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Genetic susceptibility and gastric cancer risk: The importance of meta-analyses as a statistical tool

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Abstract   Gastric cancer (GC) is a complex disease and a worldwide health burden due to its high prevalence and poor prognosis. A deeper knowledge of the factors involved in the development and progression of GC could help to identify subpopulations at risk that therefore require surveillance or early treatment strategies. Current research is based on the study of genetic variants that confer a higher risk of GC and their interactions with environmental exposure. Recently, meta-analysis has emerged as an important statistical method involving pooling of data from individual association studies to increase statistical power and obtain more conclusive results. Given the importance of chronic inflammation in the process of gastric carcinogenesis, the present article reviews the most recent meta-analyses of the contribution of cytokine gene polymorphisms to GC risk.

Susceptibilidad genética y riesgo de cáncer gástrico. Importancia del meta-análisis como herramienta estadística

Resumen   El cáncer de estómago es una patología compleja que representa un grave problema sanitario a nivel mundial tanto por su incidencia como por el pobre pronóstico de los pacientes que lo padecen. Un mejor conocimiento de los factores implicados en el desarrollo y evolución del cáncer gástrico (CG) nos ayudará a identificar qué sub-poblaciones de individuos tienen un mayor riesgo de desarrollar CG y precisan, por tanto, un seguimiento más detallado o una actuación terapéutica precoz. En la actualidad, la investigación sobre epidemiología genética de enfermedades complejas está orientada a la identificación de variantes genéticas que aumenten la susceptibilidad y al estudio de su relación con factores ambientales. En los últimos años, el meta-análisis ha surgido como una importante herramienta estadística que permite englobar los datos obtenidos en los estudios de asociación, aumentando el poder estadístico de dichos

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estudios y obteniendo resultados más concluyentes. Dada la importancia de la inflamación crónica en el proceso de carcinogénesis gástrica, revisaremos en nuestro artículo los meta-análisis realizados en los últimos años sobre polimorfismos en genes que codifican la síntesis de citocinas y su implicación en el desarrollo del CG.

Introduction

Gastric cancer (GC) represents the fourth most common cancer and the second most frequent cause of cancer deaths worldwide.[1] Despite advances in diagnosis and treatment, most patients with GC present with late-stage disease and an overall 5-year survival of approximately 20–30% in Western countries.[2,3] GC is well known to be a heterogeneous disease which shows distinct clinical, epidemiological, and molecular features among tumours arising from the cardia or non-cardia within the stomach, and among intestinal and diffuse histological subtypes.[4,5] These phenotypic differences are determined by the combined effects of multiple environmental, namely smoking habit and diet,[6,7] and genetic risk factors. Among them, *Helicobacter pylori* (*H. pylori*) infection has been identified as the single most common cause of GC.[8] This organism, which colonizes over half of the world's population, first induces a chronic superficial gastritis in most infected people, initiating a process that in certain individuals may lead to GC. However, it is still a matter of speculation as to why only a minority (<1%) of the population infected with *H. pylori* develops gastric malignancy, suggesting that factors other than bacterial infection alone participate in the carcinogenesis process.

Gastric cancer and genetic susceptibility

Additional host genetic risk factors are also likely to contribute in gastric carcinogenesis. In this context, gene polymorphisms have been thought to be attractive biomarkers of GC risk since they may modify the effect of environmental exposures. In fact, individual genetic susceptibility may be critical in several processes relevant to gastric carcinogenesis such as mucosal protection, immune response to *H. pylori* infection, carcinogen detoxification and antioxidant protection, repair of DNA damage, and cell proliferation ability.[9]

In the year 2000, El-Omar and co-workers first reported the association of specific gene variants with an increased risk of GC.[10] According to the authors, the interleukin-1 beta *IL1B*-31T (rs1143627) and IL-1 receptor antagonist *IL1RN**2/*2 genotypes were associated with an increased risk of both, chronic hypochlorhydria and GC, presumably by altering IL-1β levels in the stomach. Since this first landmark report, numerous studies concerning the association of candidate gene polymorphisms and GC risk have been conducted. However, results are inconsistent among studies.[11–16] The reasons for these discrepancies are unclear and differences in ethnicities, methodologies, and dominance of different etiologic factors in different populations have been suggested as possible explanations. Nevertheless, most of the studies reported in the literature are small sized and underpowered to detect a robust association. In order to solve this problem, meta-analysis became an important statistical method involving pooling of data from individual association studies to increase sample size, improve statistical power and draw more reliable conclusions.[17]

