Association of IL4, IL13, and IL4R polymorphisms with gastrointestinal cancer risk: A meta-analysis

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Abstract

Background: Previous studies have suggested that IL4, IL13, and IL4R are associated with serum IgE levels and allergies, and common variants of these genes may alter cancer risk. To clarify these associations, we conducted a meta-analysis to investigate the associations of IL4, IL13, and IL4R polymorphisms with gastrointestinal cancer risk.

Methods: We used 27 eligible case-control studies describing the associations of six polymorphisms of IL4, IL13, and IL4R with gastrointestinal cancer risk to calculate summary odds ratios (ORs) and 95% confidence intervals (CIs) using five different genetic models. The Q-statistic and I² statistic were calculated to examine heterogeneity.

Results: The IL4 rs2070874 T allele seems to be associated with an increased risk of gastrointestinal cancer (OR 1.11; 95% CI, 1.00–1.24 for T allele vs. C allele). This association was significant in studies conducted outside of Asia (OR 1.28; 95% CI, 1.03–1.58 for T allele vs. C allele) and in studies investigating the association with gastric cancer (OR 1.17; 95% CI, 1.03–1.34 for T allele vs. C allele). However, the IL4R rs1801275 heterozygote seems to be associated with a reduced risk of gastrointestinal cancer (OR 0.79; 95% CI, 0.65–0.96 for AG vs. AA). Other polymorphisms did not show any significant associations with gastrointestinal cancer risk in any of the genetic models and subgroup analyses.

Conclusions: Our results suggest that certain polymorphisms of IL4 and IL4R may affect susceptibility to gastrointestinal cancer. However, further studies are required to confirm these findings.

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IL4R genes with gastrointestinal cancer risk, we conducted a meta-analysis using six polymorphisms of these genes.

**Methods**

*Identification and eligibility of relevant studies*

To identify all articles that explored the associations of six polymorphisms of IL4, IL13, and IL4R with gastrointestinal cancer risk, we conducted a literature search on PubMed and EMBASE from the year 2000 through February 3, 2016. Information on the risk, we conducted a literature search on PubMed and EMBASE.

**Data extraction**

Two investigators extracted the data independently and reached a consensus on all items. The following information was extracted from each article: author name, year of publication, country of study, source of controls, cancer type, genotype frequencies for cases and controls, and investigated polymorphisms.

**Statistical analysis**

The strengths of the associations between the polymorphisms and gastrointestinal cancer risk were measured using ORs with the following genetic models: 1) homozygote comparison, 2) heterozygote comparison, 3) dominant genetic model, 4) recessive genetic model, and 5) allele comparison. This meta-analysis re-examined unadjusted pooled results. Before analysis, the genotype frequencies of the polymorphisms were assessed for HWE using a Chi-squared test. A p-value <0.01 was considered a significant deviation from HWE. The Q-statistic and I² statistic were calculated to examine heterogeneity. The summary OR estimated for each study was calculated using either a fixed- or a random-effects model based on the Q-statistic.

Potential sources of heterogeneity were sought via subgroup analyses. For each genetic comparison, stratified analyses were performed according to cancer type, geographic location (Asia/non-Asia), and source of controls (hospital/population). Publication bias was investigated using a funnel plot, and funnel plot asymmetry was assessed using Egger’s linear regression test.

All statistical analyses were performed using Stata software (version 11; Stata Corporation, College Station, TX, USA). Two-sided p-values <0.05 were considered statistically significant.

**Results**

*Literature search and study characteristics*

According to our search criteria, a total of 279 articles were retrieved. After screening these articles based on title and abstract, 238 articles were excluded. We then evaluated the full text of the remaining 41 articles, and 15 articles were excluded for several reasons. A study flow chart depicting the literature search and selection is presented in Fig. 1. Ultimately, we found 26 articles describing 27 studies on the associations of the IL4, IL13, and IL4R polymorphisms with gastrointestinal cancer that matched our inclusion criteria: IL4 rs2243250 (16 studies; 3783 cases/4895 controls) and rs2070874 (6 studies; 3662 cases/3388 controls), IL13 rs1800925 (5 studies; 1054 cases/1384 controls) and rs20541 (3 studies; 2162 cases/2568 controls), and IL4R rs1805010 (5 studies; 1215 cases/2004 controls) and rs1801275 (6 studies; 1013 cases/1065 controls).

