Published in final edited form as:

Cancer Causes Control. 2013 December ; 24(12): . doi:10.1007/s10552-013-0284-z.

Circulating cytokines and gastric cancer risk

Meira Epplein¹, Yong-Bing Xiang², Qiuyin Cai¹, Richard M. Peek Jr.³, Honglan Li², Pelayo Correa³, Jing Gao², Jie Wu¹, Angelika Michel⁴, Michael Pawlita⁴, Wei Zheng¹, and Xiao Ou Shu¹

¹Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

²Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

³Division of Gastroenterology, Departments of Medicine and Cancer Biology, Vanderbilt University, Nashville, TN

⁴Division of Genome Modifications and Carcinogenesis, Infection and Cancer Program, German Cancer Research Center (DFKZ), Heidelberg, Germany

Abstract

Purpose: Chronic inflammation has been hypothesized to play a significant role in the etiology of cancer, including gastric cancer. In the present study we sought to examine pre-diagnostic systemic cytokine levels in plasma, which can be seen as markers of aggregate inflammation, and risk of distal gastric cancer in a case-control study nested within the prospective Shanghai Men's Health Study.

Methods: Circulating levels of eight inflammation-related cytokines were measured in the plasma collected at baseline for 180 incident cases of distal gastric cancer and 358 matched controls. *Helicobacter pylori* sero-positivity was assessed using multiplex serology. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals.

Results: Individuals with IL-8 levels above the lowest quartile were at two-fold increased odds of gastric cancer [OR 1.91 (95% CI 1.05-3.46), OR 2.10 (95% CI 1.19-3.74), and OR 2.30 (95% CI 1.26-4.19), for the second through fourth quartiles, respectively]. While there were suggestions of an increase in risk with increased level of many of the other cytokines measured (IL-1, IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ), no significant associations were found at the $p < 0.05$ level. Infection with CagA-positive *H. pylori* did not modify these associations.

Conclusions: In a population with high gastric cancer incidence and high *H. pylori* prevalence, increased circulating levels of IL-8 may indicate increased risk of gastric cancer. These findings add to our understanding of the disease, and further efforts to uncover biomarkers of disease risk.

Keywords

inflammation; cytokines; gastric cancer; epidemiology

INTRODUCTION

The strong association between cancer and inflammation has long been observed, and currently it is believed that many if not most cancers arise in an inflammatory environment. Inflammation both provides a fertile, pro-growth background for cancer to develop and aids in cancer progression [1]. As the leading cause of gastric cancer, infection with *Helicobacter pylori* and in its interaction with the host immune response causes inflammation, and the resulting degree of inflammation is related to the risk of the development of cancer [2]. Additionally, many epidemiologic studies have shown that regular use of non-steroidal anti-inflammatory drugs reduce the risk of gastric cancer [3-5].

To investigate chronic inflammation in the host, a number of recent studies have examined inflammatory cytokine polymorphisms and gastric cancer risk, with many focusing on interleukin-1 beta gene promoter polymorphisms, with inconsistent findings [6,7]. Other genes that encode proteins related to inflammation and *H. pylori*, including IL-8, IL-10, and tumor necrosis factor- α , have been examined as to their association with gastric cancer risk, also with mixed results [6]. Many of the challenges in studying genetic polymorphisms and gastric cancer risk are similar to those in any gene association study, such as multiple comparisons, phenotype heterogeneity, locus heterogeneity, population stratification, and variation in allele frequency among populations [6].

In the present study we sought to examine pre-diagnostic systemic cytokine levels in plasma, which can be seen as markers of aggregate inflammation, and risk of distal gastric cancer in a prospective cohort study in China.

MATERIALS AND METHODS

Study population

From 2002 to 2006, the Shanghai Men's Health Study (SMHS) recruited 61,582 men, aged 40-74 years and without a history of cancer, who were permanently residing in urban Shanghai. A structured, in-person interview was conducted by trained former medical professionals to collect information on demographic factors, medical history, family cancer history, usual diet and other lifestyle factors [8,9]. Following an established protocol [10], a 10-ml blood sample was drawn from each participant. Samples were then transported by insulated portable boxes with ice packs and were processed within 6 hours for long-term storage at -80°C . Plasma samples were used for inflammatory cytokines and *H. pylori* assays. Approximately 75% of SMHS participants provided blood samples at baseline.

