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Review

# Interleukin-23 receptor genetic variants contribute to susceptibility of multiple cancers

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ABSTRACT

*Aim:* Interleukin-23 (IL-23) and IL-23 receptor (IL23R) play an important role during the T-helper 17 (Th17) cell-mediated inflammatory process as well as pathogenesis of multiple cancers. Several *IL-23R* single nucleotide polymorphisms (SNPs), especially rs6682925, rs10889677 and rs1884444 polymorphisms, are considered to have significant impacts on susceptibility of multiple cancers. A number of case-control studies have explored the role these genetic polymorphisms in development of carcinogenesis, but the conclusions are inconsistent. Therefore, we conducted this meta-analysis to systematically investigate the associations between the three genetic variants and multiple cancer risk.

*Methods:* A total of ten studies are eligible (12,211 patients and 14,650 controls). Pooled odds ratios (ORs) and the 95% confidence interval (95% CI) were appropriately calculated using either fixed-effect model or random-effect model.

*Results:* Significant associations between rs6682925 or rs10889677 polymorphism and cancer risk were found (OR = 1.11, 95% CI = 1.03–1.21, $P = 0.007$; or OR = 0.85, 95% CI = 0.71–0.92, $P = 0.001$). However, there was no such association between rs1884444 genotypes and cancer susceptibility ($P > 0.05$).

*Conclusion:* These findings reveal that the *IL-23R* rs6682925 and rs10889677 genetic variants play a more important part in pathogenesis of multiple cancers.



**Contents**



## 1. Introduction

It has been showed that Interleukin-23 (IL-23) and IL-23 receptor (IL23R) play an important role during the T-helper 17 (Th17) cell-mediated inflammatory process as well as pathogenesis of multiple cancers (Chen et al., 2007; Volpe et al., 2008). As a recently identified pro-inflammatory $CD4^+$ effecter T-cell population, Th17 cells can clear

*Abbreviations:* IL-23, interleukin-23; IL23R, Interleukin-23 receptor; SNP, single nucleotide polymorphism; Th17, T-helper 17; OR, odds ratios; 95% CI, 95% confidence interval; 3′-UTR, 3′-untranslated region; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

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pathogen and mediate tissue inflammation by secreting high levels of the pro-inflammatory cytokine IL-17 in response to stimulation (Romagnani, 2008). IL-23/IL-23R is essential for Th17 cell-mediated immune response, tumor-promoting pro-inflammatory processes and the failure of the adaptive immune surveillance (Chen et al., 2007; Volpe et al., 2008). It has been reported that IL-23R could also decrease immunosurveillance by $CD8^+$ T cells and promote tumor growth (Langowski et al., 2006). In tumor microenvironment, IL-23R signaling pathway in regulatory T cells (Tregs) might also promote the immunosuppressive function of Tregs facilitating evasion of the immune system by cancer cells (Fontenot et al., 2003; Hori et al., 2003; Kim et al., 2007). Interestingly, both Th17 cells and Tregs can enhance proliferation of tumor cells, and it has been suggested that there may be a link between these two kinds of T-cells (Voo et al., 2009). The abovementioned findings indicate that IL-23R might play an important part in cancer development and progression.

*IL-23R* gene, which encodes IL-23R, locates on chromosome 1p31.3. Several *IL-23R* single nucleotide polymorphisms (SNPs) have been identified. For example, there is an rs10889677A>C polymorphism in the 3′-untranslated region (3′-UTR) of *IL-23R*, which could increase the binding affinity of microRNA let-7f and, thus, elevated the transcription of the *IL-23R* gene *in vitro* and *in vivo*. Functional studies demonstrated that rs10889677CC carriers had less Tregs and a faster T-cell proliferation than individuals carrying the rs10889677AA homozygous genotype (Zheng et al., 2012). Accumulated evidences showed that rs10889677 and other SNPs in *IL-23R* may be associated with the risk of multiple cancers, including breast cancer, lung cancer, esophageal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, colorectal cancer, nasopharyngeal carcinoma, oral cancer and acute myeloid leukemia (Chen et al., 2010, 2011; Chien et al., 2012; Chu et al., 2012; Poole et al., 2012; Qian et al., 2013; Wang et al., 2012; Xu et al., 2013; Zhang et al., 2010; Zheng et al., 2012). However, the results are inconsistent and inconclusive. Considering the importance of IL-23R in cancer development, we systematically analyzed the differential role of *IL-23R* genetic variants on multiple cancers through a meta-analysis.