The number of meta-analyses assessing genetic markers of GC risk has dramatically increased in recent years. Given the relevance of *H. pylori* infection in chronic inflammation and gastric carcinogenesis, one of the more extensively explored pathways has been that related to the inflammatory response to *H. pylori* infection (Table 1). The innate immune response constitutes the first line of defence against infection by microbes such as *H. pylori*. This system senses, recognizes, and responds to bacterial components (lipopolysaccharide, peptidoglycan, lipoproteins, flagellin and bacterial DNA) by activating a complex signalling cascade of pattern-recognition receptors (PRRs) located on the surface and cytosol of gastrointestinal epithelial cells, which include CARD15/NOD2, CARD4/NOD1, CD14 and TLRs receptors[18] (Fig. 1). Several variants in genes of this arm of the immune system have been shown to affect responsiveness to *H. pylori* infection, leading to an aberrant activation of the NF-kB pathway and up-regulation of pro-inflammatory molecules. Hold et al. reported the association of the *TLR4*+896A>G (rs4986790) polymorphism, which results in amino acid substitution (Asp299Gly) affecting TLR4 extracellular domain, with increased risk of noncardia GC and its precursors in *H. pylori* infected patients.[19] This finding has been corroborated by two recent meta-analyses in which the *TLR4*+896 (rs4986790) G allele was significantly associated with distal GC risk mainly in Western populations.[20,21] However, no association between other *TLR4* (rs4986791, rs11536889), TLR2 (−196 to −174del), and *CD14* (rs2569190) gene polymorphisms extensively studied in several populations were found.

Genes encoding pro- and anti-inflammatory mediators, such as *IL1B*, *TNF*, *LTA*, *IL6*, *IL1RN*, *IL10* and *TGFB*, are also of special interest since they are thought to play a key role in GC development and progression[22] (Fig. 2). A large number of epidemiological studies have investigated the impact on GC susceptibility of 3 functionally important base transitions at positions −31T>C (rs1143627), −511C>T (rs16944), and +3954C>T (rs1143634) in the *IL1B* gene, and a variable number of an 86-bp tandem repeat polymorphism (VNTR) in intron 2 of the *IL1RN* gene. Recently, two meta-analyses performed by Zhang et al.[23] and Xu et al.[24] report the association of *IL1RN2* and *ILIB* −511T alleles with an increased risk of distal GC with less conclusive results for the *IL1B*+3954 variant. Interestingly, the *IL1RN2* allele has been associated with high circulating IL-1β levels.[25] The relevance of this finding derives from the biological properties of IL-1β as a potent pro-inflammatory cytokine and a powerful inhibitor of acid secretion. As suggested by El-Omar et al.[10] those

Table 1 Innate and adaptive immunity-related gene polymorphisms (SNPs) associated with gastric cancer risk.

Gene	Chromosome	refSNP ID: rs	Chromosome position[a]	Base change	Aa change	MAF (%)
Innate immunity-related gene polymorphisms						
TLR4	9q32-q33	rs4986790	120475302	A>G	Asp299Gly	G (3)
		rs4986791	120475602	C>T	Thre399Ile	T (5)
		rs11536889	120478131	G>C		C (14.3)
CD14	5q31.1	rs2569190	140012916	G>A		A (42)
Adaptive immunity-related gene polymorphisms						
IL1B	2q14	rs16944	113594867	C>T		T (32.8)
		rs1143627	113594387	T>C		C (32.8)
		rs1143634	113590390	C>T	Phe105Phe	T (20)
TNFA	6p21.3	rs1800629	31543031	G>A		A (13.3)
		rs361525	31543101	G>A		A (6.4)
LTA	6p21.3	rs909253	31540313	A>G		G (26)
		rs746868	31540429	C>G		G (41.2)
IL6	7p21	rs1800797	22766221	G>A		A (35)
		rs1800796	22766246	G>C		C (5)
		rs1800795	22766645	G>C		C (25)
IL10	1q31-q32	rs1800896	206946897	A>G		G (43.8)
		rs1800871	206946634	C>T		T (23)
		rs1800872	206946407	A>C		A (23)
TGFB1	19q13.2	rs1800469	41860296	C>T		T (30)
		rs1800470	41858921	C>T	Pro10Leu	C (44)
		rs1800471	41858876	G>C	Arg25Pro	C (6.4)