Case identification

Linkage with the Shanghai Cancer Registry and the Shanghai Vital Statistics Unit allowed for ascertainment of incident gastric cancer cases in the SMHS. All possible links were confirmed by home visits and cancer diagnoses were further confirmed through medical chart review from notifying hospitals. Between 2002 and 2009, 255 gastric cancer cases were identified among SMHS participants who donated a blood sample at baseline and who were not diagnosed with cancer within one month of blood sample collection. The 29 (11.4%) gastric cancer cases classified as gastric cardia cancer (an International Classification of Diseases for Oncology [ICD-O] code of 160) as well as the 5 (2.2%) cases coded as overlapping (ICD-O 168) and the 41 cases coded as unspecified (ICD-O 169) were excluded, as cardia and non-cardia gastric cancer are believed to have different etiologies and we sought to explore the specific association of circulating cytokines with distal gastric cancer. Thus, the present study includes 180 incident cases of distal gastric cancer (an ICD-O code of 161-166), for whom the median time span from blood collection to diagnosis was 3.6 years (range, 1 month to 8 years).

Control selection

For each case, two controls were chosen matched on age (± 2 years), date (± 30 days) and time (morning or afternoon) of sample collection; time interval since last meal (± 2 hours); and use of antibiotics in the previous week. These matching factors were selected due to the *a priori* belief that details relevant to blood collection can affect the sensitivity and specificity of many biological assays. After excluding a sample with heavy hemolysis which failed the cytokine assay, this study included 180 cases of distal gastric cancer and 358 matched controls.

Circulating cytokine assay

Circulating levels of eight inflammation-related cytokines – IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, TNF- α , and IFN- γ – were measured by using MILLIPLEX MAP High Sensitivity Human Cytokine Magnetic Bead Panel assay kit (Millipore, HSCYTMAG-60SK) on Luminesx 200™ Analyzer following the manufacturer's protocols. A standard curve was run for each assay batch and two controls (higher and lower) were run for each of the seven plates (for a total of 14 quality control samples). The samples from the same case-control set were analyzed in the same plate. All the samples were tested in duplicate. The inter-assay coefficients of variation were 7-14%.

Helicobacter pylori multiplex serology

As previously described [11,12], *H. pylori* multiplex serology, based on a glutathione *S*-transferase capture immunosorbent assay combined with fluorescent-bead technology [13,14], was used to determine sero-status of antibodies to fifteen *H. pylori* specific antigens (UreA, Catalase, GroEL, NapA, CagA, CagM, Cag ϵ , HP0231, VacA, HpaA, Cad, HyuA, Omp, HcpC, HP0305). For each of these antigens, specific cut-point values were created based on 46 *H. pylori* sero-negative sera from a previous study [15] and run within this assay. Individuals were classified as *H. pylori* sero-positive if they had sero-positive results to 4 *H. pylori* proteins examined. This definition of *H. pylori* seropositivity was found to have excellent agreement ($\kappa=0.70$) with commercial serological assay classification [11].

Statistical analysis

The individual associations of circulating levels of each cytokine and distal gastric cancer risk were assessed using conditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Levels of each of the cytokines analyzed were categorized in quartiles based on the distribution in the controls, and the second through fourth quartiles were included in the models as indicator variables (with the lowest quartile serving as the reference group). To test for a linear trend across quartiles of each cytokine, an ordinal variable was created and assigned the quartile rank (1-4) for each individual cytokine. Baseline characteristics that were *a priori* considered to be associated with both cytokine levels and gastric cancer were considered for inclusion in the adjusted models. The final adjusted models included those characteristics that were associated with both the exposure and the outcome in the data, specifically: history of gastritis (yes/no); regular aspirin use (yes/no); smoking status (current/not current); and number of sero-positive results to 6 *H. pylori* virulence proteins (Omp, HP0305, HyuA, HpaA, CagA, and VacA).

To determine if infection with *H. pylori* magnifies the effect of circulating cytokine levels on gastric cancer risk, analyses were performed among high-risk sub-groups of the study population. Specifically, separate models were run among only those individuals who were *H. pylori* sero-positive and both *H. pylori* sero-positive and CagA sero-positive. To test for effect modification by *H. pylori* status, a likelihood ratio test was used for the product of the

cytokine as a linear trend by category and the dichotomous categorization of *H. pylori* status, as measured in the two ways above.

