comprehensive meta-analysis of all eligible studies to derive a more precise estimation of the relationship between IL-27 polymorphism and cancer risk. After pooling all the available data, the finding suggested that IL-27 rs153109 (-964 A>G) significantly increased the risk of overall cancer. Stratified analysis by cancer type designated that rs153109 polymorphism...
Table 2. Characteristics of All Studies Included in the Meta-Analysis for IL-27 rs17855750 Polymorphism.

| Author         | Year | Country | Ethnicity | Cancer Type | Source of Control | HWE             | Genotyping Method | Case | Control |
|----------------|------|---------|-----------|-------------|-------------------|-----------------|-------------------|------|---------|
| Ghavami        | 2018 | Iran    | Asian     | ALL         | HB                | 0.001           | PCR-RFLP         | 200  | 210     |
| Guo            | 2012 | China   | Asian     | CRC         | HB                | 0.151           | PCR-RFLP         | 170  | 160     |
| Huang          | 2012 | China   | Asian     | CRC         | HB                | 0.083           | PCR-RFLP         | 410  | 450     |
| Nie            | 2016 | China   | Asian     | PTC         | HB                | 0.118           | PCR-RFLP         | 496  | 629     |
| Peng           | 2013 | China   | Asian     | HCC         | HB                | 0.304           | PCR-RFLP         | 107  | 105     |
| Pu             | 2015 | China   | Asian     | RCC         | HB                | 0.104           | PCR-RFLP         | 329  | 386     |
| Tang           | 2014 | China   | Asian     | Osteosarcoma| HB                | 0.118           | PCR-RFLP         | 160  | 250     |
| Tao            | 2012 | China   | Asian     | ESC         | HB                | 0.042           | PCR-RFLP         | 426  | 432     |
| Wang           | 2009 | China   | Asian     | NPC         | HB                | 0.098           | PCR-RFLP         | 100  | 0       |
| Wei            | 2012 | China   | Asian     | central cancer| HB            | 0.216           | PCR-RFLP         | 404  | 406     |
| Wei            | 2012 | China   | Asian     | ESC         | HB                | 0.098           | PCR-RFLP         | 100  | 0       |
| Yu             | 2016 | China   | Asian     | NPC         | HB                | 0.116           | PCR-RFLP         | 111  | 0       |
| Zhao           | 2009 | China   | Asian     | NPC         | HB                | 0.115           | PCR-RFLP         | 302  | 310     |
| Zhang          | 2016 | China   | Asian     | Breast cancer| HB            | 0.058           | PCR-RFLP         | 332  | 320     |

ALL, acute lymphoblastic leukemia; CRC, colorectal cancer; ESC, esophageal cancer; PTC, papillary thyroid carcinoma; NPC, nasopharyngeal carcinoma; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; HB, hospital-based.
| Author | Year | Country | Ethnicity | Cancer type | Source of control | Genotyping Method | Cases | Controls | OR (95%CI) | Test of association | Test of heterogeneity |
|--------|------|---------|-----------|-------------|-------------------|-------------------|-------|------------|------------|---------------------|----------------------|
| Zhang  | 2009 | China   | Asian     | CRC         | HB                | PCR-RFLP          | 210/220 | 166        | 1.26 (1.06-1.49) | 2.68                 | <0.00001             |
| Wei    | 2009 | China   | Asian     | CRC         | HB                | PCR-RFLP          | 201/211 | 179        | 1.18 (1.01-1.37) | 2.13                 | 0.033                |
| Wang   | 2010 | China   | Asian     | CRC         | HB                | PCR-RFLP          | 190/200 | 157        | 1.25 (1.07-1.47) | 2.73                 | <0.00001             |
| Pan    | 2012 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 190/200 | 157        | 1.18 (1.01-1.37) | 2.13                 | 0.033                |
| Huang  | 2012 | China   | Asian     | CRC         | HB                | PCR-RFLP          | 190/200 | 157        | 1.25 (1.07-1.47) | 2.73                 | <0.00001             |
| Pan    | 2012 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 190/200 | 157        | 1.18 (1.01-1.37) | 2.13                 | 0.033                |
| Tang   | 2014 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 190/200 | 157        | 1.25 (1.07-1.47) | 2.73                 | <0.00001             |
| Tao    | 2012 | China   | Asian     | ESC         | HB                | PCR-RFLP          | 160/250 | 131        | 1.25 (1.07-1.47) | 2.73                 | <0.00001             |
| Wang   | 2016 | China   | Asian     | cervical cancer | HB | PCR-RFLP | 380/380 | 226 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Wei    | 2009 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Zhao   | 2009 | China   | Asian     | Glioma      | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Wei    | 2009 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Tang   | 2014 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Tao    | 2012 | China   | Asian     | ESC         | HB                | PCR-RFLP          | 160/250 | 131 | 1.25 (1.07-1.47) | 2.73 | <0.00001 |
| Wang   | 2016 | China   | Asian     | cervical cancer | HB | PCR-RFLP | 380/380 | 226 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Wei    | 2009 | China   | Asian     | NPC         | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |
| Zhao   | 2009 | China   | Asian     | Glioma      | HB                | PCR-RFLP          | 201/211 | 179 | 1.18 (1.01-1.37) | 2.13 | 0.033 |

