Interactions between pork consumption, CagA status and IL-1B-31 genotypes in gastric cancer

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Abstract

AIM: To explore potential interactions among Helicobacter pylori (H. pylori), CagA status, interleukin (IL)-1B-31 genotypes, and non-cardiac gastric cancer (GC) risk.

METHODS: A case-control study of non-cardia GC was performed at 3 hospitals located in Xi’an, China, between September 2008 and July 2010. We included 171 patients with histologically diagnosed primary non-cardia GC and 367 population based controls (matched by sex, age and city of residence). A standardized questionnaire was used to obtain information regarding potential risk factors, including pork consumption. H. pylori CagA status was assessed by enzyme-linked immunosorbent assay, and IL-1B-31 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism. Multivariate unconditional logistic regression was used to explore potential interactions among the factors.

RESULTS: The CagA appeared to confer an increased risk of GC (OR = 1.81, 95%CI: 1.25-2.61). The main associations with IL-1B-31C allele were 0.98 (95%CI: 0.59-1.63) for CC vs TT and 0.99 (95%CI: 0.64-1.51) for C Carriers vs TT. However, no associations were observed for CagA or IL-1B-31 genotype status among subjects who reported low pork consumption (P for interaction = 0.11). In contrast, high pork consumption and IL-1B-31C genotypes appeared to synergistically increase GC risk (P for interaction = 0.048) after adjusting for confounding factors, particularly among subjects with CagA (OR = 3.07, 95%CI: 1.17-10.79). We did not observe effect modification of pork consumption by H. pylori CagA status, or between H. pylori CagA status and IL-1B-31 genotypes after adjustment for pork consumption and other factors.

CONCLUSION: These interaction relationships among CagA, IL-1B-31 and pork consumption may have implications for development of the preventive strategies for the early detection of non-cardiac GC.

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Key words: Gastric cancer; Pork; CagA; interleukin-1B; Interaction; Helicobacter pylori
genetic factors are implicated in gastric carcinogenesis, which is a long, complicated, and multi-stage process. The Helicobacter pylori (H. pylori) virulence factor CagA has been shown to be polymorphic and to contribute to disease pathogenesis in an allele-dependent manner. The interleukin (IL)-1 gene plays an important role in determining the long-term outcome of H. pylori infection. Dietary factors such as pork consumption may contribute to the malignancy process in synergy with these genetic factors and infectious agents. Our study further explores potential interactions among dietary (pork intake), infectious (H. pylori CagA positive) and genetic factors (IL-1B-31 genotypes) on gastric cancer risk.

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INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related mortality in the world. It is widely known that infectious, dietary, and genetic factors are implicated in gastric carcinogenesis, which is a long, complicated, and multi-stage process[4]. GC is strongly associated with Helicobacter pylori (H. pylori) infection; however, most infected persons never develop this malignancy. The H. pylori virulence factors CagA and VacA have each been shown to be polymorphic and to contribute to disease pathogenesis in an allele-dependent manner[4]. The most studied of these is CagA effector protein[5], a 120e 145-kDa protein[6], which is located at the end of an approximately 40-kb cluster of genes called cag pathogenicity island (PAI). Cag PAI encodes a type-IV secretion system and transfers CagA protein into host cells[7]. Upon entering the host cells, CagA can trigger IL-8 secretion, thereby priming an inflammatory response[8,9] and promoting cell proliferation, scattering and migration through phosphorylation-dependent and independent mechanisms[10].

The interleukin (IL)-1 gene plays an important role in determining the long-term outcome of H. pylori infection[8]. It contains three related genes, IL-1A, IL-1B, and IL-1RN, which encode the pro-inflammatory cytokines IL-1a and IL-1b[9]. IL-1b regulates the expression of several genes involved in inflammation. It is encoded by a 7.5 kb gene, and the expression is regulated by both distal and proximal promoter elements[10,11]. The polymorphisms of IL-1B-31T/C in the promoter region of the gene have been intensively studied[12]. The first published report showed a positive association between GC and the IL-1B-31C allele[13], which has been confirmed in subsequent studies[14,15].