To minimize the possibility of reverse causation, whereby undiagnosed subclinical or pre-malignant lesions are inflating cytokine levels, we performed a time lag analysis, by running separate models on the study population by time between baseline blood draw and diagnosis.

All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Differences in baseline characteristics between distal gastric cancer cases and their matched controls are shown in Table 1. The vast majority of all participants tested sero-positive for *H. pylori*, including both cases and controls (98% vs. 95%, respectively; $P=0.10$). Cases were more likely to be current smokers, to have had a diagnosis of chronic gastritis, to have a lower average fruit intake, and to not be regular users of aspirin. For all cytokines examined, cases had higher median levels than controls, but only for IL-8 was there a significant difference in the distribution of scores by case-control status, assessed by the Wilcoxon rank sum test ($p=0.03$).

In fully adjusted regression models, individuals classified in the top quartiles of all of the eight cytokines examined had a suggested increase in risk of gastric cancer compared to individuals in the lowest quartile of these cytokines, although only for the cytokine IL-8 did these odds ratios reach statistical significance at the $p<0.05$ level (ORs of 1.91, 2.10, and 2.30, respectively) (Table 2).

While the majority of our study population was not only sero-positive for *H. pylori*, but for the *H. pylori* virulence protein CagA, we still sought to assess whether *H. pylori* infection magnifies the effect of high circulating cytokine levels on gastric cancer risk. However, we found no appreciable differences in these higher risk groups as compared to the associations in the entire group. Specifically, among only those individuals sero-positive for CagA-positive *H. pylori* (94% of cases and 92% of controls), the respective ORs were 1.0 (reference), 1.6 (0.9-3.1), 2.1 (1.2-3.9), and 2.1 (1.1-4.0), P for trend of 0.01, for the association of increasing IL-8 levels in quartiles with distal gastric cancer risk.

Limiting the analyses by excluding individuals diagnosed within one, two, three, or four years after blood draw did not change the interpretation of the results from the primary findings. Specifically, for those individuals diagnosed more than four years after recruitment (and their matched controls), individuals in the second, third, and fourth quartiles of IL-8 levels, compared to those in the lowest quartile, continued to have an excess risk of gastric cancer (ORs and 95% CIs of 2.0 [0.7-5.9], 2.7 [0.9-8.2], and 3.4 [1.1-10.8], respectively; P for trend=0.04).

DISCUSSION

This prospective study of the association of circulating plasma levels of eight different inflammation-associated cytokines and gastric cancer risk found that increasing levels of IL-8 were associated with increasing risk of distal gastric cancer. Specifically, individuals with IL-8 levels above the lowest quartile were at two-fold increased odds of this deadly disease. While almost all risk estimates above the lowest quartile for the other seven cytokines measured (IL-1, IL-2, IL-4, IL-6, IL-10, TNF-, and IFN-) were suggestive of a direct association with gastric cancer risk, no other significant associations were found.

Previously, in a nested case-control study of systemic cytokine levels and gastric cancer risk among Chinese *women* in Shanghai, we also observed a positive association between gastric cancer risk and plasma IL-8 levels (highest tertile compared to lowest tertile: OR, 1.41; 95% CI, 0.85-2.36; *P* for trend, 0.18) [16], although neither the point estimate nor the trend test was statistically significant, perhaps due to a small sample size (141 cases and 221 controls). In the study conducted among women, we found a direct association between increasing plasma IL-6 levels and gastric cancer risk (highest tertile compared to lowest tertile: OR, 1.73; 95% CI, 1.00-3.00; *P* for trend, 0.04). When we analyzed the associations of IL-6 and IL-8 and gastric cancer risk among participants in the present study, from the Shanghai Men's Health Study (SMHS), in a manner similar to that done in the Shanghai Women's Health Study (SWHS) – categorizing cytokine levels in tertiles, adjusting for education only, including all gastric cancer cases (such as those coded as overlapping or unspecified, although we were not able to include cardia cancer cases as done in the women's study) and stratifying by time interval between blood collection and diagnosis, the results were similar, although in the SMHS they did not reach statistical significance. Specifically, for the SWHS main finding that individuals in the highest tertile of IL-6 levels had an increased risk of gastric cancer after more than four years of follow-up (OR, 2.45; 95% CI, 1.0-6.7; *P* for trend, 0.04), the equivalent analysis in the SMHS resulted in a similar suggestion of increased risk for men in the highest tertile of IL-6 levels (OR, 1.87; 95% CI, 0.9-4.1; *P* for trend, 0.14). There are, however, still noticeable differences in the cohorts, as women in Shanghai overall have a significantly lower risk of gastric cancer than men and very few women smoked cigarettes regularly (5% are ever smokers).