## 2. Materials and methods

### 2.1. Literature search and data extraction

HuGE Navigator (version 2.0), PubMed (US National Library of Medicine, National Institutes of Health), EMBASE and Web of science were used for the electronic literature searches with search terms of "Interleukin-23 receptor," "IL-23 receptor," "IL23R," "polymorphism," "variant," "SNP," "cancer," "tumor," as well as their combinations. Case-control studies of *IL-23R* polymorphisms published from October, 2009 to April, 2013 were identified without language restrictions. Additional studies have also identified by screening reference lists of important studies and reviews. Criteria for selection of an eligible study included: (a) original studies; (b) studies that investigated the association between *IL-23R* polymorphism(s) and cancer risk; (c) studies that reported crude odds ratio (OR) with 95% confidence interval (CI) values or sufficient data to calculate crude OR and 95% CI. Criteria for exclusion of studies were (a) case-only studies, family-based studies and review articles and (b) overlapping data. The raw data and demographic information, including first author, published year, original country, ethnicity, sample size, cancer types and genotypes were independently extracted. If essential data were not provided in the original articles, every effort was made to contact the authors.

### 2.2. Statistical analysis

Association between *IL-23R* polymorphisms and cancer risk was recalculated using crude ORs together with their corresponding 95% CIs. A fixed effect model (the Mantel–Haenszel method) was used to calculate the combined OR if the *P* value of the heterogeneity test was ≥0.05 (Mantel et al., 1959). The Mantel–Haenszel method assumed the same homogeneity of effect size across all studies. If the *P* value of the heterogeneity test was <0.05, it showed that the between-study heterogeneity was statistically significant. A random effects mode (the DerSimonian and Laird method) was performed to calculate the combined OR (Petitti, 1994). Funnels plots, in which the standard error was plotted against the log(OR) to form a simple scatter plot, were used to test publication bias. The funnel plot asymmetry was assessed by the method of Egger's test (Egger et al., 1997). Asymmetric plots could indicate potential existing publication bias. The statistical analyses were performed using Stata Statistical package (version 11.0; Stata Corp., College Station, Tex). All *P* values were two-sided.

## 3. Results

### 3.1. Literature search and data extraction

We searched HuGE Navigator, NCBI PubMed, EMBASE and Web of science using the keywords "Interleukin-23 receptor," "IL-23 receptor," "IL23R," "polymorphism," "variant," "SNP," "cancer," or "tumor," and found 11 studies. Of these 11 studies, one study was excluded either because the results do not meet the purpose of the current meta-analyses. The remaining 10 studies (12,211 patients and 14,650 controls) fulfilled inclusion criteria (Chen et al., 2010, 2011; Chien et al., 2012; Chu et al., 2012; Poole et al., 2012; Qian et al., 2013; Wang et al., 2012; Xu et al., 2013; Zhang et al., 2010; Zheng et al., 2012). There are two studies on breast cancer (Wang et al., 2012; Zheng et al., 2012), one on lung cancer (Zheng et al., 2012), one on esophageal cancer (Chu et al., 2012), one on ovarian cancer (Zhang et al., 2010), two on gastric cancer (Chen et al., 2010, 2011), one on hepatocellular carcinoma (Xu et al., 2013), one on colorectal cancer (Poole et al., 2012), one on nasopharyngeal carcinoma (Zheng et al., 2012), one on oral cancer (Chien et al., 2012) and one on acute myeloid leukemia (Qian et al., 2013). A total of 6 *IL-23R* SNPs (rs6682925, rs1884444, rs10889677, rs6683039, rs7517847 and rs11465817) have been investigated in these 10 studies. Since there is only one data set for rs6683039, rs7517847 or rs11465817 genetic variant, we excluded these SNPs in the current meta-analyses. A database, including information extracted from each article, was created. Table 1 showed the essential information, including first author, year of publication, SNPs genotyped, sample size, country, ethnicity, cancer types and genotyping methods.

### 3.2. Quantitative data synthesis

For the *IL-23R* rs6682925 SNP, we got our meta-analysis data from 5 data sets consisting of 5020 cases and 6473 normal controls [both *P* for Hardy–Weinberg equilibrium (HWE) >0.05; minor allele frequency (MAF) of cases = 0.418, MAF of controls = 0.394]. The association between the rs6682925 T>C genotypes and risk of multiple cancers was estimated using a fixed effect model since no heterogeneity between studies existed ($P_{\text{heterogeneity}} > 0.05$). Compared with rs6682925 TT genotype, the carriers of TC genotype showed an increased risk to develop cancer (OR = 1.09, 95% CI = 1.00–1.19, $P = 0.040$) (Table 2 and Fig. 1A). However, the association between CC genotype and cancer susceptibility was not statistically significant (OR = 1.19, 95% CI = 0.96–1.47, $P = 0.110$) (Table 2 and Fig. 1A). If the heterozygotes are combined, the rare homozygotes, the OR for rs6682925 TC and CC genotypes are 1.11 (95% CI = 1.03–1.21, $P = 0.007$).

The effects of the functional *IL-23R* rs10889677 polymorphism were also examined in 6731 patients and 7296 controls (both *P* for HWE <0.05; MAF of cases = 0.262, MAF of controls = 0.316). Compared with the rs10889677 AA genotype, a 0.85-fold decreased risk to develop multiple cancers was observed for individuals with AC and CC genotypes in a random effect model (95% CI = 0.71–0.92, $P = 0.001$; $P_{\text{heterogeneity}} < 0.001$) (Table 2 and Fig. 1B). Interestingly, the OR