MAF: Minor Allele Frequency. Data concerning Caucasian population.
[a] Nomenclature according to the Cancer Genome Anatomy Project SNP500Cancer Database.

genotypes that enhanced IL-1β production may favour the initiation of a set of events leading to chronic hypochlorhydria, corpus atrophy and increased risk of GC.

Similar to IL-1β, tumour necrosis factor-α (TNF-α) and lymphotoxin-α (LT-α, formerly known as TNF-β) are extremely pleiotropic cytokines which play a key role in controlling the inflammatory response in the gastrointestinal mucosa. Although not as potent as IL-1β, TNF-α is also capable of inhibiting gastric acid secretion.[26] Among many polymorphisms identified in the *TNFA* and *LTA* genes, two
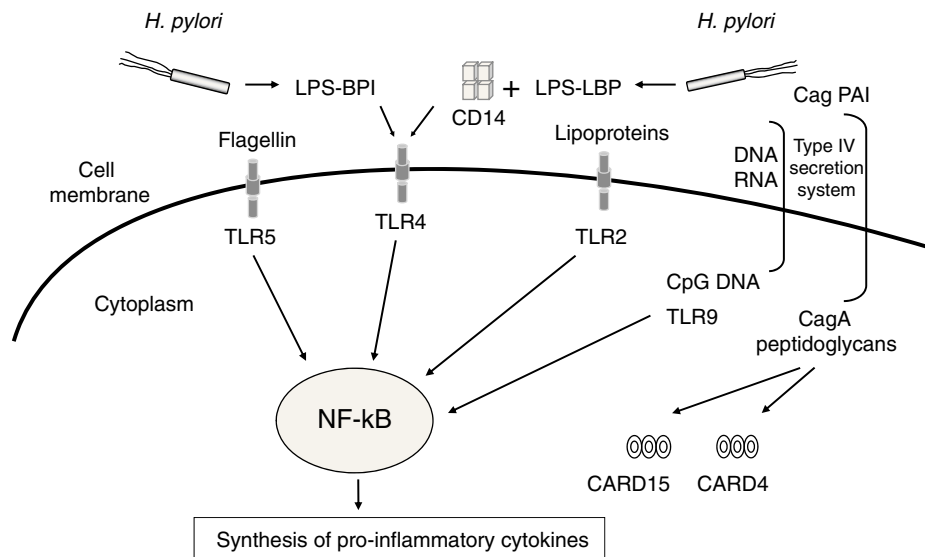