The few other studies of circulating IL-8 levels and gastric cancer have also found significant associations, including a small Italian cross-sectional study that found higher mean levels of serum IL-8 in gastric cancer cases than in healthy volunteers or in individuals with other diseases (all *P* < 0.001) [17]. A larger, Polish case-control study also found significantly higher IL-8 levels in gastric cancer cases than controls (*P* < 0.001) [18]. However, the present study is only the second *prospective* study we are aware of, after the study discussed above in Shanghai women, to explore pre-diagnostic circulating IL-8 levels and gastric cancer risk.

A number of studies have investigated IL-8 polymorphisms and gastric cancer risk, and a recent meta-analysis that included 18 studies found that the AA genotype of the IL-8 -251 promoter polymorphism, located on chromosome 4q12-21, is significantly associated with overall risk of gastric cancer, and among Asian populations, specifically [19]. Interestingly, and consistent with the findings of the present study, the authors of the meta-analysis did not find that this high-risk AA genotype was modified by *H. pylori* infection.

The use of plasma levels of cytokines in the present study allowed for an estimation of an aggregate measure of multiple genetic variants, reflecting each individual's phenotype, and enhancing the statistical power of the study. At the same time, circulating cytokine levels are also reflective of current inflammation not related to *H. pylori* or gastric atrophy, such as that arising from colds as well as chronic or acute illnesses. Nonetheless we do not expect systemic differences in rates of such illnesses at baseline between cases and controls in this prospective study. While examination of plasma cytokines is still relatively new, a recent study examining within-person variation of plasma adipokine levels, including IL-1, IL-6, IL-8, and TNF- α , found no significant seasonal variation, and intraclass coefficients ranging from reasonably high values (0.77 for IL-1 and 0.73 IL-6) to a bit lower (0.51 for IL-8 and 0.48 for TNF- α). [20] Systemic cytokine levels have previously been found to be associated with colorectal cancer rates of proliferation and apoptosis [21], risk of celiac disease [22], and, most recently, lung cancer risk [23]. Thus, the findings of the present study of the association of increased circulating IL-8 levels with increased gastric cancer risk,

independent of *H. pylori* status, add to our understanding of the disease, and further efforts to uncover biomarkers of disease risk.

Acknowledgments

GRANT SUPPORT

This work was supported by the National Cancer Institute at the National Institutes of Health (K07 CA151782-01A1 to M.E. and R01 CA82729-11 to X.-O.S.) and the Joint Initiative for Innovation and Research of the German Helmholtz Association (A.M. and M.P.). The plasma sample preparations were performed at the Survey and Biospecimen Core, which is supported in part by the Vanderbilt-Ingram Cancer Center (P30 CA68485). R.M.P. is supported by DK R01 58587, CA R01 77955, CA P01 116087, and DK P30 058404.

