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Original Article

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 I^2 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.

Introduction

Previous epidemiologic studies have suggested that allergic disease may be associated with either a reduced or an increased risk of cancer.[1,2] Individuals with allergies have been found to have higher circulating levels of IgE, which is a product of T helper 2 (Th2) responses that are promoted in tissues by cytokines, such as IL4 and IL13. The *IL4* and *IL13* genes are located within the cytokine gene cluster on chromosome 5q31–31.1 They share a common IL4R chain on their receptors and are involved in the same signaling pathways.[3] These cytokines may play a central role in allergies via stimulating IgE synthesis and reducing the production of pro-inflammatory cytokines by macrophages.[2,4] Therefore, polymorphisms of the *IL4*, *IL13*, and *IL4R* genes may disrupt the balance of the cytokine network and may be involved in allergies and various cancers.[5–7]

Gastrointestinal cancer is the leading cause of cancer-related death worldwide.[8] Recently, several studies were conducted investigating the influence of these allergy-related polymorphisms on gastrointestinal cancer in different populations.[9,10] Because the effect of genetic polymorphisms on cancer risk is small, a single study may be underpowered to detect a true association. Meta-analysis takes advantage of reduced random error in the observed effect estimates and produces a single estimate with enhanced precision.[11] Some previous meta-analyses were conducted to investigate the association of *IL4* rs2243250 with either gastric cancer[12] or colorectal cancer.[9,10] However, the findings of these meta-analyses were inconclusive, and other polymorphisms of the IL4/IL13 pathway may help to clarify the role of polymorphisms in these genes in gastrointestinal carcinogenesis. Therefore, to gain more comprehensive knowledge of the associations of polymorphisms of the *IL4*, *IL13*, and

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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 selected polymorphisms is listed in Table 1. We used the following search terms: 1) "interleukin-4 (*IL-4* or *IL4*), interleukin-13 (*IL-13* or *IL13*), and interleukin-4R (*IL-4R* or *IL4R*)"; 2) "SNP, polymorphism, mutation, and variant"; 3) "cancer, tumor, carcinoma, and neoplasm"; and 4) "esophagus, gastric, colorectal, colon, rectal, hepatocellular, gallbladder, pancreatic, and gastrointestinal." To identify additional studies, we also screened the references of retrieved publications. Searches were limited to human studies and publications written in English. We did not consider abstracts or unpublished reports.

Studies included in this meta-analysis were required to meet the following criteria: 1) investigated the associations of *IL4*, *IL13*, and *IL4R* polymorphisms with gastrointestinal cancer risk; 2) used a case–control design; 3) provided genotype frequencies for cases and controls, so that odds ratios (ORs) with 95% confidence intervals (CIs) and a Hardy–Weinberg Equilibrium (HWE) could be calculated; and 4) featured a control population genotype distribution that did not deviate from HWE. Studies containing duplicated data were excluded. One study by El-Omar et al.[13] presented genotype frequencies separately according to cancer type and was thus considered two studies in this meta-analysis.

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 corresponding 95% CIs. Forest plots were used to illustrate the results of the included studies. Five different ORs were calculated using the following models: 1) homozygote comparison, 2) heterozygote comparison, 3) dominant genetic model, 4) recessive genetic model, and 5) allele comparison. This meta-analysis reported 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 I^2 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; 2202 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 listed 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,[13,14] gastric,[13,15–23] colorectal,[24–32] hepatocellular,[33,34] and pancreatic cancer.[35–37]

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[a]	
							Asian	Non-Asian
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	0.19

Ch, chromosome; IL4, interleukin-4; IL13, interleukin-13; IL4R, interleukin-4 receptor; MAF, minor allele frequency.
[a] Frequency of variant allele in controls in studies included in this meta-analysis.