The allele frequency of each polymorphism in the controls is presented in Table 1. The frequency of the T allele in IL4 rs2243250 and rs2070874 was higher in the controls from Asian countries than in the controls from non-Asian countries (0.78 vs. 0.17 for rs2243250; 0.80 vs. 0.13 for rs2070874). Table 2 presents the characteristics of the studies included in the meta-analysis. The studies were conducted using either population or hospital controls in various countries and investigated gastrointestinal cancers, including esophageal, gastric, colorectal, hepatocellular, and pancreatic cancer.

*Outcome from eligible studies*

IL4 rs2243250 was not associated with gastrointestinal cancer risk for any of the genetic models and subgroup analyses (Fig. 2 and eTable 1). For IL4 rs2070874, an increased risk was observed for T allele carriers (OR 1.11; 95% CI 1.00−1.24 for T allele vs. C allele), and

**Table 1** Primary information for the six polymorphisms included in the meta-analysis.

| Gene | Function and pathway | Ch. location | rs number | Location | Trivial name | Base change | MAF in controls, mean* |
|------|----------------------|--------------|-----------|----------|--------------|-------------|------------------------|
| IL4  | Th2 differentiation and IgE induction | 5q31.1 | rs2243250 | Promoter | C-590T | C > T | 0.78 | 0.17 |
|      |                      |            | rs2070874 | 5’UTR    | C-33T | C > T | 0.80 | 0.13 |
| IL13 | Th2 effector functions | 5q31 | rs1800925 | Promoter | C-1112T, C-1055T | C > T | 0.17 | 0.17 |
|      |                      |            | rs20541 | Exon4   | G2044A, Arg130Gln | C > T | 0.19 | 0.40 |
| IL4R | α-chain of the IL4 and IL13 receptors | 16p12.1-p11.2 | rs1805010 | Exon5   | Ile50Val, I75V | A > G | 0.57 | 0.45 |
|      |                      |            | rs1801275 | Exon12  | Gln551Arg, Q675R | A > G | 0.17 | 0.35 |

Ch, chromosome; IL4, interleukin-4; IL13, interleukin-13; IL4R, interleukin-4 receptor; MAF, minor allele frequency.

* Frequency of variant allele in controls included in this meta-analysis.
Fig. 1. Flowchart depicting the literature search and selection.

Table 2
Characteristics of the studies included in the meta-analysis.

| First author (year) | Country      | Cancer type | Number of cases/controls | Source of control | SNPs                          |
|---------------------|--------------|-------------|--------------------------|-------------------|-------------------------------|
| El-Omar (2003)      | USA          | Gastric     | 112/209                  | P                 | rs2243250, rs1805010, rs1801275 |
| El-Omar (2003)      | USA          | Esophageal  | 90/209                   | P                 | rs2243250                     |
| Wu (2003)           | Taiwan       | Gastric     | 220/230                  | H                 | rs2243250, rs1805010, rs1801275 |
| Lai (2005)          | China        | Gastric     | 123/162                  | P                 | rs2243250                     |
| Cozar (2007)        | Spain        | Colorectal  | 96/174                   | H                 | rs2243250                     |
| Garcia-Gonzalez (2007) | Spain    | Gastric     | 404/404                  | P                 | rs2243250                     |
| Landi (2007)        | Spain        | Colorectal  | 281/269                  | H                 | rs2243250, rs2070874, rs1805010, rs1801275 |
| Olson (2007)        | USA          | Pancreatic  | 405/212                  | H                 | rs2243250, rs1801275          |
| Yannopoulos (2007) | Greece       | Colorectal  | 95/108                   | P                 | rs2243250                     |
| Crusius (2008)      | 10 European countries | Gastric | 244/1160                  | P                 | rs2243250, rs2070874, rs1805010 |
| Suchy (2008)        | Poland       | Colorectal  | 350/350                  | H                 | rs2243250                     |
| Wilkening (2008)    | Sweden       | Colorectal  | 304/582                  | P                 | rs2243250                     |
| Zambon (2008)       | Italy        | Gastric     | 142/171                  | H                 | rs2243250, rs1805010, rs1801275 |
| Ando (2009)         | Japan        | Gastric     | 330/190                  | H                 | rs2243250, rs1805010          |
| Ko (2009)           | Korea        | Gastric     | 81/324                   | P                 | rs2243250, rs2070874          |
| Scola (2009)        | Italy        | Pancreatic  | 48/131                   | H                 | rs1801275, rs1800925          |
| Wu (2009)           | China        | Gastric     | 1042/1099                | P                 | rs2070874                     |
| Lee (2010)          | Korea        | Colorectal  | 170/130                  | P                 | rs1801275                     |
| Sainz (2012)        | Sweden       | Colorectal  | 1789/1771                | P                 | rs20541                       |
| Walczak (2012)      | Poland       | Colorectal  | 191/205                  | P                 | rs1800925                     |
| Sun (2013)          | China        | Esophageal  | 365/369                  | H                 | rs1800925                     |
| Lu (2014)           | China        | Hepatocellular | 154/170             | P                 | rs2243250, rs2070874          |
| Pan (2014)          | China        | Gastric     | 308/308                  | P                 | rs2243250                     |
| Yu (2014)           | China        | Colorectal  | 299/296                  | P                 | rs2070874                     |
| Cotterchio (2015)   | Canada       | Pancreatic  | 172/566                  | P                 | rs20541                       |
| Deng (2015)         | China        | Hepatocellular | 192/192                | P                 | rs1800925, rs20541            |
| Yin (2015)          | China        | Gastric     | 234/465                  | H                 | rs1800925                     |