REFERENCES

1. Keibel A, Singh V, Sharma MC. Inflammation, microenvironment, and the immune system in cancer progression. *Curr Pharm Des.* 2009; 15(17):1949–1955. [PubMed: 19519435]
2. Stoicov C, Li H, Cerny J, Houghton JM. How the study of *Helicobacter infection* can contribute to the understanding of carcinoma development. *Clin Microbiol Infect.* 2009; 15(9):813–822. [PubMed: 19702586]
3. Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer.* 2009; 100(3):551–557. [PubMed: 19156150]
4. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC-Y. Non-steroidal anti-inflammatory drug use and risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2003; 95(23):1784–1791. [PubMed: 14652240]
5. Epplein M, Nomura AM, Wilkens LR, Henderson BE, Kolonel LN. Nonsteroidal antiinflammatory drugs and risk of gastric adenocarcinoma: the multiethnic cohort study. *Am J Epidemiol.* 2009; 170(4):507–514. [PubMed: 19584132]
6. Schneider BG, Camargo MC, Ryckman KK, Sicinski LA, Piazuelo MB, Zabaleta J, Correa P, Williams SM. Cytokine polymorphisms and gastric cancer risk: an evolving view. *Cancer Biol Ther.* 2008; 7(2):157–162. [PubMed: 18059184]
7. Yu J, Zeng Z, Wang S, Tian L, Wu J, Xue L, Lee CW, Zhang M, Goggins WB, Chen M, Hu P, Sung JJ. IL-1B-511 polymorphism is associated with increased risk of certain subtypes of gastric cancer in Chinese: a case-control study. *Am J Gastroenterol.* 2010; 105(3):557–564. [PubMed: 19904240]
8. Cai H, Zheng W, Xiang YB, Xu WH, Yang G, Li H, Shu XO. Dietary patterns and their correlates among middle-aged and elderly Chinese men: a report from the Shanghai Men's Health Study. *Br J Nutr.* 2007; 98(5):1006–1013. [PubMed: 17524168]
9. Lee SA, Wen W, Xu WH, Zheng W, Li H, Yang G, Xiang YB, Shu XO. Prevalence of obesity and correlations with lifestyle and dietary factors in Chinese men. *Obesity (Silver Spring).* 2008; 16(6):1440–1447. [PubMed: 18356829]
10. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, Li HL, Wen W, Ji BT, Li Q, Shu XO, Gao YT. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol.* 2005; 162(11):1123–1131. [PubMed: 16236996]
11. Michel A, Waterboer T, Kist M, Pawlita M. *Helicobacter pylori* multiplex serology. *Helicobacter.* 2009; 14(6):525–535. [PubMed: 19889070]
12. Epplein M, Zheng W, Xiang YB, Peek RM Jr, Li H, Correa P, Gao J, Michel A, Cai Q, Pawlita M, Shu XO. Prospective study of *Helicobacter pylori* biomarkers for gastric cancer risk among Chinese men. *Cancer Epi Biomarkers Prev.* 2012; 21(12):2185–92.
13. Waterboer T, Sehr P, Michael KM, Franceschi S, Nieland JD, Joos TO, Templin MF, Pawlita M. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. *Clin Chem.* 2005; 51(10):1845–1853. [PubMed: 16099939]
14. Waterboer T, Sehr P, Pawlita M. Suppression of non-specific binding in serological Luminex assays. *J Immunol Methods.* 2006; 309(1-2):200–204. [PubMed: 16406059]

15. Epplein M, Signorello LB, Zheng W, Peek RM Jr, Michel A, Williams SM, Pawlita M, Correa P, Cai Q, Blot WJ. Race, African ancestry, and *Helicobacter pylori* infection in a low-income United States population. *Cancer Epidemiol Biomarkers Prev.* 2011; 20(5):826–834. [PubMed: 21357376]
16. Wong HL, Rabkin CS, Shu XO, Pfeiffer RM, Cai Q, Ji BT, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Chow WH. Systemic cytokine levels and subsequent risk of gastric cancer in Chinese Women. *Cancer Sci.* 2011; 102(10):1911–1915. [PubMed: 21740481]
17. Macri A, Versaci A, Loddo S, Scuderi G, Travagliante M, Trimarchi G, Teti D, Famulari C. Serum levels of interleukin 1beta, interleukin 8 and tumour necrosis factor alpha as markers of gastric cancer. *Biomarkers.* 2006; 11(2):184–193. [PubMed: 16766394]
18. Konturek SJ, Starzynska T, Konturek PC, Karczewska E, Marlicz K, Lawniczak M, Jaroszewicz-Heigelman H, Bielanski W, Hartwich A, Ziemniak A, Hahn EG. *Helicobacter pylori* and CagA status, serum gastrin, interleukin-8 and gastric acid secretion in gastric cancer. *Scand J Gastroenterol.* 2002; 37(8):891–898. [PubMed: 12229962]
19. Xue H, Liu J, Lin B, Wang Z, Sun J, Huang G. A meta-analysis of interleukin-8 -251 promoter polymorphism associated with gastric cancer risk. *PloS one.* 2012; 7(1):e28083. [PubMed: 22279522]
20. Lee SA, Kallianpur A, Xiang YB, Wen W, Cai Q, Liu D, Fazio S, Linton MF, Zheng W, Shu XO. Intra-individual variation of plasma adipokine levels and utility of single measurement of these biomarkers in population-based studies. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(11):2464–2470. [PubMed: 18006938]
21. Evans C, Morrison I, Heriot AG, Bartlett JB, Finlayson C, Dalglish AG, Kumar D. The correlation between colorectal cancer rates of proliferation and apoptosis and systemic cytokine levels; plus their influence upon survival. *Br J Cancer.* 2006; 94(10):1412–1419. [PubMed: 16641913]
22. Manavalan JS, Hernandez L, Shah JG, Konikkara J, Naiyer AJ, Roland AL, Ciaccio E, Minaya MT, Green PH, Bhagat G. Serum Cytokine Elevations in Celiac Disease: Association with Disease Presentation. *Hum Immunol.* 2009; 71(1):50–7. [PubMed: 19735687]
23. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, Bowman ED, Engels EA, Caporaso NE, Harris CC. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst.* 2011; 103(14):1112–1122. [PubMed: 21685357]