The consumption of red meat and processed meat has risen in developed and developing countries, which may have implications for GC occurrence[16-18]. Pork is the major red meat consumed by people in China[19]. Some previous studies have found positive associations between the consumption of pork and GC risk[20,21], whereas others have not[22-24]. Five studies were included in a meta-analysis in 2013, and the summary relative risk of the association between pork and GC risk was 1.31 (95%CI: 0.97-1.78)[25]. Hence, a positive association has been suggested, but remains inconclusive.

Several interactions have been noted among these variables. For example, H. pylori infected individuals with the IL-1B-31CC genotype tend to secrete less IL-1B and appear to be more susceptible to precancerous lesions[26]. Perhaps noteworthy, a statistically significant interaction was found between IL-1B-31 and CagA status for the risk of intestinal-type GC in a Mexican population[27]. Furthermore, red meat intake was found to interact with H. pylori infection in the development of GC in the EPIC study[28], which showed that red meat intake was associated with an increased risk of non-cardia gastric cancer, particularly in H. pylori antibody-positive subjects. In contrast, our previous case-control study found that red meat intake did not interact with H. pylori infection in the process of gastric carcinogenesis[29], possibly because specific host genetic factors, such as IL-1B-31, were not considered. Therefore, our present study aimed to explore potential interactions among H. pylori status, IL-1B-31C genotypes, pork consumption and GC risk.

MATERIALS AND METHODS

Ethics

This study was approved by the Ethics Committee of the School of Medicine, Xi’an Jiaotong University. All patients provided informed written consent.

Study population

We included 171 patients with non-cardia GC and 367 population-based controls who had serum samples available for DNA extraction. The original study included 257 cases and 514 controls, and was undertaken between September 2008 and July 2010[25]. All cases were aged 30 to 79 years and had pathologically confirmed non-cardia GC. Patients with other major chronic diseases, including other forms of cancer (particularly diseases affecting dietary patterns or communication), were excluded. After identification, eligible patients or their family members were invited to sign consent forms and participate in the study. Two population-based controls were matched to each case by age (± 5 years), sex, and city of residence. The control subjects were confirmed to be free of cancer, diabetes, and gastrointestinal disorders.

Pork consumption

We measured the pork consumption of study participants using a Food Frequency Questionnaire[28]. Participants were asked about the average frequencies and
portion sizes of 121 food items consumed during the preceding year, including the type of pork dishes that were typically consumed in the study region. If dietary changes had occurred during the past year, information regarding dietary habits prior to the change was elicited.

The quantity of each food item was represented by a Chinese food weight unit, Liang (equivalent to 50 g), for most investigated food items. Food consumption frequency was ranked in 9 categories: from “never or less than 1 time per month” to “2 or more times per day.” Food items were grouped based on the China Food Composition 2004 classification proposed by the Chinese Center for Disease Control[31]. We previously validated the food frequency questionnaire using a 24-h diet record[32]. For pork consumption, the Pearson correlation coefficients of the validity and reproducibility of the food frequency questionnaire were 0.49 and 0.58, respectively.

Other measured variables
Several non-dietary variables were assessed through the use of a general questionnaire. This questionnaire included items regarding personal and family medical history, medications used, physical activity (number of hours of sedentary activities, and light, moderate, or heavy physical activities), alcohol consumption (number of alcoholic beverages per week), smoking (age at commencement and smoking intensity), and lifestyle factors (e.g., vitamin supplement intake, refrigerator use).

H. pylori CagA status
The antibody to H. pylori was tested with an enzyme-linked immunosorbert assay kit (Human HP-Ap enzyme-linked immunosorbert assay Kit, San Diego, CA). A finding of at least 10 units per milliliter in the blood was considered to indicate the presence of antibody against H. pylori. CagA-positive H. pylori infection was defined as the presence of CagA antibody in the serum.

