available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Interleukin-10 -1082 promoter polymorphism associated with gastric cancer among Asians

Yong Zhou[a], *Ni Li*[b], *Wen Zhuang*[a], *Guan-Jian Liu*[c], *Tai-Xiang Wu*[c], *Xun Yao*[c], *Liang Du*[c], *Mao-Ling Wei*[c], *Xiao-Ting Wu*[a,*]

[a]*Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, 37 Guo Xue Road, Chengdu, 610041, China*
[b]*Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, 610041, China*
[c]*Chinese Evidence-Based Medicine/Cochrane Center, Chengdu, 610041, China*

ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 22 June 2008
Accepted 9 July 2008
Available online 15 August 2008

Keywords:
Gastric cancer
Interleukin-10
Gene polymorphism
Meta-analysis

ABSTRACT

Studies investigating the association between interleukin-10 (IL-10) -1082 promoter polymorphism and gastric cancer risk report conflicting results. The objective of this study was to quantitatively summarise the evidence for such a relationship. Two investigators independently searched the Medline and Embase databases. This meta-analysis included 13 case-control studies, which included 2227 gastric cancer cases and 3538 controls. The combined results based on all studies showed that there was no significant difference in genotype distribution [AA odds ratio (OR) = 0.92, 95% confidence interval (CI) = 0.73, 1.14; AG (OR = 1.09, 95% CI = 0.87, 1.36); GG (OR = 1.03, 95% CI = 0.85, 1.25)] between gastric cancer and noncancer patients. When stratifying for race, results were similar except that patients with gastric cancer had a significantly lower frequency of AA (OR = 0.71, 95% CI = 0.52, 0.97) and higher frequency AG (OR = 1.53, 95% CI = 1.15, 2.03) than noncancer patients among Asians. When stratifying by the location of gastric cancer, we found that patients with cardia gastric cancer had a significantly lower frequency of AA (OR = 0.53, 95% CI = 0.34, 0.83) and higher frequency AG (OR = 1.50, 95% CI = 1.06, 2.11) than those with noncardia gastric cancer among Caucasians. When stratifying by the Lauren's classification of gastric cancer, we observed no statistically significant differences in genotype distribution. This meta-analysis suggests that the IL-10 -1082 promoter polymorphism may be associated with gastric cancer among Asians, and that differences in genotype distribution may be associated with the location of gastric cancer.

1. Introduction

Gastric cancer, the second leading cause of death from cancer throughout the world, is an important health problem. A 2005 analysis of the worldwide incidence of, and mortality from, cancer showed that 934,000 cases of gastric cancer occurred in 2002 and that 700,000 patients die annually of this disease.[1] Despite the overall decline in gastric cancer rates in most of the Western World, gastric cancer remains a serious fatal disease throughout much of the rest of the world.[2–4] Thirty-eight percent of worldwide cases occur in China, where it remains the most common cancer in both sexes, as it is elsewhere in Eastern Asia.[5] Conversely, the incidence rates of adenocarcinomas of the proximal stomach and distal oesophagus have been increasing, particularly in the Western World.[6] A major strategy for facing this health care problem

* *Corresponding author:* Tel./fax: +86 28 85424110.
E-mail address: nutritioner@hotmail.com (X.-T. Wu).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.07.017

is the identification of individuals at risk, contributing to the prevention and early detection of the disease The knowledge on molecular alterations, which are involved in the carcinogenic process of gastric cancer, may lead to new and, hopefully more effective, means for controlling this lethal disease. In this perspective, the role of genetic polymorphisms in gastric cancer risk has motivated increasing interest in recent years.[7]

Interleukin-10 (IL-10) is an anti-inflammatory cytokine, which is involved in down-regulating cell-mediated and cytotoxic inflammatory responses.[8] The gene encoding IL-10 is located on chromosome 1 (1q31-1q32). IL-10 has three confirmed biallelic polymorphisms in the gene promoter region: -1082 A/G, -819 C/T, and -592 C/A. Presence of -1082A is associated with lower production of IL-10 *in vitro* and *in vivo*, and an accordingly stronger inflammatory response.[9]

It has been suggested that the subclass of T lymphocytes, T helper 3, may influence the outcome of *Helicobacter pylori* infection by reducing the grade of inflammation via the production of IL-10.[10] Over the last two decades, a number of case-control studies were conducted to investigate the association between IL-10 -1082 promoter polymorphism and gastric cancer risk in humans. But these studies have reported conflicting results. No quantitative summary of the evidence has ever been performed. The purpose of this meta-analysis was to quantitatively summarise the evidence for such a relationship.

