World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v3.i9.128

World J Clin Oncol 2012 September 10; 3(9): 128-136
ISSN 2218-4333 (online)

EDITORIAL

Advances in gastric cancer prevention

Antonio Giordano, Letizia Cito

Antonio Giordano, Letizia Cito, INT-CROM, "Pascale Foundation" National Cancer Institute-Cancer Research Center, 83013 Mercogliano, Italy
Antonio Giordano, Human Pathology and Oncology Department, University of Siena, 53100 Siena, Italy
Author contributions: Cito L wrote this manuscript; and Giordano A supervised and edited the final version.
Correspondence to: Letizia Cito, PhD, INT-CROM, "Pascale Foundation" National Cancer Institute-Cancer Research Center, 83013 Mercogliano, Italy. letizia.cito@cro-m.eu
Telephone: +39-825-1911736 Fax: +39-825-1911705
Received: April 20, 2012 Revised: August 19, 2012
Accepted: September 6, 2012
Published online: September 10, 2012

Abstract

Gastric cancer is a multifactorial neoplastic pathology numbering among its causes both environmental and genetic predisposing factors. It is mainly diffused in South America and South-East Asia, where it shows the highest morbility percentages and it is relatively scarcely diffused in Western countries and North America. Although molecular mechanisms leading to gastric cancer development are only partially known, three main causes are well characterized: *Helicobacter pylori* (*H. pylori*) infection, diet rich in salted and/or smoked food and red meat, and epithelial cadherin (*E-cadherin*) mutations. Unhealthy diet and *H. pylori* infection are able to induce in stomach cancer cells genotypic and phenotypic transformation, but their effects may be crossed by a diet rich in vegetables and fresh fruits. Various authors have recently focused their attention on the importance of a well balanced diet, suggesting a necessary dietary education starting from childhood. A constant surveillance will be necessary in people carrying *E-cadherin* mutations, since they are highly prone in developing gastric cancer, also within the inner stomach layers. Above all in the United States, several carriers decided to undergo a gastrectomy, preferring changing their lifestyle than living with the awareness of the development of a possible gastric cancer. This kind of choice is strictly personal, hence a decision cannot be suggested within the clinical management. Here we summarize the key points of gastric cancer prevention analyzing possible strategies referred to the different predisposing factors. We will discuss about the effects of diet, *H. pylori* infection and *E-cadherin* mutations and how each of them can be handled.

Key words: Cancer; Prevention; Diet; Vegetables; Cell cycle; Lifestyle; *Helicobacter pylori*

Peer reviewers: Jing Shen, MD, PhD, Assistant Professor, Department of Environmental Health Sciences, Columbia University, 630 West 168th Street, P and S 19-418, New York, NY 10032, United States; Wei-Hong Wang, MD, PhD, Professor, Departmant of Gastroenterology, First Hospital, Peking University, No.8, Xishiku street, West District, Beijing 100034, China

Giordano A, Cito L. Advances in gastric cancer prevention. *World J Clin Oncol* 2012; 3(9): 128-136 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i9/128.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i9.128

INTRODUCTION

Gastric carcinoma is one of the most frequent cancers and it can be considered one of the major contributors to mortality worldwide[1]. Environmental and genetic causes may be involved and a pivotal role in reducing the incidence of gastric carcinoma may be addressed to prevention. Diet rich in salted and smoked food, so as *Helicobacter pylori* (*H. pylori*) infection, are the best known environmental causes[2-6], whereas epithelial cadherin (*E-cadherin*) and runt-related transcription factor 3 (*RUNX3*) loss of expression are often genetic trademarks of gastric cancer[7-11]. Hence, prevention might be considered from different viewpoints. A general improvement of lifestyle, including a diet rich in vegetables and a reduced intake of red meat and of alcohol[12] may be helpful in preventing gastric cancer, yet more specific strategy have

to be adopted according to different people environmental and genetic background. In some cases, such as in families carrying *E-cadherin* mutations, prevention may be focused above all on well scheduled endoscopies and, sometimes, preventive gastrectomy may be the most suitable choice[13,14].

H. pylori infection and unhealthy diet cause epigenetic and genetic modification, respectively, in stomach cells. In fact, higher methylation levels were found both in some marker CpG islands[15] and in promoter regions of microRNA genes[16,17] in patients suffering from *H. pylori* infection. On the other hand, high N-nitroso compounds were found in case of diet rich in red meat, whereas polycyclic aromatic hydrocarbons and heterocyclic amines are typical of high intake of smoked and roasted food. All these compounds are highly mutagenic, hence their introduction through nutrition represents an important predisposing factor to stomach cells carcinogenic transformation. Mechanisms by which high consumption of salted food contribute to gastric cancer development have been not completely clarified so far, yet a synergic action with *H. pylori* and N-nitroso compounds[18-20] and an increase in inflammatory response of gastric epithelium were found[21].

Prevention of gastric cancer has to be performed acting on two different directions: removing and contrasting possible causes. Considering diet habits, a powerful strategy is represented by replacing processed with fresh food, taking care of introducing high intake of vegetables. Adopting a healthy diet is an effective approach to prevent stomach tumors in people suffering or not, from *H. pylori* infection. Yet, in this last case a suitable eradication therapy has to be established and a well scheduled follow-up has to performed. Here we will discuss in detail all these different sides, together with the prevention strategy of gastric cancer caused by *E-cadherin* mutations.