H, hospital; P, population.
this association was significant in studies conducted in studies outside of Asia (OR 1.28; 95% CI, 1.03–1.58 for T allele vs. C allele) and was significant in studies investigating the association with gastric cancer (OR 1.17; 95% CI, 1.03–1.34 for T allele vs. C allele) (Fig. 3 and eTable 1). Both IL13 rs20541 and rs1800925 were not associated with gastrointestinal cancer risk for any of the genetic models and subgroup analyses (eTable 2). For IL4R rs1801275, heterozygote seems to be associated with a reduced risk of gastrointestinal cancer (OR 0.79; 95% CI, 0.65–0.96 for AG vs. AA; OR 0.82; 95% CI, 0.68–0.99 for GG/AG vs. AA) (Fig. 4 and eTable 3). However, IL4R rs1805010 was not associated with gastrointestinal cancer risk for any of the genetic models and subgroup analyses (eTable 3).

**Publication bias**

Begg’s funnel plot and Egger’s test were performed to evaluate publication bias. The funnel plot of the selected studies showed significant symmetry, and the results of Egger’s test indicated no significant publication bias (data not shown).

**Discussion**

To derive more precise conclusions about the associations between allergy-related polymorphisms and gastrointestinal cancer risk, we performed a comprehensive meta-analysis of 27 case–control studies that included six polymorphisms of IL4, IL13, and IL4R genes. In this meta-analysis, an increased risk of gastrointestinal cancer was observed in those carrying the IL4 rs2070874 T variant, whereas a reduced risk of gastrointestinal cancer was observed in those who were heterozygous for IL4R rs1801275.

The role of IL4 rs2243250 in carcinogenesis has been investigated in many studies, but the findings are still inconclusive. In previous meta-analyses, Sun et al.12 reported a possible positive association between gastric cancer and the IL4 rs2243250 T allele in Caucasians, but Li et al.10 and Wu et al.9 reported no association between IL4 rs2243250 and colorectal cancer risk. We also found no association of the IL4 rs2243250 T allele with gastrointestinal cancer. However, a positive association between IL4 rs2070874 T allele carriers and gastrointestinal cancer risk was observed. Cruysius et al.18 studied a Caucasian population from 10 European countries and found a significant positive association for IL4 rs2070874 T variant, whereas a reduced risk of gastrointestinal cancer was observed. Cruysius et al.18 studied a Caucasian population from 10 European countries and found a significant positive association for IL4 rs2070874 T allele carriers. Our findings may support the role of this polymorphism in gastrointestinal carcinogenesis. However, we also found a reduced risk of gastrointestinal cancer in IL4R rs1801275.
heterozygote carriers, which is in contrast to the findings for IL4 rs2070874. This may be a chance finding, but the underlying mechanisms should be investigated further.

Polymorphisms of IL4, IL13, and IL4R are suggested to affect the level of IgE because these polymorphisms are associated with greater expression of these genes and cytokines. A meta-analysis by Wang et al. indicated that variants of IL4 (rs2243250 and rs2070874) and IL13 (rs1800925 and rs20541) were associated with an increased risk of asthma. In in vitro experiments, higher total serum IgE levels were observed in T allele carriers of IL4 rs2243250 and rs2070874 and IL13 rs1800925 and rs20541. Rosenwasser et al. reported that four single nucleotide polymorphisms tested in the IL4/IL13 pathway are suspected of altering the function of specific genes. Several mechanisms have been proposed to explain the role of IgE in carcinogenesis. It is possible that the capacity for Th2 responses to simultaneously promote and suppress natural surveillance may lead to consistent findings. High IgE reflects immune hyperresponsiveness, leading to the detection and eradication of dysregulated cells. However, Th2 cytokines, such as IL4 and IL13, suppress interferon-γ associated inflammatory Th1 and cytolytic responses. Thus, allergies may be positively associated with cancer.