Figure 1 Schematic representation of PRRs (pattern-recognition receptors) and their activating ligands involved in the signalling of the innate immune response against *Helicobacter pylori* infection. This system recognizes and responds to bacterial components (lipopolysaccharide, peptidoglycan, lipoproteins, flagellin and bacterial DNA) by activating a complex signalling cascade of PRRs located on the surface and cytosol of gastrointestinal epithelial cells (TLRs receptors, CD14, CARD15/NOD2, CARD4/NOD1), leading to the activation of the NF-kB pathway and up-regulation of pro-inflammatory molecules.
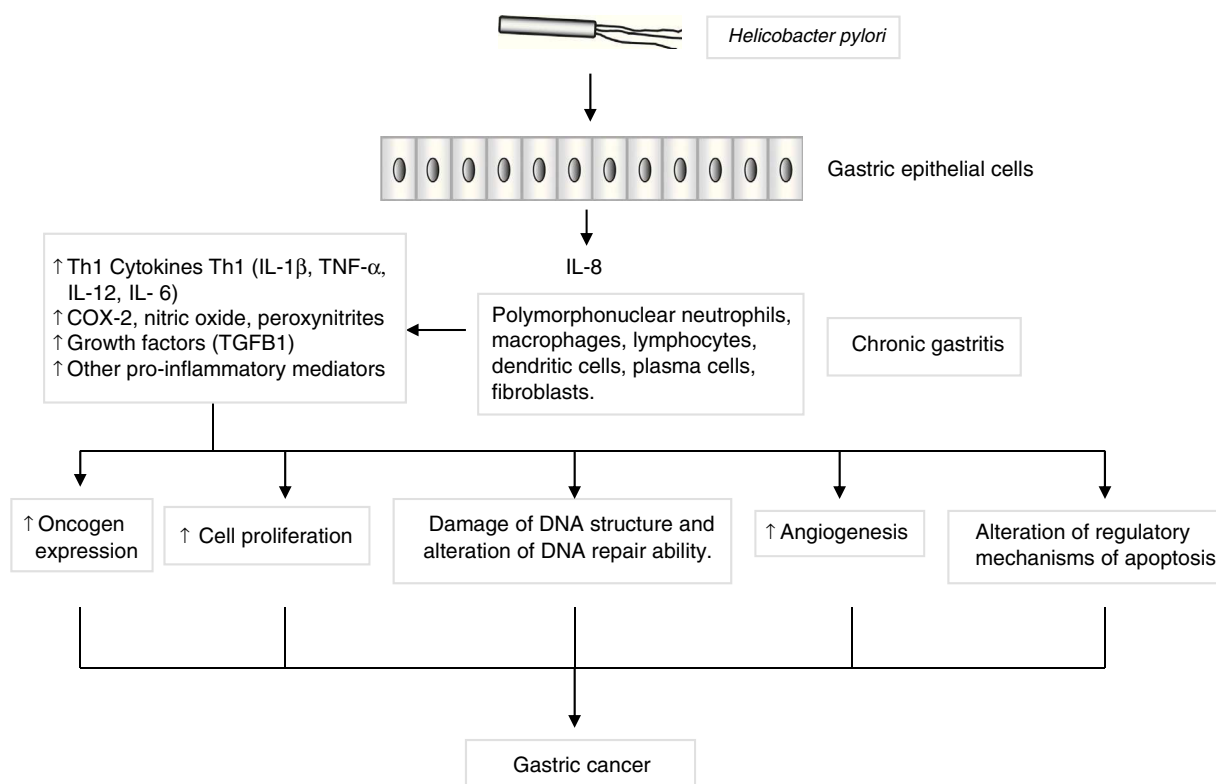
Figure 2 *Helicobacter pylori* induces a chronic superficial gastritis characterized by an infiltration of polymorphonuclear neutrophils, lymphocytes, macrophages and plasma cells. The main biological mediators in this inflammatory response are cytokines (IL-1, IL-6, IL-12, TNF-α, IFN-γ), low-molecular-weight peptide molecules produced by a large variety of cells that possess a broad range of physiological functions. However, persistent inflammation with the subsequent release of pro-inflammatory mediators may induce changes in the epithelium, initiating a process that in certain individuals may lead to the development of gastric cancer.

G>A nucleotide substitutions at positions −308 (rs1800629) and −238 (rs361525) in the promoter region of the *TNFA* gene and two restriction fragment length polymorphisms (RFLP) (*Nco*I +252 G>A rs909253, and *Asp*HI +318 G>C rs746868) in the first intron of the *LTA* gene, affecting TNF-α and LT-α production, have been extensively studied in relation to GC. To date, two published meta-analyses[27,28] on this issue have suggested that the *TNFA* −308 A allele is associated with GC in Caucasians, but not in Asian populations. However, a recent large two-stage case-control study performed by Hong et al.[29] reported the association of the *TNFA* −308 A variant with GC risk and progression in a Chinese population. Moreover, another meta-analysis by Lu et al.[30] showed the association of the *LTA* rs909253 G>A polymorphism with a higher risk of GC in *H. pylori* infected patients, specific for the Asian population. However, no association between GC risk and either the *TNFA* -238 or the *LTA* rs746868 polymorphism was found.