2. Materials and methods

2.1. Literature search strategy

The search was applied to the following electronic databases: MEDLINE (1966 to January 2008), EMBASE (1980 to January 2008). The following key words were used: 'interleukin-10' or 'IL-10', 'gastric' or 'stomach', 'carcinoma' or 'cancer' or 'tumor'. The search was done without restriction on language but was focused on studies that had been conducted on human subjects. The reference lists of reviews and retrieved articles were hand searched simultaneously. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, we selected the study with higher sample size.

2.2. Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. For inclusion in the meta-analysis, the identified articles had to provide information on: (i) the number of gastric cancer cases and controls studied; (ii) the number of individual genotypes (AA, AG, GG) in cases and controls. Major reasons for exclusion of studies were (i) no control; (ii) duplicate; (iii) no usable data reported.

2.3. Data extraction

All data were extracted independently by two reviewers (Zhou Y and Li N) according to the prespecified selection criteria. Disagreement was resolved by discussion. The following data were extracted: study design and period, statistical methods, population, number of gastric cancer cases and controls studied, and study results.

2.4. Statistical analysis

The statistical analysis was conducted using STATA 8.2 (StataCorp, College Station, Tex); $P < 0.05$ was considered statistically significant. Dichotomous data were presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical heterogeneity was measured using the Q statistic ($P < 0.10$ was considered representative of statistically significant heterogeneity).[11] Heterogeneity was also assessed through visual examination of L'Abbe plots. The fixed effects model was used when there was no heterogeneity of the results of the trials. Otherwise, the random effects model was used. For dichotomous outcomes, patients with incomplete or missing data were included in sensitivity analyses by counting them as treatment failures. To establish the effect of clinical heterogeneity between studies on meta-analysis conclusions, subgroup analysis was conducted on the basis of race and the location, stage, Lauren's classification and histological differentiation of the gastric cancer.

Several methods were used to assess the potential for publication bias. Visual inspection of asymmetry in funnel plots was conducted. The Begg rank correlation method and the Egger weighted regression method were also used to statistically assess publication bias ($P < 0.05$ was considered representative of statistically significant publication bias).[12,13]

3. Results

3.1. Study characteristics

There were 140 papers relevant to the search words (Fig. 1). Through the step of screening the title, 107 of these articles were excluded (91 were not polymorphisms, ten were not

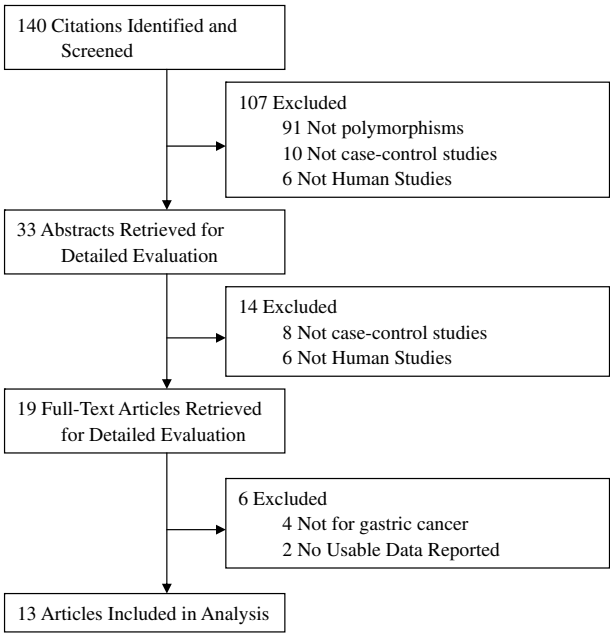

Fig. 1 – Studies identification, inclusion and exclusion.