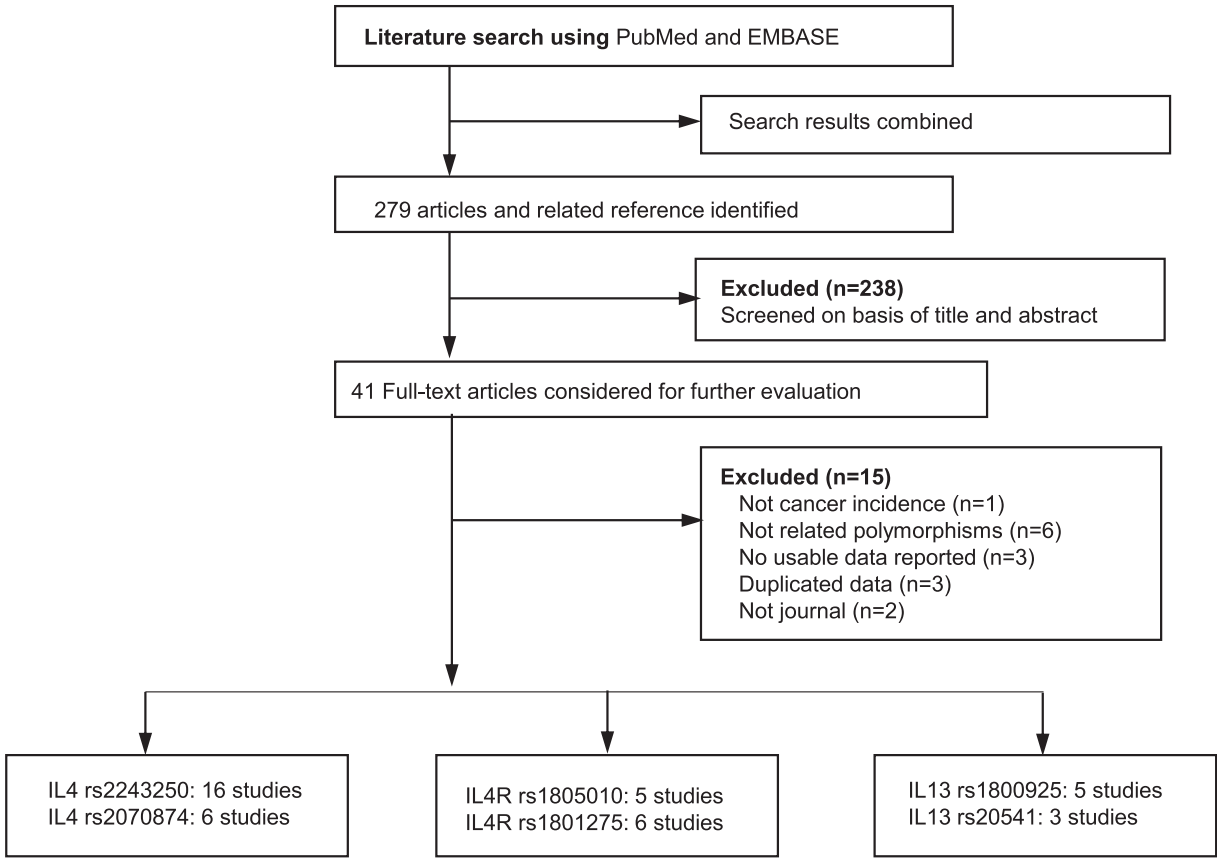

Fig. 1. Flowchart depicting the literature search and selection.