Genotyping
The primer was designed with Primer Premier 5 software and synthesized by the Invitrogen Company (ILB-31 forward, GAAGCTTCCACCAATACTC and reverse, AGCACCTAGTTGTAAGGAAG). Genotyping for IL-1B-31 (T/C) polymorphisms was performed by means of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). It was performed in a 50 μL PCR mixture containing 10 × buffer 5 μL, MgCl2 23 μL, dNTP 3 μL, upstream and downstream primers 1 μL, respectively, 1.25 U DNA polymerase, DNA 50 ng, with sterile distilled water added to 50 μL. Thermal cycling conditions were 94 ℃ for 5 min 45 s; 35 cycles of 94 ℃ for 45 s, 56 ℃ for 45 s, and 72 ℃ for 45 s, and 72 ℃ for 5 min. PCR products were digested by Alu I restriction enzyme (the mixture: PCR product 10 μL, Alu I 10 U, 10 × buffer Tango TM 3 μL, with sterile distilled water added to 30 μL, followed by incubation at 37 ℃ overnight). The genotype was determined by agarose gel electrophoresis.

Statistical analysis
For selected sociodemographic characteristics, IL-1B-31 genotype frequencies, pork consumption and H. pylori CagA status, comparisons between cases and controls were made using t tests and χ2 tests. The association between IL-1B-31 genotypes and GC risk according to H. pylori CagA status and pork consumption was evaluated using unconditional logistic regression models with adjustment for age, gender, education, smoking, alcohol, and family history. To estimate the combined effects of pork consumption, H. pylori CagA status, and IL-1B-31 genotypes, pork consumption was separated in two categories according to the mean distribution of the control group, the low (< 25 g/d) and high consumption categories (> 25 g/d). The multiplicative terms between pork consumption (high/low), H. pylori CagA status (positive/negative) and/or IL-1B-31 (C/T alleles) were introduced in separate models to determine the statistical significance of the Wald χ2 test for the interaction term. SPSS software version 17.0 (IBM, Armonk, NY) was used to perform all statistical analyses.

RESULTS
The characteristics of study subjects are presented in Table 1. The distributions of gender and education levels were not significantly different between cases and controls. The proportion of individuals with seropositive status was higher in cases (59.06%) than in controls (44.41%) (P = 0.002). The main association with Cag A here was 1.81 (95%CI: 1.25-2.61). There were no significant crude differences between groups based on pork consumption and genotype frequencies of IL-1B-31. The IL-1B-31C allele didn’t appeared to confer an increased risk of GC (OR = 0.98, 95%CI: 0.59-1.63). There were no significant differences between cases and controls in serum anti-CagA antibody levels. Furthermore, no significant interaction between pork consumption and genotype frequencies of IL-1B-31 did not depart from those expected under Hardy-Weinberg equilibrium[32].

The IL-1B-31C allele appeared to confer an increased risk, particularly among CagA-positive subjects with high pork consumption (OR = 3.07, 95%CI: 1.17-10.79) (Table 2). Pork consumption and IL-1B-31C alleles synergistically increased GC risk (P for interaction = 0.048), whereas pork consumption did not show interaction with H. pylori CagA status (P for interaction = 0.11).

No association was found among high pork consumers who were H. pylori CagA seronegative. Furthermore, no associations with GC risk were found among low pork consumers based on their CagA or IL-1B-31 genotype status. In multivariate models that adjusted for pork consumption and other factors, we did not observe statistically significant interaction between H. pylori CagA status.
and IL-1B-31 genotypes.

**DISCUSSION**

In the present study, we observed an increased GC risk among individuals with high pork consumption, particularly among subjects who were both *H. pylori* (CagA) positive and genetically susceptible (IL-1B-31C) allele carriers. If further studies confirm that CagA, IL-1B-31 and high pork consumption interact in the development of GC, this would have implications for cancer prevention in China, a country with notably high rates of GC.

Regarding a possible interaction between IL-1B-31 genotype and CagA status, our present study showed a marginally significant interaction term for the risk of GC (P = 0.078), a finding we consider interesting in light of the results of three previously epidemiological studies. Charkravorty's study showed that *H. pylori*-infected individuals with the IL-1B-31CC genotype secrete less IL-1B and may have increased susceptibility to precancerous lesions.[32] Rad's study found that carriers of the proinflammatory *IL-1B-511T/-31C* and *IL-1RN2* alleles had an increased risk for the development of intestinal metaplasia, atrophic gastritis (AG), and severe inflammation, with ORs of 1.7 (95%CI: 0.8-3.4) to 4.4 (95%CI: 1.5-12.9).[33] Liviu's study found a statistically significant interaction between *IL-1B-31* and *CagA* status for the risk of intestinal-type GC (*P* = 0.023).[34]