Table 1 – Characteristics of studies included in the meta-analysis

Study (author, year)	Design	Study period	Population (country)	Genotyping method	No. of cases	No. of controls	AA of cases	AG of cases	GG of cases	AA of controls	AG of controls	GG of controls
Wu 2002[8]	HCC	1993–1999	Asians(China)	PCR	120	220	106	13	1	208	11	1
Wu 2003[19]	HCC	1998–2000	Asians(China)	PCR	220	230	195	23	2	217	11	2
El-Omar 2003[20]	PCC	DNR	Caucasians(USA)	TaqMan	314	210	120	133	61	59	103	48
Savage2004[21]	PCC	1991–1996	Asians(China)	PCR	84	385	4	20	60	20	81	284
Lu 2005[22]	PCC	1994–2003	Asians(China)	PCR-DHPLC	250	300	201	43	6	268	29	3
Zambon 2005[23]	HCC	DNR	Caucasians(Italy)	PCR-RFLP	129	644	48	56	25	232	326	86
Guo 2005[24]	PCC	2001–2003	Asians(China)	PCR-RFLP	152	443	93	DNR	DNR	267	DNR	DNR
Lee 2005[25]	PCC	DNR	Asians(Korea)	PCR-RFLP	122	120	104	17	1	101	18	1
Alpizar 2005[26]	PCC	1999–2000	Latinos(Costa Rica)	PCR-RFLP	45	44	45	0	0	43	1	0
Kamangar 2006[27]	PCC	1985–1999	Caucasians(Finland)	TaqMan	112	208	38	47	27	72	96	37
Morgan 2006[28]	PCC	2002–2004	Latinos(Honduras)	TaqMan	170	162	121	42	7	102	49	11
Garcia 2007[29]	PCC	2002–2005	Caucasians(Spain)	PCR-RFLP	404	404	123	204	77	133	189	82
Sugimoto 2007[30]	PCC	2001–2005	Asians(Japan)	ASP-PCR	105	168	79	26	0	134	34	0

Abbreviations: HCC, hospital-based case-control; PCC, population-based case-control; DNR, data not reported; PCR, polymerase chain reaction; ASP, allele-specific PCR; RFLP, restriction fragment length polymorphism; DHPLC, denaturing high performance liquid chromatography.

case-control studies, six were not conducted in humans). Abstracts from 33 articles were reviewed and an additional 14 trials were excluded (eight were not case-control studies, six were not conducted in humans), leaving 19 studies for full publication review. Of these, six were excluded (four were not for gastric cancer[9,14–16], two did not report usable data[17,18]); thus, 13 papers[8,19–30], which included 2227 gastric cancer cases and 3538 controls, were found to match our inclusion criteria. Thirteen studies, including ten population-based case-control studies and three hospital-based case-control studies, were included in this meta-analysis. Studies had been carried out in China, Japan, Korea, USA, Italy, Finland, Spain, Honduras and Costa Rica. Characteristics of studies included in this meta-analysis are presented in Table 1.

3.2. *Quantitative data synthesis*

The combined results based on all studies showed that there was no significant difference in genotype distribution [AA odds ratio (OR) = 0.92, 95% confidence interval (CI) = 0.73, 1.14; AG (OR = 1.09, 95% CI = 0.87, 1.36); GG (OR = 1.03, 95% CI = 0.85, 1.25)] between gastric cancer and noncancer patients. When stratifying for race, results were similar except that patients with gastric cancer had a significantly lower frequency of AA (OR = 0.71, 95% CI = 0.52, 0.97) and higher frequency AG (OR = 1.53, 95% CI = 1.15, 2.03) than noncancer patients among Asians. (Figs. 2–4).