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)[13]	USA	Gastric	112/209	P	rs2243250
El-Omar (2003)[13]	USA	Esophageal	90/209	P	rs2243250
Wu (2003)[15]	Taiwan	Gastric	220/230	H	rs2243250, rs1805010, rs1801275
Lai (2005)[16]	China	Gastric	123/162	P	rs2243250
Cozar (2007)[24]	Spain	Colorectal	96/174	H	rs2243250
Garcia-Gonzalez (2007)[17]	Spain	Gastric	404/404	P	rs2243250
Landi (2007)[25]	Spain	Colorectal	281/269	H	rs2243250, rs2070874, rs1805010, rs1801275
Olson (2007)[36]	USA	Pancreatic	405/212	H	rs2243250, rs1801275
Yannopoulos (2007)[26]	Greece	Colorectal	95/108	P	rs2243250
Crusius (2008)[18]	10 European countries	Gastric	244/1160	P	rs2243250, rs2070874, rs1805010
Suchy (2008)[27]	Poland	Colorectal	350/350	H	rs2243250
Wilkening (2008)[28]	Sweden	Colorectal	304/582	P	rs2243250
Zambon (2008)[19]	Italy	Gastric	142/171	H	rs2243250, rs1805010, rs1801275
Ando (2009)[20]	Japan	Gastric	330/190	H	rs2243250, rs1805010
Ko (2009)[21]	Korea	Gastric	81/324	P	rs2243250, rs2070874
Scola (2009)[35]	Italy	Pancreatic	48/131	H	rs1801275, rs1800925
Wu (2009)[44]	China	Gastric	1042/1099	P	rs2070874
Lee (2010)[29]	Korea	Colorectal	170/130	P	rs1801275
Sainz (2012)[30]	Sweden	Colorectal	1789/1771	P	rs20541
Walczak (2012)[31]	Poland	Colorectal	191/205	P	rs1800925
Sun (2013)[14]	China	Esophageal	365/369	H	rs1800925
Lu (2014)[33]	China	Hepatocellular	154/170	P	rs2243250, rs2070874
Pan (2014)[22]	China	Gastric	308/308	P	rs2243250
Yu (2014)[32]	China	Colorectal	299/296	P	rs2070874
Cotterchio (2015)[37]	Canada	Pancreatic	172/566	P	rs20541
Deng (2015)[34]	China	Hepatocellular	192/192	P	rs1800925, rs20541
Yin (2015)[23]	China	Gastric	234/465	H	rs1800925

H, hospital; P, population.

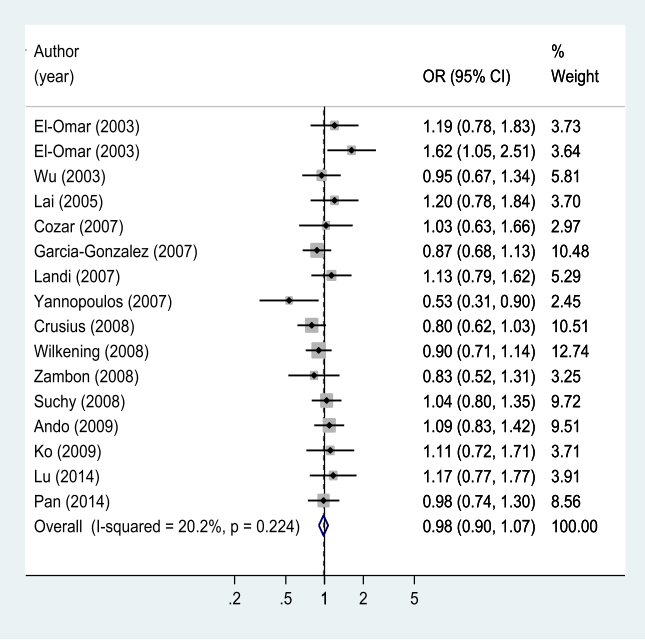

Fig. 2. Forest plot of gastrointestinal cancer risk associated with *IL4* rs2243250 (T allele vs. C allele). CI, confidence interval; OR, odds ratio.

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. Crusius 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