It was hypothesized that some GCs may be the outcome of a synergy between effects of the *IL-1B-31C* carrier and the *CagA* positive *H. pylori* microorganisms, which can induce and amplify the inflammatory response, and thereby cause *IL-1B* secretion and hypochlorhydria.[35]

As the major virulence factor of *H. pylori*, CagA disturbs cellular functions by physically interacting with and deregulating intracellular signaling molecules *via* both tyrosine phosphorylation dependent and independent mechanisms after delivery into gastric epithelial cells.[34] Once translocated into host cytoplasm, CagA may bind to the inner surface of the cell membrane and undergo

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**Table 1** Demographic data of cases and controls *n* (%)

| Characteristic               | Cases *n* = 171 | Controls *n* = 367 | t/*t*² | *P* value |
|------------------------------|-----------------|--------------------|--------|-----------|
| Age (yr, mean ± SD)          |                 |                    |        |           |
| Male                         | 56.93 ± 14.01   | 56.81 ± 13.90      | 0.093  | 0.440     |
| Female                       | 118 (69.01)     | 243 (66.21)        | 0.412  | 0.521     |
| Education                    |                 |                    |        |           |
| Primary                      | 51 (29.82)      | 177 (48.23)        | 0.332  | 0.847     |
| Secondary                    | 84 (49.12)      | 179 (48.77)        |        |           |
| Tertiary and postgraduate    | 36 (21.06)      | 71 (19.35)         |        |           |
| BMI (kg/m²)                  |                 |                    |        |           |
| ≤ 25                         | 110 (64.33)     | 244 (66.49)        | 0.365  | 0.794     |
| > 25                         | 61 (35.67)      | 123 (33.51)        |        |           |
| *H. pylori* CagA positive    |                 |                    |        |           |
| IL-1B-31                      |                 |                    |        |           |
| TT                           | 41 (23.98)      | 89 (24.25)         | 0.005  | 0.997     |
| TC                           | 84 (49.12)      | 180 (49.05)        |        |           |
| CC                           | 46 (26.90)      | 98 (26.70)         |        |           |
| C carrier                     | 130 (76.02)     | 278 (75.75)        |        |           |
| Pork consumption             |                 |                    |        |           |
| < 25 g/d                     | 89 (52.05)      | 177 (48.23)        | 0.680  | 0.410     |
| ≥ 25 g/d                     | 82 (47.95)      | 190 (51.77)        |        |           |

1For t test. *P* < 0.05 vs control group. BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; IL: Interleukin.

**Table 2** Joint effects of pork consumption, CagA status and interleukin-1B-31 genotypes on the risk of gastric cancer¹

| Genotype of IL-1B-31 | Low (< 25 g/d) | High (≥ 25 g/d) |
|----------------------|----------------|-----------------|
|                      | CagA (-) | CagA (+) | Case/control OR | CagA (-) | CagA (+) | Case/control OR |
|                      |          |          |                  |          |          |                  |
| TT                   | 9/15     | 1/30     | 0.42 (0.14-1.11) | 20/49    | 1.25 (0.47-2.81) | 23/34    | 2.98 (0.99-11.30) |
| TC                   | 11/58    | 30/39    | 0.71 (0.31-1.98) | 27/25    | 0.86 (0.29-2.35) | 16/23    | 3.11 (1.08-12.66) |
| CC                   | 12/27    | 11/23    | 0.46 (0.16-1.54) | 27/74    | 1.00 (0.48-2.06) | 39/57    | 3.07 (1.17-10.79) |
| C carrier            | 23/85    | 41/62    | 0.45 (0.18-1.37) | 27/74    | 1.00 (0.48-2.06) | 39/57    | 3.07 (1.17-10.79) |