Table 1

Baseline demographic characteristics of the gastric cancer cases and matched controls in the Shanghai Men's Health Study, 2002–2009

	Cases (n=180) No. (%)	Controls (n=358) No. (%)
<i>H. pylori</i> sero-positive, n (%)	176 (97.8)	339 (94.7)
Smoking status, n (%)		
Never smoker	48 (26.7)	117 (32.7)
Former smoker	30 (16.7)	70 (19.6)
Current smoker	102 (56.7)	171 (47.8)
Fruit intake, g/day, median (IQR)	51.5 (16.4-93.7)	58.9 (21.3-119.2)
Regular aspirin use, n (%)	16 (8.9)	53 (14.8)
Diagnosis of chronic gastritis, n (%)	44 (24.4)	59 (16.5)
IL-1 , pg/mL, median (IQR)	1.03 (0.46-1.94)	0.93 (0.41-1.92)
IL-2, pg/mL, median (IQR)	4.02 (1.60-8.32)	3.86 (1.40-7.50)
IL-4, pg/mL, median (IQR)	22.00 (6.62-47.2)	17.11 (3.72-43.0)
IL-6, pg/mL, median (IQR)	1.18 (0.72-2.07)	1.17 (0.69-2.03)
IL-8, pg/mL, median (IQR)	2.38 (1.71-3.44)	2.11 (1.45-3.17)
IL-10, pg/mL, median (IQR)	18.73 (11.4-31.6)	16.63 (8.58-31.8)
TNF- , pg/mL, median (IQR)	4.57 (3.12-6.63)	4.11 (2.85-6.40)
IFN- , pg/mL, median (IQR)	12.74 (6.12-21.7)	11.12 (5.74-21.5)

Abbreviation: IQR, interquartile range

Table 2

Risk of distal gastric cancer by circulating cytokine level among 180 cases and 358 controls in the Shanghai Men's Health Study