When stratifying by the location of gastric cancer, we found that patients with cardia gastric cancer had a significantly lower frequency of AA (OR = 0.53, 95% CI = 0.34, 0.83) and higher frequency AG (OR = 1.50, 95% CI = 1.06, 2.11) than those with noncardia gastric cancer among Caucasians. When stratifying by the Lauren's classification of gastric cancer, we observed no statistically significant differences in genotype distribution. (Table 2).

Statistically significant heterogeneity was observed between trials in two analyses with the Q statistic (AA

Fig. 2 – Meta-analysis of IL-10 -1082 promoter AA and gastric cancer risk.

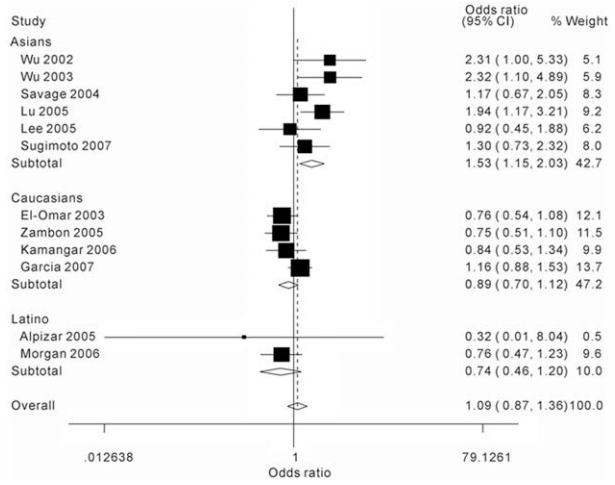

Fig. 3 – Meta-analysis of IL-10 -1082 promoter AG and gastric cancer risk.

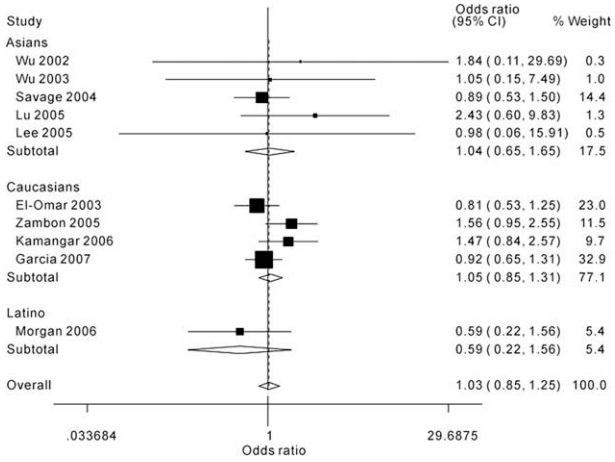

Fig. 4 – Meta-analysis of IL-10 -1082 promoter GG and gastric cancer risk.

$P = 0.008$; AG $P = 0.01$; GG $P = 0.44$). In addition, L'Abbe plots did show evidence of heterogeneity (Fig. 5). Review of funnel plots could not rule out the potential for publication bias for all analyses. Publication bias was not evident when the Begg

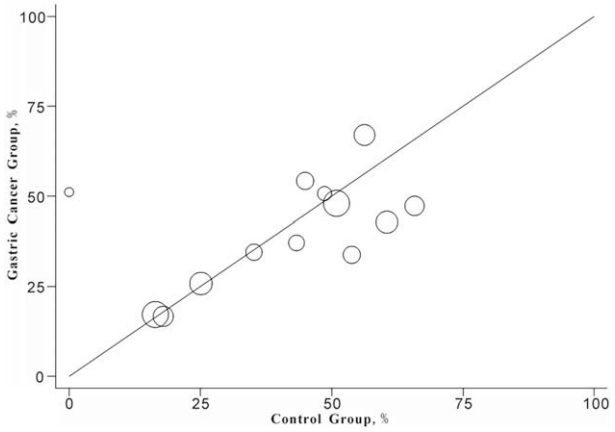

Fig. 5 – L'Abbe plots of IL-10 -1082 promoter polymorphism and gastric cancer risk.

rank correlation method (AA $P = 0.54$; AG $P = 0.07$; GG $P = 0.66$) and the Egger weighted regression method (AA $P = 0.74$; AG $P = 0.17$; GG $P = 0.55$) were used (Figs. 6 and 7).