1Adjusted for the following confounding factors: age, gender, education, smoking, alcohol, and family history. P for multiplicative interaction: Pork consumption and *Helicobacter pylori* (*H. pylori*) CagA status: 0.11 (adjusted by age, gender, education, smoking, alcohol, family history and interleukin (IL)-1B-31 C carrier); Pork consumption and IL-1B-31 C carrier: 0.048 (adjusted by age, gender, education, smoking, alcohol, family history and *H. pylori* CagA status).
tyrosine phosphorylation\cite{38}. The phosphorylated and unphosphorylated forms of CagA interact with a number of host proteins to activate downstream signal pathways, such as inducing ornithine decarboxylase upregulation via Src/MEK/ERK/c-Myc pathway\cite{39} and directing REG3γ expression in gastric epithelial cells via activation of the IL-11/gp130/STAT3 pathway\cite{40}. Non-phosphorylated CagA may activate the hepatocyte growth factor/scatter factor receptor c-Met and adaptor protein Grb2, induce phosphorylation of phospholipase C gamma and impair the E-cadherin/b-catenin complex formation, and mediate the inhibition of the kinase partitioning-defective 1b/microtubule affinity-regulating kinase 2 (PAR1b/ MARK2) to perturb atypical protein kinase C signaling\cite{30}. In a recent experiment\cite{30}, transgenic zebrafish expressing either the wild-type or a phosphorylation-resistant form of CagA exhibited significantly increased rates of intestinal epithelial cell proliferation and showed significant up-regulation of the Wnt target genes cyclinD1, axin2 and the zebrafish c-mycolthromyoga. Additionally, CagA was shown to induce higher levels of IL-8 production, activate nuclear factor κB (NF-κB), AP-1 and FAK\cite{37}, and enhance the activity of transforming growth factor-β-activated kinase 1 (TAK1) and TAK1-induced NF-κB activation via the TRAF6-mediated K63-linked ubiquitination of TAK1, which in turn is used by CagA for the H. pylori induced inflammatory response\cite{39}. This might also inhibit miR-370 expression, which may lead to over-expression of FoxM1 and consequent increased intestinal cell proliferation\cite{40}. These findings suggest multiple roles of CagA in gastric carcinogenesis.

Our study has several limitations. Given our case-control study design, information regarding past pork consumption may have been misclassified to some extent. To reduce misclassification of dietary exposures, we designed and validated our questionnaire using the 24-h diet record method\cite{41}. The results showed that the questionnaire had reasonable validity and reliability. Nonetheless, the misclassification of diet remains a potential source of bias in our data. Another limitation is the potential misclassification of H. pylori infection status. In the present study, H. pylori was detected after non-cardia GC was diagnosed; hence, infection may not have been present in all subjects as premalignant lesions progressed\cite{42}. This type of misclassification would tend to attenuate the association between H. pylori infection and non-cardia GC. Additionally, the sample size of the present study was not optimal for the analysis of the potential interactions among pork intake, infectious (CagA) and genetic factors (IL-1B-31C genotypes) on GC risk. Therefore, it is possible that some of our modeled interaction terms did not reach statistical significance due to insufficient sample size.

In summary, we found statistically significant interactions among CagA, IL-1B-31 and high pork consumption in their association with non-cardiac GC. In China, people consume much more pork than beef and lamb, and the majority of individuals are H. pylori CagA positive. These findings may have implications for primary prevention, and also secondary preventive measures aimed at the early detection of GC in China. For example, a greater understanding of how common exposures interact in GC etiology may lead to selective screening of high-risk individuals based, at least in part, on levels of those interacting risk factors.

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COMMENTS

Background

It is widely known that infectious, dietary, and genetic factors are implicated in gastric carcinogenesis, which is a long, complicated, and multi-stage process. Thus, gastric cancer might be caused by potential interactions among dietary (pork intake), infectious and genetic factors.

Research frontiers

The Helicobacter pylori (H. pylori) virulence factor CagA has been shown to be polymorphic and to contribute to disease in an allele-dependent manner. The interleukin (IL)-1 gene plays an important role in determining the long-term outcome of H. pylori infection. Dietary factors such as pork consumption may contribute to the malignant process in synergy with these genetic factors and infectious agents.

Innovations and breakthroughs

The study further explores potential interactions among dietary (pork intake), infectious (H. pylori CagA positive) and genetic factors (IL-1B-31C genotypes) on gastric cancer (GC) risk.

Applications

These findings may have implications for preventive measures aimed at the early detection of GC in China. For example, a greater understanding of how common exposures interact in GC etiology may lead to selective screening of high-risk individuals based, at least in part, on levels of those interacting risk factors.