Several other factors may affect the association between the investigated polymorphisms and gastrointestinal cancer risk. In this meta-analysis, the positive association between IL4 rs2070874 T allele carriers and gastrointestinal cancer risk was stronger in studies conducted outside of Asia. The T allele frequency of IL4 rs2243250 and rs2070874 was very different between Asians and non-Asians; differences in the IL4 genetic background among ethnicities may explain the different roles of this gene in the same disease. In addition to this, the positive association with IL4 rs2070874 T allele carriers was only significant in studies investigating the association with gastric cancer, suggesting that the role of this polymorphism in carcinogenesis could differ by cancer type. Of the six included studies that evaluated this polymorphism, only a study by Crusius et al. found a significant positive association for IL4 rs2070874 T allele carriers, particularly among patients with non-cardia intestinal type gastric cancer infected with H. pylori in a Caucasian population. However, other studies showed no association. Even though differences in study design (e.g., sample size and ethnicity) may affect the inconsistent findings between studies, the intrinsic heterogeneity of gastrointestinal carcinogenesis, sub-classified by anatomic location and histologic changes, should also be considered when interpreting the findings. Finally, different environmental and lifestyle factors can interact with gene polymorphisms and strengthen or weaken the effect of the studied polymorphisms. Gene—gene interactions may also contribute to the complexity of genetic diseases. An analysis of genotype data from a large population of German children showed that when polymorphisms of IL4, IL13, IL4R, and STAT6 were combined, the risk of high serum IgE levels increased by 10.8 times, and the risk of the development of asthma increased by 16.8 times compared with the effect of any individual polymorphism.

The present findings should be interpreted with caution because of some limitations of the meta-analysis. First, the quality of a meta-analysis depends on the quality of the original studies. In our case, all studies were retrospective case–control studies, some of which involved small sample sizes and used hospital-based controls. Second, we evaluated only two polymorphisms per gene, which may limit our ability to elucidate the role of related cytokines in gastrointestinal cancer risk. Third, some inevitable publication bias may exist because only published studies were retrieved, although the funnel plot and Egger’s test did not reveal significant publication bias. Finally, the numbers of published studies collected in our analysis were not large enough for comprehensive analysis. Considering all of these factors, future studies should be designed to overcome these limitations.

In conclusion, we investigated the role of six potentially functional variants of the IL4, IL13, and IL4R genes in gastrointestinal cancer risk based on the hypothesis that total serum IgE levels may affect carcinogenesis. The results of this meta-analysis indicated that some of these cytokine polymorphisms may affect susceptibility to gastrointestinal cancer. Therefore, case–control studies with larger sample sizes and multi-ethnic groups are needed to further investigate these associations in detail. Moreover, detailed gene—gene and gene—environment interaction data are needed for a comprehensive understanding of the association between the studied polymorphisms and cancer risk.

**Conflicts of interest**

None declared.

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**Table 1: Forest plot of gastrointestinal cancer risk associated with IL4R 1801275 (AG vs. AA)**

| Author (year) | % | OR (95% CI) | Weight |
|--------------|---|-------------|--------|
| Wu (2003)    |   | 0.96 (0.63, 1.46) | 21.63 |
| Landi (2007) |   | 0.88 (0.61, 1.26) | 29.37 |
| Olson (2007) |   | 0.79 (0.47, 1.34) | 13.99 |
| Zambon (2008) |   | 0.96 (0.58, 1.57) | 15.55 |
| Scala (2009) |   | 0.57 (0.26, 1.23) | 6.43  |
| Lee (2010)   |   | 0.41 (0.24, 0.71) | 13.01 |
| Overall (I-squared = 36.2%, p = 0.165) |   | 0.79 (0.65, 0.96) | 100.00 |

**Fig. 4**: Forest plot of gastrointestinal cancer risk associated with IL4R 1801275 (AG vs. AA). CI, confidence interval; OR, odds ratio.

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**Footnotes**

1. Forest plot of gastrointestinal cancer risk associated with IL4R 1801275 (AG vs. AA). CI, confidence interval; OR, odds ratio.

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**Author information**

None declared.
Acknowledgments

This work was supported by the National Cancer Center, Korea (1410260), and the National Research Foundation of Korea (2015R1C1A2A01053728).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.06.002.

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