IL-6 is also a multifunctional cytokine that plays a major role in the inflammatory response. Production of IL-6 by GC cell lines[31] and high levels of IL-6 in serum and tumour tissue in GC patients have been reported.[32] Three single nucleotide polymorphisms (SNPs) at positions −174G>C (rs1800795), −572G>C (rs1800796) and −597G>A (rs1800797) in the promoter region of the *IL6* gene, influencing IL-6 gene transcription and serum levels,[33] have been investigated for GC association in several studies. El-Omar et al.[11] first evaluated the association of the *IL6*-174G>C polymorphism and GC risk in Caucasians and no association was found. Similar results have been reported in two recent meta-analyses by Wang et al.[34] and Yin et al.[35] in which no associations between *IL6*-174, -572, and -597 variants and GC risk were observed. However, and as point out by the authors, these results should be interpreted with caution due to the limited number of subjects included in the analyses and the selection bias detected in some studies.

On the other side of the balance, the anti-inflammatory cytokine IL-10 and the transforming growth factor β1 (TGF-β1) are potent suppressors of the Th1-type immune response resulting in down-regulation of the production of pro-inflammatory mediators by macrophages and other immune cells.[36,37] Three SNPs in the *IL10* promoter at positions −1082G>A (rs1800896), −819C>T (rs1800871), and −592C>A (rs1800872) have been found to be biologically relevant.[38] Correlated with variations in IL-10 levels, these functional polymorphisms were suspected to influence GC susceptibility by altered inflammatory responses at the gastrointestinal mucosa. However, data reported in the literature showed very inconsistent results. Four meta-analyses exploring the role of *IL10*-1082,[39,40] -819[41] and -592[42] gene polymorphisms in GC risk have been published during the year 2012. In summary, the results suggest that *IL10*-819 TT and *IL10*-592 AA genotypes may be protective factors for GC in Asians,[41,42] while the IL10-1082 A allele was found to be a protective allele for GC risk in the overall population.[39,40] Concerning *TGFB1*, several polymorphisms have been reported to affect

TGF-β1 expression and plasma levels.[43,44] Among them, a SNP at position -509C>T (rs1800469) in the promoter region and two SNPs at positions +869T>C (rs1982073) and +915G>C (rs1800471) in the signal protein sequence of the gene, which change codon 10 (Leu/Pro) and codon 25 (Arg/Pro), respectively, have been extensively studied in relation to *H. pylori* infection-related diseases, including GC. However, three recent meta-analyses[45–47] found no significant association between the *TGFB1* +869T>C and +915G>C polymorphisms and risk of GC with less conclusive results for the *TGFB1* −509C>T variant.

In summary, current research is based on the study of genetic variants that confer a higher risk of GC and their interactions with environmental exposure, namely *H. pylori* infection. In spite of some limitations (only published studies are included, heterogeneity between studies, source of controls, representativeness of cases or quality of studies), meta-analysis is emerging as a promised statistical tool to evaluate the contribution of host genetic factors in GC risk. Our review points out the relevance of well-designed meta-analyses assessing the role of candidate cytokine gene polymorphisms in GC susceptibility, and suggests the association between specific variants of the *IL1RN* VNTR, *IL1B*-511 (rs16944), *TNFA*-308 (rs1800629), and *IL10* -1082 (rs1800896) gene polymorphisms and GC risk. A deeper knowledge of factors involved in CG development and progression may allow identification of those individuals at risk and may provide useful predictive information for subgroups of patients who need surveillance or early treatment strategies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