Terminology

CagA effector protein, a 120E 145-kDa protein, is located at the end of an approximately 40-kb cluster of genes called cag pathogenicity island. The IL-1 gene contains three related genes, IL-1α, IL-1β, and IL-1RN, which encode the pro-inflammatory cytokines IL-1α and IL-1β. IL-1β regulates the expression of several genes involved in inflammation. Both CagA and IL-1B-31 may play a modifying role in the association between pork and GC risk.

Peer review

This is a good case-control study in which authors explored the interactions among dietary (pork intake), infectious (H. pylori) and genetic factors (IL-1B-31C genotypes). These findings may have implications for preventive measures aimed at the early detection of GC in China. The results are interesting and may represent multi-factor interaction mechanism of gastric carcinogenesis.

REFERENCES

1. Kuo SH, Chen LT, Lin CW, Wu MS, Hsu PN, Tsai HJ, Chu CY, Tseng YS, Wang HP, Yeh KH, Cheng AL. Detection of the Helicobacter pylori CagA protein in gastric mucosa-associated lymphoid tissue lymphoma cells: clinical and biological significance. Blood Cancer J 2013; 3: e125 [PMID: 23852160 DOI: 10.1038/bcj.2013.22]
2. Bridge DR, Merrell DS. Polymorphism in the Helicobacter pylori CagA and VacA toxins and disease. Gut Microbes 2013; 4: 101-117 [PMID: 23836466 DOI: 10.4161/gmic.23797]
3. Wandler AM, Guillem K. Transgenic expression of the Helicobacter pylori virulence factor CagA promotes apoptosis or tumorigenesis through JNK activation in Drosophila.
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PLoS Pathog 2012; 8: e1002939 [PMID: 23093933 DOI: 10.1371/journal.ppat.1002939]

Cavaci 2012; 4: 1573-1581 [PMID: 20141053 DOI: 10.1111/j.1465-5228.2008.01156.x]

Wei GC 2012; 4: 1039-1044 [PMID: 23226771]

Backert 2012; 5: 1369-1379 [PMID: 22307293]

Dinarello 2012; 18: 478-486 [PMID: 28663705]

Shirakawa 2012; 5: 985-995 [PMID: 22745034]

Lind H 2012; 13: 1332-1344 [PMID: 24413797]

Monks BG 2012; 1993; 13: 1332-1344 [PMID: 24413797]

Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Kubo T, Tamakoshi A. Dietary habits and stomach cancer in the JACC Study. J Epidemiol 2005; 15 Suppl 2: 598-108 [PMID: 16127240]

Zhu H, Yang X, Zhang C, Zhu C, Tao G, Zhao L, Tang S, Hu Z, Cai J, Dai S, Qin Q, Xu L, Cheng H, Sun X. Red and processed meat intake is associated with higher gastric cancer risk: a meta-analysis of epidemiological observational studies. PLoS One 2013; 8: e70955 [PMID: 23967140 DOI: 10.1371/journal.pone.0070955]

Chakravorty M, Ghosh A, Choudhury A, Sastra A, Hembru J, Roychoudhury S. Interaction between IL1B gene promoter polymorphisms in determining susceptibility to Helicobacter pylori associated duodenal ulcer. Hum Mutat 2006; 27: 411-419 [PMID: 16505502]

Queiroz DM, Guerra JB, Rocha GA, Rocha AM, Santos A, De Oliveira AG, Cabral MM, Nogueira AM, De Oliveira CA. IL1B and IL1RN polymorphic genes and Helicobacter pylori cagA strains decrease the risk of reflux esophagitis. Gastroenterology 2004; 127: 73-79 [PMID: 15256174]

González CA, Jakszyn P, Pera G, Agudo A, Bingham S, Fali delli, F, Ferrari P, Boeing H, del Giudice G, Plebani M, Carneiro F, Nesi G, Berrino F, Sacerdote C, Tumino R, Ber- lugund G, Simán H, Nyrén O, Hallmans G, Martinez C, Dor- ronoro M, Barricarte A, Navarro C, Quirós JR, Allen N, Key TJ, Day NE, Linseisen J, Nagel G, Bergmann MM, Overvad K, Jensen MK, Tjønneland A, Olsen A, Bueno-de-Mesquita HB, Ocke M, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Trichopoulou A, Psaltopoulou T, Rouskos D, Lund E, Hemon B, Kaaks R, Norat T, Riboli E. Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006; 98: 345-354 [PMID: 16507831]