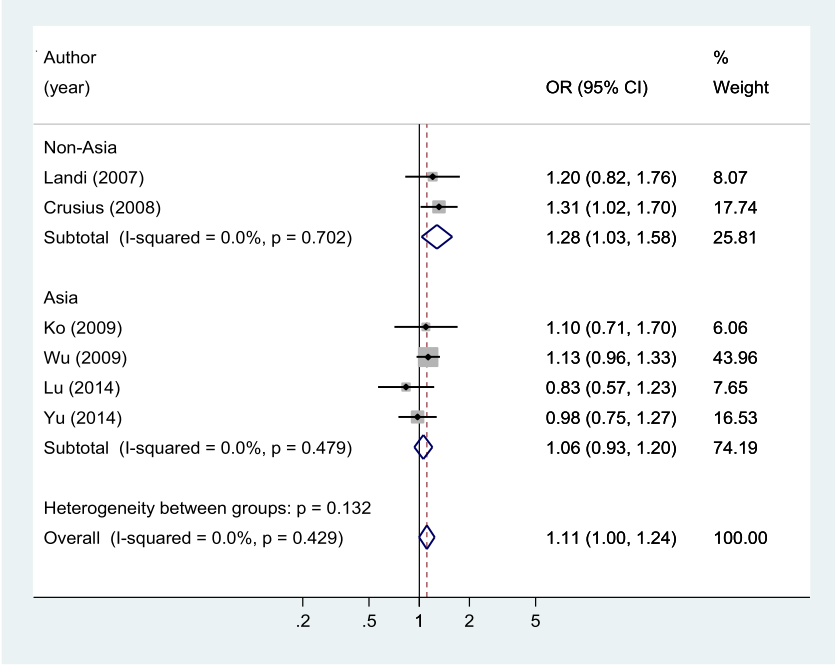

Fig. 3. Forest plot of gastrointestinal cancer risk associated with *IL4* rs2070874 (T allele vs. C allele), stratified by geographic location. CI, confidence interval; OR, odds ratio.

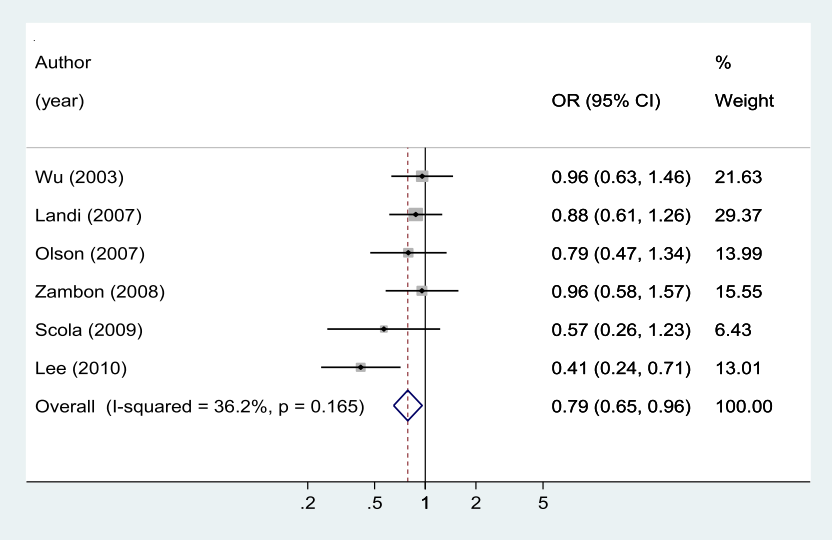

Fig. 4. Forest plot of gastrointestinal cancer risk associated with *IL4R* 1801275 (AG vs. AA). CI, confidence interval; OR, odds ratio.

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.[5,38,39] A meta-analysis by Wang et al.[40] 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.[41] Rosenwasser et al.[39] 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 inconsistent findings.[42] High IgE reflects immune hyper-responsiveness, leading to the detection and eradication of dysregulated cells.[2] 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.[42]

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.[33] 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.[18] 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.[43] Finally, different environmental and lifestyle factors can interact with gene polymorphisms and strengthen or weaken the effect of the studied polymorphisms.[40] Gene–gene interactions may also contribute to the complexity of genetic diseases.[5] 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.[41]

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.

Acknowledgments

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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.