References

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46:765–81.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
3. Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer. 2004;90:1727–32.
4. Kim MA, Lee HS, Yang HK, Kim WH. Clinicopathologic and protein expression differences between cardia carcinoma and noncardia carcinoma of the stomach. Cancer. 2005;103:1439–46.
5. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
6. Gonzalez CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Int J Cancer. 2003;107:629–34.
7. Gonzalez CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, et al. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Int J Cancer. 2006;118:2559–66.
8. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.
9. Gonzalez CA, Sala N, Capella G. Genetic susceptibility gastric cancer risk. Int J Cancer. 2002;100:249–60.
10. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000;404:398–402.
11. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology. 2003;124:1193–201.
12. Garza-Gonzalez E, Bosques-Padilla FJ, El-Omar E, Hold G, Tijerina-Menchaca R, Maldonado-Garza HJ, et al. Role of the polymorphic IL-1B, IL-1RN and TNF-A genes in distal gastric cancer in Mexico. Int J Cancer. 2005;114:237–41.
13. Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, et al. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. Gastroenterology. 2001;121:823–9.
14. Gatti LL, Burbano RR, de Assumpcao PP, Smith Mde A, Payao SL. Interleukin-1beta polymorphisms. Helicobacter pylori infection in individuals from Northern Brazil with gastric adenocarcinoma. Clin Exp Med. 2004;4:93–8.
15. Kamangar F, Abnet CC, Hutchinson AA, Newschaffer CJ, Helzlsouer K, Shugart YY, et al. Polymorphisms in Inflammation-related Genes and Risk of Gastric Cancer (Finland). Cancer Causes Control. 2006;17:117–25.
16. Garcia-Gonzalez MA, Lanas A, Quintero E, Nicolas D, Parra-Blanco A, Strunk M, 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;102:1878–92.
17. Taioli E, Bonassi S. Methodological issues in pooled analysis of biomarker studies. Mutat Res. 2002;512:85–92.
18. Hold GL, Mukhopadhya I, Monie TP. Innate immune sensors and gastrointestinal bacterial infections. Clin Dev Immunol. 2011;2011, http://dx.doi.org/10.1155/2011/579650.
19. Hold GL, Rabkin CS, Chow WH, Smith MG, Gammon MD, Risch HA, et al. A functional polymorphism of toll-like receptor 4 gene increases risk of gastric carcinoma and its precursors. Gastroenterology. 2007;132:905–12.
20. Castano-Rodriguez N, Kaakoush NO, Goh KL, Fock KM, Mitchell HM. The role of TLR2, TLR4 and CD14 genetic polymorphisms in gastric carcinogenesis: a case-control study and meta-analysis. PLoS One. 2013;8:e60327.
21. Zhang K, Zhou B, Wang Y, Rao L, Zhang L. The TLR4 gene polymorphisms and susceptibility to cancer: a systematic review and meta-analysis. Eur J Cancer. 2013;49:946–54.
22. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–7.
23. Zhang Y, Liu C, Peng H, Zhang J, Feng Q. IL1 receptor antagonist gene IL1-RN variable number of tandem repeats polymorphism and cancer risk: a literature review and meta-analysis. PLoS One. 2012;7:e46017.
24. Xu J, Yin Z, Cao S, Gao W, Liu L, Yin Y, et al. Systematic review and meta-analysis on the association between IL-1B polymorphisms and cancer risk. PLoS One. 2013;8:e63654.
25. Santtila S, Savinainen K, Hurme M. Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. Scand J Immunol. 1998;47:195–8.

26. Beales IL, Calam J. Interleukin 1 beta and tumour necrosis factor alpha inhibit acid secretion in cultured rabbit parietal cells by multiple pathways. Gut. 1998;42:227–34.

27. Gorouhi F, Islami F, Bahrami H, Kamangar F. Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer. 2008;98:1443–51.

28. Zhang J, Dou C, Song Y, Ji C, Gu S, Xie Y, et al. Polymorphisms of tumor necrosis factor-alpha are associated with increased susceptibility to gastric cancer: a meta-analysis. J Hum Genet. 2008;53:479–89.

29. Hong Y, Ge Z, Jing C, Shi J, Dong X, Zhou F, et al. Functional promoter −308G>A variant in tumor necrosis factor alpha gene is associated with risk and progression of gastric cancer in a Chinese population. PLoS One. 2013;8:e50856.