4. Discussion

The rapid growth of human genetics creates countless opportunities for studies of disease association. Given the number of potentially identifiable genetic markers and the multitude of clinical outcomes to which these may be linked, the testing and validation of statistical hypotheses in genetic epidemiology is a task of unprecedented scale. Meta-analysis provides a quantitative approach for combining the results of various studies on the same topic, and for estimating and explaining their diversity. A meta-analysis of 379 studies addressing 36 genetic associations with disease found that association studies of the same disease are often inconsistent in their findings, and that the first study to report an association often indicates a stronger effect than in subsequent studies. This can lead to a distorted impression of the genetic etiology underlying a given disease. A systematic meta-analytic approach may assist in estimating population-wide effects of genetic risk factors in human disease.[31,32]

A genetic predisposition to gastric cancer has been suggested by both epidemiological studies and case reports of

Table 2 – Meta-analysis of interleukin-10 -1082 promoter polymorphism and gastric cancer

Stratification of gastric cancer	No. of studies	OR (95% CI) of AA	P for heterogeneity	OR (95% CI) of AG	P for heterogeneity	OR (95% CI) of GG	P for heterogeneity
Location: Cardia versus Noncardia	3	0.51(0.35,0.73)	0.40	1.56(1.12,2.18)	0.56	1.28(0.84,1.95)	0.26
Asians	1	0.31(0.07,1.34)	NA	3.22(0.75,13.89)	NA		
Caucasians	2	0.53(0.34,0.83)	0.25	1.50(1.06,2.11)	0.68	1.28(0.84,1.95)	0.26
Lauren's classification: Diffuse versus Intestinal	2	1.14(0.73,1.77)	0.05	1.16(0.76,1.77)	0.19	0.57(0.30,1.06)	NA
Asians	1	0.48(0.18,1.27)	NA	2.10(0.79,5.59)	NA		
Caucasians	1	1.41(0.86,2.31)	NA	1.02(0.64,1.63)	NA	0.57(0.30,1.06)	NA

Abbreviations: OR, odds ratio; CI, confidence interval; NA: not applicable.

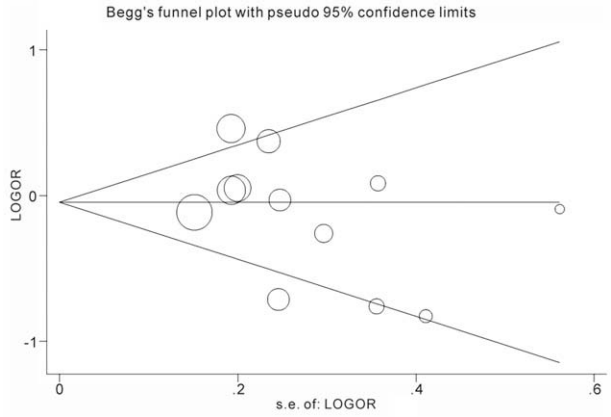

Fig. 6 – Begg's funnel plot of IL-10 -1082 promoter polymorphism and gastric cancer risk.

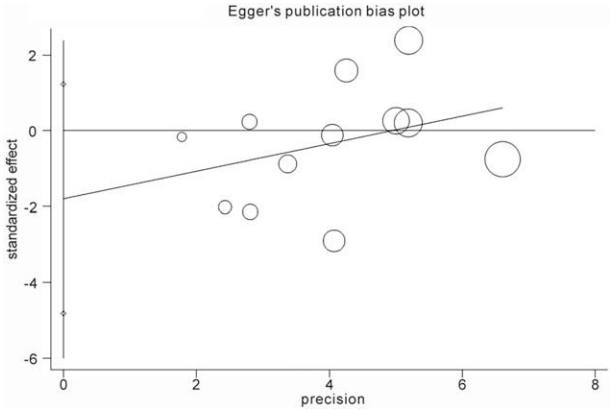

Fig. 7 – Egger's publication bias plot of IL-10 -1082 promoter polymorphism and gastric cancer risk.