References

1. Josephs DH, Spicer JF, Corrigan CJ, Gould HJ, Karagiannis SN. Epidemiological associations of allergy, IgE and cancer. *Clin Exp Allergy*. 2009;43:1110–1123.
2. Jensen-Jarolim E, Achatz G, Turner MC, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. *Allergy*. 2008;63:1255–1266.
3. Yang XX, Li FX, Wu YS, Wu D, Tan JY, Li M. Association of TGF-beta1, IL-4 and IL-13 gene polymerphisms with asthma in a Chinese population. *Asian Pac J Allergy Immunol*. 2011;29:273–277.
4. de Vries JE. The role of IL-13 and its receptor in allergy and inflammatory responses. *J Allergy Clin Immunol*. 1998;102:165–169.
5. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol*. 2008;8:169–182.
6. Rosenwasser LJ, Klemm DJ, Dresback JK, et al. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. *Clin Exp Allergy*. 1995;25(Suppl 2):74–78. discussion 95–96.
7. Heinzmann A, Mao XQ, Akaiwa M, et al. Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet*. 2000;9:549–559.
8. Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2013;2013(63):11–30.
9. Wu H, Hu J, Liu B, Tao Y, Zhou X, Yuan X. Lack of association between interleukin-4 -524C>T polymorphism and colorectal cancer susceptibility. *Tumour Biol*. 2014;35:3657–3662.
10. Li Q, Wang Q, Xu X, Ren S, Wang L. Association between IL-4 -589C>T polymorphism and colorectal cancer risk. *Tumour Biol*. 2014;35:2675–2679.
11. Kavvoura FK, Ioannidis JP. Methods for meta-analysis in genetic association studies: a review of their potential and pitfalls. *Hum Genet*. 2008;123:1–14.
12. Sun Z, Cui Y, Jin X, Pei J. Association between IL-4 -590C>T polymorphism and gastric cancer risk. *Tumour Biol*. 2014;35:1517–1521.
13. El-Omar EM, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology*. 2003;124:1193–1201.
14. Sun JM, Li Q, Gu HY, Chen YJ, Wei JS, Zhu Q. Interleukin 10 rs1800872 T>G polymorphism was associated with an increased risk of esophageal cancer in a Chinese population. *Asian Pac J Cancer Prev*. 2013;14:3443–3447.
15. Wu MS, Wu CY, Chen CJ, Lin MT, Shun CT, Lin JT. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. *Int J Cancer*. 2003;104:617–623.
16. Lai KC, Chen WC, Jeng LB, Li SY, Chou MC, Tsai FJ. Association of genetic polymorphisms of MK, IL-4, p16, p21, p53 genes and human gastric cancer in Taiwan. *Eur J Surg Oncol*. 2005;31:1135–1140.
17. Garcia-Gonzalez MA, Lanas A, Quintero E, et al. Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain. *Am J Gastroenterol*. 2007;102:1878–1892.
18. Crusius JB, Canzian F, Capella G, et al. Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). *Ann Oncol*. 2008;19:1894–1902.
19. Zambon CF, Basso D, Marchet A, et al. IL-4 -588C>T polymorphism and IL-4 receptor alpha [Ex5+14A>G; Ex11+828A>G] haplotype concur in selecting H. pylori cagA subtype infections. *Clin Chim Acta*. 2008;389:139–145.
20. Ando T, Ishikawa T, Kato H, et al. Synergistic effect of HLA class II loci and cytokine gene polymorphisms on the risk of gastric cancer in Japanese patients with Helicobacter pylori infection. *Int J Cancer*. 2009;125:2595–2602.
21. Ko KP, Park SK, Cho LY, et al. Soybean product intake modifies the association between interleukin-10 genetic polymorphisms and gastric cancer risk. *J Nutr*. 2009;139:1008–1012.
22. Pan XF, Wen Y, Loh M, et al. Interleukin-4 and -8 gene polymorphisms and risk of gastric cancer in a population in Southwestern China. *Asian Pac J Cancer Prev*. 2014;15:2951–2957.
23. Yin J, Wang X, Wei J, et al. Interleukin 12B rs3212227 T>G polymorphism was associated with an increased risk of gastric cardiac adenocarcinoma in a Chinese population. *Dis Esophagus*. 2015;28:291–298.