Wang XQ, Yan H, Terry PD, Wang JS, Cheng L, Wu WA, Hu SK. Interaction between dietary factors and Helicobacter pylori infection in noncardia gastric cancer: a population-based case-control study in China. J Am Coll Nutr 2012; 31: 375-384 [PMID: 23529995]

Wang X, Sa R, Yan H. Validity and reproducibility of a food frequency questionnaire designed for residents in north China. Asia Pac J Clin Nutr 2008; 17: 629-634 [PMID: 19114401]

Yang Y, Wang G, Pan X. “Food Composition Table of China 2004.” Beijing: Beijing University Press, 2004: 5-150

Sham P. Statistics in human genetics. London: Arnold Publishers, 2001: 50-79

Rad R, Frinz C, Neu B, Neuhofer M, Zeirnmer M, Voland P, Becker I, Scheppe W, Gerhard M. Synergistic effect of Heli-
cobacter pylori virulence factors and interleukin-1 polymorphisms for the development of severe histological changes in the gastric mucosa. J Infect Dis 2003; 188: 272-281 [PMID: 12854083]

34 Liu Z, Xu X, Chen L, Li W, Sun Y, Zeng J, Yu H, Chen C, Jia J. Helicobacter pylori CagA inhibits the expression of Runx3 via Src/MEK/ERK and p38 MAPK pathways in gastric epithelial cell. J Cell Biochem 2012; 113: 1080-1086 [PMID: 22266963 DOI: 10.1002/jcb.23440]

Available from: URL: http://www.fsis.usda.gov/wps/portal/fsis/topics/food-safety-education/get-answers/food-safety-fact-sheets/meat-preparation/fresh-pork-from-farm-to-table/CT-Index

36 Xu X, Liu Z, Fang M, Yu H, Liang X, Li X, Liu X, Chen C, Jia J. Helicobacter pylori CagA induces ornithine decarboxylase upregulation via Src/MEK/ERK/c-Myc pathway: implication for progression of gastric diseases. Exp Biol Med (Maywood) 2012; 237: 435-441 [PMID: 22442341 DOI: 10.1258/ebm.2011.011199]

37 Lee KS, Kalantzis A, Jackson CB, O’Connor L, Murata-Kamiya N, Hatakeyama M, Judd LM, Giraud AS, Menheniott TR. Helicobacter pylori CagA triggers expression of the bactericidal lectin REG3γ via gastric STAT3 activation. PLoS One 2012; 7: e30786 [PMID: 22312430 DOI: 10.1371/journal.pone.0030786]

38 Neal JT, Peterson TS, Kent ML, Guillemain K. H. pylori virulence factor CagA increases intestinal cell proliferation by Wnt pathway activation in a transgenic zebrafish model. Dis Model Mech 2013; 6: 802-810 [PMID: 23471915 DOI: 10.1242/dmm.011163]

39 Lamb A, Yang XD, Tsang YH, Li JD, Higashi H, Hatakeyama M, Peek RM, Blanke SR, Chen LF. Helicobacter pylori CagA activates NF-kappaB by targeting TAK1 for TRAF6-mediated Lys 63 ubiquitination. EMBO Rep 2009; 10: 1242-1249 [PMID: 19820695 DOI: 10.1038/embor.2009.210]

40 Feng Y, Wang L, Zeng J, Shen L, Liang X, Yu H, Liu S, Liu Z, Sun Y, Li W, Chen C, Jia J. FoxM1 is overexpressed in Helicobacter pylori-induced gastric carcinogenesis and is negatively regulated by miR-370. Mol Cancer Res 2013; 11: 834-844 [PMID: 23576572 DOI: 10.1158/1541-7786.MCR-13-0007]

41 Muñoz N, Kato I, Peraza S, Lopez G, Carrillo E, Ramirez H, Vivas J, Castro D, Sanchez V, Andrade O, Buatti E, Oliver W. Prevalence of precancerous lesions of the stomach in Venezuela. Cancer Epidemiol Biomarkers Prev 1996; 5: 41-46 [PMID: 8770465]