Table 3. Characteristics of all studies included in the meta-analysis for IL-27 rs181206 polymorphism.

Table 4. The Pooled ORs and 95%CIs for the Association between IL-27 Polymorphisms and Cancer Susceptibility.
| rs181206 T>C | rs17855750 T>C | rs153109 A>G | rs17855750 A>G |
|---------------|---------------|--------------|---------------|
| **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| Nasopharyngeal carcinoma | Colorectal cancer | GI cancer | Breast cancer |
| CT vs TT | CC vs TT | CC vs TT | CT+CC vs TT |
| 1.07 (0.86-1.32) | 1.40 (1.02-1.97) | 1.40 (1.01-1.97) | 1.40 (1.17-1.67) |
| 0.89 (0.70-1.18) | 0.88 (0.70-1.18) | 0.89 (0.70-1.18) | 0.89 (0.70-1.18) |
| C VS T | C VS T | C VS T | C VS T |
| 0.17 | 0.17 | 0.17 | 0.17 |
| 1.21 (0.92-1.59) | 1.22 (0.94-1.59) | 1.11 (0.74-1.65) | 1.12 (0.82-1.52) |
| 0.01 | 0.01 | 0.01 | 0.01 |
| 0.65 | 0.65 | 0.65 | 0.65 |
| 0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Cytokines, secreted by cells of innate and adaptive immune systems, are small proteins that play key roles in immune responses. IL-27 is produced early after activation by antigen-presenting cells, including monocyte-derived dendritic cells and lipopolysaccharide-stimulated monocytes (Chiyoh et al., 2004; Owaki et al., 2005). IL-27 mediates its biological functions via a heterodimeric receptor consisting of WSX-1 and glycoprotein 130 (gp130) (Pflanz et al., 2004). Binding of IL-27 to its receptor activates Janus kinase (JAK)-signal transducer and activator of transcription (STAT) and mitogen-activated protein kinase (MAPK) signaling (Kastelein et al., 2007). IL-27 has potent antitumor activity (Hisada et al., 2004; Chiyoh et al., 2005). It exerts antitumor activity by promoting the generation of myeloid progenitor cells that can differentiate into M1 macrophages (Chiba et al., 2018). In addition, IL-27 synergizes with IL-12 to potentiate IFN-γ production by activated naïve T-cell and natural killer-cell populations (Pflanz et al., 2004). Beside, IL-27 is a major stimulus of IL-10 production by T cell (Hunter and Kastelein, 2012; Liu et al., 2013).

Some limitations should be addressed in our meta-analysis. First, heterogeneity among studies was observed which may be result of difference of ethnicity, source of control, and cancer type. Second, this study focused on the impact of limited variants of IL-27 and cancer susceptibility. Gene-gene as well as gene-environment interactions could influence cancer risk. Third, all studies were from Asian populations; consequently, conclusions drawn may not apply to the all population. Finally, the sample sizes of the studies are relatively small particularly in subgroup analysis. So, the results should be interpreted with caution.

In conclusion, the findings of this meta-analysis provide evidence for an association between IL-27 rs153109 polymorphism and cancer risk. Well-designed studies with larger sample sizes in various cancer and different ethnicities are still needed in the future.

**Acknowledgments**

The authors like to acknowledge the Zahedan University of Medical Sciences research office to provide...
Figure 3. Begg’s Funnel Plot for Publication Bias Test for IL-27 rs153109 A>G Polymorphism and Cancer Risk for G vs A.

Figure 4. Sensitivity Analyses for Association between IL-27 rs153109 A>G Polymorphism and Cancer Risk for G vs A.

logistics for the literature search. The work was not supported by any operating grant and fund and was not a part of any graduate and under graduate thesis.

We would like to dedicate this article to Professor Mohamad Hashemi who passed away recently after the submission of this work. He was a pioneer in genetic studies.

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Conflict of interest

The authors declare that they have no conflict of interest.

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