gastric cancer families.[6] Recent studies suggest that single nucleotide polymorphisms may be related to the tumourigenesis of gastric cancer.[33] Individual genetic susceptibility may be critical in a variety of processes relevant to gastric cancer tumourigenesis, such as (i) mucosal protection in the face of *Helicobacter pylori* infection and other carcinogens, (ii) the inflammatory response, which conditions the maintenance, severity and outcome of the *Helicobacter pylori* infection, (iii) the functioning of carcinogen detoxification and antioxidant protection, (iv) cell proliferation ability, (v) the intrinsic variability of DNA repair processes; and (vi) the cell apoptotic pathway.[7] The mechanism of human gastric tumourigenesis is still relatively unknown, and single nucleotide polymorphisms can be used as a tool in searching for genetic variations of the disease gene and susceptibility, and to increase understanding of the disease mechanism.[34]

Statistically significant heterogeneity was observed between trials in two analyses with the Q statistic. The most important factor that contributed to the heterogeneity was whether or not the genotype frequencies were in Hardy–Weinberg equilibrium, because the equilibrium may not hold among a case group if the genotype is truly associated with disease. Observed departures from equilibrium therefore suggest possible issues with the control group, or the study population in general, that might have generated less than ideal circumstances for the investigation of the IL-10 -1082 promoter polymorphism and gastric cancer. A departure from Hardy–Weinberg equilibrium can also imply possible ethnic admixture in the population, if the polymorphic site varies in genotype by race.[35,36] In fact, race-specific variation in the distribution of genotypes in the IL-10 -1082 promoter polymorphism has been demonstrated. Because race may be related to disease, either through common risk factors or other genes in linkage disequilibrium with IL-10, confounding by race, or population stratification, may have biased results in studies conducted on ethnically diverse populations that did not account for possible confounding.[37] In this meta-analysis, subgroup analysis was conducted on the basis of race. In fact, seven studies were conducted among Asians, four studies were conducted among Caucasians, and two studies were conducted among Latinos. When stratifying for race, patients with gastric cancer had a significantly lower frequency of AA and higher frequency AG than noncancer patients among Asians.

IL-10 polymorphism has also been extensively studied and reported to be associated with other cancers and diseases. A case-control study including 500 female patients with histologically confirmed breast cancer and 500 female, age-matched, healthy control subjects conducted by Langsenlehner and colleagues suggested that IL-10 promoter polymorphism was associated with decreased breast cancer risk.[38] A prospective, case-control study including 147 patients with advanced ovarian cancer conducted by Ioana and colleagues showed that IL-10 promoter polymorphism may be related with the ability to achieve optimal tumour debulking, and it seemed to influence the overall and disease-free survival rate.[39] A study conducted by Shih and colleagues showed that the frequency for IL-10-1082 G allele, IL-10-819C allele and IL-10-592C allele was independently higher in a non-small cell lung cancer patient group than that in the control group.[40] A study conducted by Faupel and colleagues demonstrated genotypes correlated with low IL-10 production was associated with increased risk of prostate cancer and with high-grade disease.[41] A meta-analysis conducted by Nath and colleagues revealed that IL-10 promoter -1082G allele was associated with systemic lupus erythematosus in Asians (OR = 1.358, 95% CI; 1.015-1.816, P = 0.039).[42] This supported the results achieved by us.

There are some limitations to this meta-analysis. First, only published studies were included in the meta-analysis; therefore, publication bias may have occurred, even though the use of a statistical test did not show it. Second, we could not obtain information from most studies on the presence or absence of a history of infection with *Helicobacter pylori,* a strong risk factor for gastric cancer. Third, as in most meta-analyses, these results should be interpreted with caution because the population from seven countries and controls were not uniform. Fourth, our meta-analysis is based on unadjusted estimates, while a more precise analysis could be performed if individual data were available, which would allow for an adjustment estimate (by age and sex). For this approach to be made, however, requires the authors of all of the published studies to share their data. Finally, meta-analysis remains retrospective research that is subject to the

methodological deficiencies of the included studies. We minimised the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published studies, and by using explicit methods for study selection, data extraction and data analysis.