Cytokine	Controls n (%)	Cases n (%)	Matched OR (95% CI)	Adjusted, Matched OR* (95% CI)
IL-1 (pg/mL)				
Q1 (0.41)	90 (25.1)	41 (22.8)	1.00 (Reference)	1.00 (Reference)
Q2 (0.42-0.92)	89 (24.9)	43 (23.9)	1.05 (0.62, 1.78)	1.11 (0.64, 1.91)
Q3 (0.93-1.92)	90 (25.1)	50 (27.8)	1.22 (0.73, 2.04)	1.12 (0.65, 1.92)
Q4 (1.93)	89 (24.9)	46 (25.6)	1.14 (0.67, 1.93)	1.11 (0.63, 1.94)
<i>P</i> trend			0.54	0.72
IL-2 (pg/mL)				
Q1 (1.40)	91 (25.4)	40 (22.2)	1.00 (Reference)	1.00 (Reference)
Q2 (1.41-3.85)	88 (24.6)	47 (26.1)	1.21 (0.73, 2.00)	1.32 (0.77, 2.26)
Q3 (3.86-7.50)	90 (25.1)	42 (23.3)	1.07 (0.64, 1.80)	1.09 (0.63, 1.88)
Q4 (7.51)	89 (24.9)	51 (28.3)	1.34 (0.77, 2.34)	1.39 (0.77, 2.51)
<i>P</i> trend			0.39	0.39
IL-4 (pg/mL)				
Q1 (3.72)	90 (25.1)	33 (18.3)	1.00 (Reference)	1.00 (Reference)
Q2 (3.73-16.90)	89 (24.9)	45 (25.0)	1.38 (0.80, 2.36)	1.76 (0.99, 3.15)
Q3 (16.91-43.04)	90 (25.1)	52 (28.9)	1.57 (0.94, 2.63)	1.58 (0.91, 2.74)
Q4 (43.05)	89 (24.9)	50 (27.8)	1.60 (0.91, 2.82)	1.79 (0.98, 3.26)
<i>P</i> trend			0.09	0.09
IL-6 (pg/mL)				
Q1 (0.69)	90 (25.1)	44 (24.4)	1.00 (Reference)	1.00 (Reference)
Q2 (0.70-1.17)	90 (25.1)	45 (25.0)	1.02 (0.60, 1.72)	0.95 (0.55, 1.66)
Q3 (1.18-2.093)	90 (25.1)	44 (24.4)	1.01 (0.59, 1.72)	1.03 (0.59, 1.82)
Q4 (2.04)	88 (24.6)	47 (26.1)	1.10 (0.62, 1.94)	1.12 (0.62, 2.04)
<i>P</i> trend			0.77	0.68
IL-8 (pg/mL)				
Q1 (1.45)	92 (25.7)	28 (15.6)	1.00 (Reference)	1.00 (Reference)
Q2 (1.46-2.11)	88 (24.6)	43 (23.9)	1.58 (0.91, 2.76)	1.91 (1.05, 3.46)
Q3 (2.12-3.17)	90 (25.1)	55 (30.6)	1.97 (1.16, 3.35)	2.10 (1.19, 3.74)
Q4 (3.18)	88 (24.6)	54 (30.0)	2.05 (1.17, 3.60)	2.30 (1.26, 4.19)
<i>P</i> trend			0.009	0.008
IL-10 (pg/mL)				
Q1 (8.58)	90 (25.2)	35 (19.4)	1.00 (Reference)	1.00 (Reference)
Q2 (8.59-16.63)	89 (24.9)	45 (25.0)	1.31 (0.76, 2.24)	1.39 (0.79, 2.45)
Q3 (16.64-31.76)	89 (24.9)	55 (30.6)	1.59 (0.94, 2.67)	1.55 (0.89, 2.69)
Q4 (31.77)	89 (24.9)	45 (25.0)	1.30 (0.75, 2.24)	1.45 (0.81, 2.60)
<i>P</i> trend			0.26	0.18
TNF- (pg/mL)				
Q1 (2.85)	90 (25.1)	37 (20.6)	1.00 (Reference)	1.00 (Reference)

Cytokine	Controls n (%)	Cases n (%)	Matched OR (95% CI)	Adjusted, Matched OR* (95% CI)
Q2 (2.86-4.11)	90 (25.1)	44 (24.4)	1.19 (0.70, 2.01)	1.37 (0.79, 2.37)
Q3 (4.12-6.40)	89 (24.9)	51 (28.3)	1.41 (0.84, 2.37)	1.62 (0.93, 2.84)
Q4 (6.41)	89 (24.9)	48 (26.7)	1.32 (0.77, 2.28)	1.37 (0.77, 2.44)
<i>P</i> trend			0.24	0.22
IFN- (pg/mL)				
Q1 (5.74)	90 (25.1)	43 (23.9)	1.00 (Reference)	1.00 (Reference)
Q2 (5.75-11.07)	89 (24.9)	40 (22.2)	0.94 (0.55, 1.60)	0.91 (0.52, 1.60)
Q3 (11.08-21.53)	90 (25.1)	50 (27.8)	1.15 (0.69, 1.90)	1.00 (0.59, 1.71)
Q4 (21.54)	89 (24.9)	47 (26.1)	1.09 (0.65, 1.83)	1.07 (0.62, 1.85)
<i>P</i> trend			0.56	0.73

* matched odds ratio from conditional logistic regression, additionally adjusted for history of gastritis (yes/no), regular aspirin use (yes/no), smoking status (current smoker/not current smoker), and number of sero-positives to 6 *H. pylori* virulence proteins (Omp, HP0305, HyaA, HpaA, CagA, and VacA).