30. Lu R, Dou X, Gao X, Zhang J, Ni J, Guo L. A functional polymorphism of lymphotoxin-alpha (LTA) gene rs909253 is associated with gastric cancer risk in an Asian population. Cancer Epidemiol. 2012;36:e380–6.

31. Matsuo K, Oka M, Murase K, Soda H, Isomoto H, Takeshima F, et al. Expression of interleukin 6 and its receptor in human gastric and colorectal cancers. J Int Med Res. 2003;31:69–75.

32. Wu CW, Wang SR, Chao MF, Wu TC, Lui WY, P'Eng FK, et al. Serum interleukin-6 levels reflect disease status of gastric cancer. Am J Gastroenterol. 1996;91:1417–22.

33. Brull DJ, Montgomery HE, Sanders J, Dhamrait S, Luong L, Rumley A, et al. Interleukin-6 gene -174G>C and -572G>C promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. Arterioscler Thromb Vasc Biol. 2001;21:1458–63.

34. Wang J, He W, Liu J, Nong L, Wei Y, Yang F. Association of IL-6 polymorphisms with gastric cancer risk: evidences from a meta-analysis. Cytokine. 2012;59:176–83.

35. Yin YW, Sun QQ, Hu AM, Wang Q, Liu HL, Hou ZZ, et al. Associations between interleukin-6 gene -174C/G and -572C/G polymorphisms and the risk of gastric cancer: a meta-analysis. J Surg Oncol. 2012;106:987–93.

36. de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. J Exp Med. 1991;174:1209–20.

37. Letterio JJ, Roberts AB. TGF-beta: a critical modulator of immune cell function. Clin Immunol Immunopathol. 1997;84:244–50.

38. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 gene promoter. Eur J Immunogenet. 1997;24:1–8.

39. Ni P, Xu H, Xue H, Lin B, Lu Y. A meta-analysis of interleukin-10-1082 promoter polymorphism associated with gastric cancer risk. DNA Cell Biol. 2012;31:582–91.

40. Pan F, Tian J, Pan YY, Zhang Y. Association of IL-10-1082 promoter polymorphism with susceptibility to gastric cancer: evidence from 22 case-control studies. Mol Biol Rep. 2012;39:7143–54.

41. Xue H, Lin B, An J, Zhu Y, Huang G. Interleukin-10-819 promoter polymorphism in association with gastric cancer risk. BMC Cancer. 2012;12:102.

42. Xue H, Wang YC, Lin B, An J, Chen L, Chen J, Fang JY. A meta-analysis of interleukin-10-592 promoter polymorphism associated with gastric cancer risk. PLoS One. 2012;7:e39868.

43. Awad MR, El-Gamel A, Hasleton P, Turner DM, Sinnott PJ, Hutchinson IV. Genotypic variation in the transforming growth factor-beta1 gene: association with transforming growth factor-beta1 production, fibrotic lung disease, and graft fibrosis after lung transplantation. Transplantation. 1998;66:1014–20.

44. Grainger DJ, Heathcote K, Chiano M, Snieder H, Kemp PR, Metcalfe JC, et al. Genetic control of the circulating concentration of transforming growth factor type beta1. Hum Mol Genet. 1999;8:93–7.

45. Li K, Xia F, Zhang K, Mo A, Liu L. Association of a tgf-b1-509c/t polymorphism with gastric cancer risk: a meta-analysis. Ann Hum Genet. 2013;77:1–8.

46. Niu H, Niu Z, Zhang XL, Chen ZL. Absence of association between transforming growth factor B1 polymorphisms and gastric cancer: a meta-analysis. DNA Cell Biol. 2012;31:706–12.

47. Zhang CF, Wang ZW, Hou MX, Li K, Zhou X, Xia YH. Transforming growth factor beta1-509C/T and +869T/C polymorphisms on the risk of upper digestive tract cancer: a meta-analysis based on 10,917 participants. Ann Hum Genet. 2012;76:363–76.