In conclusion, this meta-analysis suggests that the IL-10 -1082 promoter polymorphism may be associated with gastric cancer among Asians, and that differences in genotype distribution may be associated with the location of gastric cancer. Since more than half of the included studies were based on a limited number of cases (<150), it is critical that larger and well-designed multicentric studies based on the same ethnic group confirm our results.

Conflict of interest statement

None declared.

Acknowledgements

The research of this paper is supported in part by the Chinese Medical Board Grant on Evidence-based Medicine, New York, USA (Grant number: 98-680).

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**:74–108.
2. Boyle P. Favorable trends in cancer mortality in the European Union but no room for complacency. *Ann Oncol* 2008;**19**:605–6.
3. Gondos A, Bray F, Brewster DH, et al. Recent trends in cancer survival across Europe between 2000 and 2004: A model-based period analysis from 12 cancer registries. *Eur J Cancer* 2008;**44**:1463–75.
4. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008;**44**:1345–89.
5. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001;**94**:153–6.
6. Devesa SS, Fraumeni Jr JF. The rising incidence of gastric cardia cancer. *J Natl Cancer Inst* 1999;**91**:747–9.
7. Gonzalez CA, Sala N, Capella G. Genetic susceptibility and gastric cancer risk. *Int J Cancer* 2002;**100**:249–60.
8. Wu MS, Huang SP, Chang YT, et al. Tumor necrosis factor-alpha and interleukin-10 promoter polymorphisms in Epstein-Barr virus-associated gastric carcinoma. *J Infect Dis* 2002;**185**:106–9.
9. Rad R, Dossumbekova A, Neu B, et al. Cytokine gene polymorphisms influence mucosal cytokine expression, gastric inflammation, and host specific colonisation during Helicobacter pylori infection. *Gut* 2004;**53**:1082–9.
10. Sutton P, Kolesnikow T, Danon S, Wilson J, Lee A. Dominant nonresponsiveness to Helicobacter pylori infection is associated with production of interleukin 10 but not gamma interferon. *Infect Immun* 2000;**68**:4802–4.
11. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.6. The Cochrane Library.* Chichester, UK: John Wiley & Sons, Ltd.; 2006. updated September 2006.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;**315**:629–34.
13. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**:1088–101.
14. Con SA, Con-Wong R, Con-Chin GR, et al. Serum pepsinogen levels, Helicobacter pylori CagA Status, and cytokine gene polymorphisms associated with gastric premalignant lesions in Costa Rica. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:2631–6.
15. Leung WK, Chan MC, To KF, et al. H. pylori genotypes and cytokine gene polymorphisms influence the development of gastric intestinal metaplasia in a Chinese population. *Am J Gastroenterol* 2006;**101**:714–20.
16. Kato I, Canzian F, Franceschi S, et al. Genetic polymorphisms in anti-inflammatory cytokine signaling and the prevalence of gastric precancerous lesions in Venezuela. *Cancer Causes Control* 2006;**17**:1183–91.
17. Bai XL, Sun LP, Liu J, Chen W, Zhang Y, Yuan Y. [Correlation of Interleukin-10-1082G/A Single Nucleotide Polymorphism to the Risk of Gastric Cancer in North China: A Case-Control Study.]. *Ai Zheng* 2008;**27**:35–40.
18. Deans C, Rose-Zerilli M, Wigmore S, et al. Host cytokine genotype is related to adverse prognosis and systemic inflammation in gastro-oesophageal cancer. *Ann Surg Oncol* 2007;**14**:329–39.
19. 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**:617–23.
20. El-Omar EM, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003;**124**:1193–201.
21. Savage SA, Abnet CC, Haque K, et al. Polymorphisms in interleukin -2, -6, and -10 are not associated with gastric cardia or esophageal cancer in a high-risk chinese population. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1547–9.