24. Cozar JM, Romero JM, Aptsiauri N, et al. High incidence of CTLA-4 AA (CT60) polymorphism in renal cell cancer. *Hum Immunol*. 2007;68:698–704.
25. Landi S, Bottari F, Gemignani F, et al. Interleukin-4 and interleukin-4 receptor polymorphisms and colorectal cancer risk. *Eur J Cancer*. 2007;43:762–768.
26. Yannopoulos A, Nikiteas N, Chatzitheofylaktou A, Tsigris C. The (-590 C/T) polymorphism in the interleukin-4 gene is associated with increased risk for early stages of corolectal adenocarcinoma. *Vivo*. 2007;21:1031–1036.
27. Suchy J, Klujszo-Grabowska E, Kladny J, et al. Inflammatory response gene polymorphisms and their relationship with colorectal cancer risk. *BMC Cancer*. 2008;8:112.
28. Wilkening S, Tavelin B, Canzian F, et al. Interleukin promoter polymorphisms and prognosis in colorectal cancer. *Carcinogenesis*. 2008;29:1202–1206.
29. Lee YS, Choi HB, Lee IK, Kim TG, Oh ST. Association between interleukin-4R and TGF-beta1 gene polymorphisms and the risk of colorectal cancer in a Korean population. *Colorectal Dis*. 2010;12:1208–1212.
30. Sainz J, Rudolph A, Hoffmeister M, et al. Effect of type 2 diabetes predisposing genetic variants on colorectal cancer risk. *J Clin Endocrinol Metab*. 2012;97:E845–E851.
31. Walczak A, Przybylowska K, Dziki L, et al. The lL-8 and IL-13 gene polymorphisms in inflammatory bowel disease and colorectal cancer. *DNA Cell Biol*. 2012;31:1431–1438.
32. Yu Y, Zheng S, Zhang S, et al. Polymorphisms of inflammation-related genes and colorectal cancer risk: a population-based case-control study in China. *Int J Immunogenet*. 2014;41:289–297.
33. Lu Y, Wu Z, Peng Q, et al. Role of IL-4gene polymorphisms in HBV-related hepatocellular carcinoma in a Chinese population. *PLoS One*. 2014;9:e110061.
34. Deng Y, Xie M, Xie L, et al. Association between polymorphism of the interleukin-13 gene and susceptibility to hepatocellular carcinoma in the Chinese population. *PLoS One*. 2015;10:e0116682.
35. Scola L, Giacalone A, Marasa L, et al. Genetic determined downregulation of both type 1 and type 2 cytokine pathways might be protective against pancreatic cancer. *Ann N Y Acad Sci*. 2009;1155:284–288.
36. Olson SH, Orlow I, Simon J, et al. Allergies, variants in IL-4 and IL-4R alpha genes, and risk of pancreatic cancer. *Cancer Detect Prev*. 2007;31:345–351.
37. Cotterchio M, Lowcock E, Bider-Canfield Z, et al. Association between variants in atopy-related immunologic candidate genes and pancreatic cancer risk. *PLoS One*. 2015;10:e0125273.
38. Mitsuyasu H, Izuhara K, Mao XQ, et al. Ile50Val variant of IL4R alpha upregulates IgE synthesis and associates with atopic asthma. *Nat Genet*. 1998;19:119–120.
39. Rosenwasser LJ, Borish L. Promoter polymorphisms predisposing to the development of asthma and atopy. *Clin Exp Allergy*. 1998;28:13–15.
40. Wang ZD, Lian D, Shen JL, et al. Association between the interleukin-4, interleukin-13 polymorphisms and asthma: a meta-analysis. *Mol Biol Rep*. 2013;40:1365–1376.
41. Kabesch M, Schedel M, Carr D, et al. IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol*. 2006;117:269–274.
42. Van Hemelrijck M, Garmo H, Binda E, et al. Immunoglobulin E and cancer: a meta-analysis and a large Swedish cohort study. *Cancer Causes Control*. 2010;21:1657–1667.
43. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process–first American cancer society Award lecture on cancer epidemiology and prevention. *Cancer Res*. 1992;52:6735–6740.
44. Wu J, Lu Y, Ding YB, et al. Promoter polymorphisms of IL2, IL4, and risk of gastric cancer in a high-risk Chinese population. *Mol Carcinog*. 2009;48:626–632.