22. Lu W, Pan K, Zhang L, Lin D, Miao X, You W. Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor alpha and risk of gastric cancer in a Chinese population. *Carcinogenesis* 2005;**26**:631–6.
23. Zambon CF, Basso D, Navaglia F, et al. Pro- and anti-inflammatory cytokines gene polymorphisms and Helicobacter pylori infection: interactions influence outcome. *Cytokine* 2005;**29**:141–52.
24. Guo W, Wang N, Wang YM, et al. Interleukin-10–1082 promoter polymorphism is not associated with susceptibility to esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma in a population of high-incidence region of north China. *World J Gastroenterol* 2005;**11**:858–62.
25. Lee JY, Kim HY, Kim KH, et al. Association of polymorphism of IL-10 and TNF-A genes with gastric cancer in Korea. *Cancer Lett* 2005;**225**:207–14.
26. Alpizar-Alpizar W, Perez-Perez GI, Une C, Cuenca P, Sierra R. Association of interleukin-1B and interleukin-1RN polymorphisms with gastric cancer in a high-risk population of Costa Rica. *Clin Exp Med* 2005;**5**:169–76.
27. Kamangar F, Abnet CC, Hutchinson AA, et al. Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). *Cancer Causes Control* 2006;**17**:117–25.
28. Morgan DR, Dominguez RL, Keku TO, et al. Gastric cancer and the high combination prevalence of host cytokine genotypes and Helicobacter pylori in Honduras. *Clin Gastroenterol Hepatol* 2006;**4**:1103–11.
29. 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**:1878–92.
30. Sugimoto M, Furuta T, Shirai N, et al. Effects of interleukin-10 gene polymorphism on the development of gastric cancer and peptic ulcer in Japanese subjects. *J Gastroenterol Hepatol* 2007;**22**:1443–9.
31. Zhou Y, Li N, Zhuang W, et al. P53 codon 72 polymorphism and gastric cancer: a meta-analysis of the literature. *Int J Cancer* 2007;**121**:1481–6.
32. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. *Nat Genet* 2001;**29**:306–9.
33. Machado JC, Pharoah P, Sousa S, et al. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* 2001;**121**:823–9.
34. Loder N. Genetic variations can point the way to disease genes. *Nature* 1999;**401**:734.
35. Schaid DJ, Jacobsen SJ. Biased tests of association: comparisons of allele frequencies when departing from Hardy-Weinberg proportions. *Am J Epidemiol* 1999;**149**:706–11.
36. Deng HW, Chen WM, Recker RR. Population admixture: detection by Hardy-Weinberg test and its quantitative effects on linkage-disequilibrium methods for localizing genes underlying complex traits. *Genetics* 2001;**157**:885–97.
37. Thomas DC, Witte JS. Point: population stratification: a problem for case-control studies of candidate-gene associations? *Cancer Epidemiol Biomarkers Prev* 2002;**11**:505–12.
38. Langsenlehner U, Krippl P, Renner W, et al. Interleukin-10 promoter polymorphism is associated with decreased breast cancer risk. *Breast Cancer Res Treat* 2005;**90**:113–5.
39. Ioana Braicu E, Mustea A, Toliat MR, et al. Polymorphism of IL-1alpha, IL-1beta and IL-10 in patients with advanced ovarian cancer: results of a prospective study with 147 patients. *Gynecol Oncol* 2007;**104**:680–5.
40. Shih CM, Lee YL, Chiou HL, et al. The involvement of genetic polymorphism of IL-10 promoter in non-small cell lung cancer. *Lung cancer* 2005;**50**:291–7.
41. Faupel-Badger JM, Kidd LC, Albanes D, Virtamo J, Woodson K, Tangrea JA. Association of IL-10 polymorphisms with prostate cancer risk and grade of disease. *Cancer Causes Control* 2008;**19**:119–24.
42. Nath SK, Harley JB, Lee YH. Polymorphisms of complement receptor 1 and interleukin-10 genes and systemic lupus erythematosus: a meta-analysis. *Hum Genet* 2005;**118**:225–34.