PREVENTION OF GASTRIC CANCER IN PEOPLE SUFFERING FROM *H. PYLORI* INFECTION

H. pylori is a gram-negative bacterium colonizing stomach which may cause gastritis in infected patients. It is able to survive in gastric acidic environment because of its capability of synthesizing urease, an enzyme which can neutralize the stomach acidic pH[22]. Various papers focused their attention on the pivotal role exerted by cytotoxic associated genes in the pathogenicity island (*Cag PAI*), vacuolating toxin A and *IceA* (induced by contact with epithelium A), whose positivity characterizes different *H. pylori* strains, in clinical response of patients[23-25]. More specifically, their data show that in genesis of gastric cancer a key role may be exerted by *Cag PAI*[26-28], a group of about 30 genes encoded by a 40 kilobases region. Among the thirty related proteins, some of them are involved in the constitution of type Ⅳ secretion system (T4SS) a "molecular syringe"[22,29] helping CagA (a protein belonging to the *Cag PAI* group) to enter into gastric cells cytosol. CagA has been considered the most important virulence factor involved in gastric cancer development mediated by *H. pylori*[30-32], although in a recent paper Rizzato *et al*[33] highlighted other important genes, such as *CagE* and *CagL*, whose polymorphisms may affect patients clinical outcome. *H. pylori* seems to exert a role in mechanisms leading to gastric cancer by inducing methylation in different genes[33], interfering with apoptotic pathways[34] and by causing inflammatory events leading to gastritis, then to atrophic gastritis and possibly to gastric cancer[35-38]. The infection is generally treated by triple therapy, based on proton pump inhibitor-clarithromycin-amoxicillin or metronidazole treatment[39], yet this strategy recently produced disappointing results[40-43]. A possible explanation was referred to an increase of *H. pylori* strains showing clarithromycin resistance[40,44-46] which challenged different studies focused on different therapeutic protocols. These are based on drugs administrations deferred over time, the so called sequential 10-d therapy[47-49], on the concomitant four drugs administration[50], or on both[51].

In spite of the increased successes and improvements of therapies to eradicate *H. pylori*, controversial data[6,52,53] are referred to similar successful decrease of gastric cancer due to eradication itself. Most of papers discussing this paradox show by consent that a key role may be referred to the step of the gastric disease development in which eradication therapy is performed. So, an early eradication therapy, during young age, is more effective in preventing gastric cancer, rather than a therapy performed in elder age, when phenotypic and genotypic transformations induced by *H. pylori* are more serious[54-57]. Then, prevention of gastric cancer in people affected by *H. pylori* may be performed starting by an early diagnosis followed by an early eradication therapy.

Recent papers describe new forms of gastric cancer developing after *H. pylori* eradication therapy. Yamamoto *et al*[58] focused their attention on phenotypic and genotypic differences gastric cancers arising in patients undergone to the therapy and patients not undergone, but suffering from the infection. Matsuo *et al*[59], instead, studied patients undergone to eradication therapy, patients not undergone and patients negative for *H. pylori* infection. Results gained by the two groups showed discrepancy about histotype of gastric cancers arisen in patients treated to eradicate *H. pylori*, since Yamamoto *et al*[58] found prevalence of diffuse histotype, while Matsuo *et al*[59] found prevalence of intestinal histotype. These differences suggest the need of considering a higher number of patients, but these studies highlight the possibility of developing gastric carcinoma also after eradication therapy.

H. pylori is a powerful carcinogen, belonging to group 1, according to the International Agency for Research on Cancer[60], since it is able to induce genetic changes, such as hypermethylation events[34,61], contributing to cell transformation[62]. Hence, a support strategy in preven-

tion *H. pylori* carcinogenic potential may be focused in reducing its infective potential. A significant contribution may derive from food. Broccoli sulforaphane exerts protective effects in case of *H. pylori* infection, since it can induce phase 2 detoxication enzymes, such as glutathione-S-transferase (GST), and may act as a bactericide in gastric rodents tissue[63]. These data may be referred to humans too, as it was shown that *H. pylori* eradication induces restored GST levels and considering that GST decreased levels are an hallmark gastric cancer, also led by *H. pylori* infection[64]. Moreover, C57BL/6 female mice infected with *H. pylori* Sydney strain 1, and whose diet was maintained in a high salt intake, when fed with broccoli rich in sulforaphane showed reduced stomach bacterial colonization, a reduced level of tumour necrosis factor-alpha and interleukin-1 beta[65]. In humans consuming 70g/d of broccoli rich in sulforaphane, a reduced level of urease (biomarker of *H. pylori* inflammation) in breath test and of serum pepsinogen I and Ⅱ (both inflammation biomarkers)[66] was found. Then, it can be deduced that the highest sulforaphane intake, the lowest *H. pylori* inflammation levels.

Considering the plethora of publications focused on *H. pylori* carcinogenic potential it can be gathered that its mutagenic effects must be stopped as more promptly, as possible. This goal may be achieved with an early diagnosis, an early eradication and a healthy diet rich in cruciferous crops.

Since most of *H. pylori* infections are asymptomatic[67], screening programs may be useful, especially among children, so as to reduce the possibility of accumulating mutations from childhood. It has to be stated that *H. pylori* infection in children is above all diffuse in developing countries, because of poor socioeconomic status, as showed from various authors[68-70]. Moreover it is also responsible of worsening their malnutrition, since *H. pylori* reduces the absorption of various micronutrients[70-72], and then of contributing to their growth failure[72-74]. Hence, an effective strategy of early diagnosis and treatment would be desirable, so as to combining short-term and long term advantages, against malnutrition/growth failure and possible gastric cancer, respectively. Yet, extensive population screening programs would represent a welfare spending disproportionately high with respect to actual advantages, so as to encourage focused screening just on really high risk groups such as Japanese[75]. Obviously, this restriction of screening programs would be more targeted to prevention of gastric cancer than of malnutrition, which may be caused by *H. pylori*. Various non invasive tests helping *H. pylori* diagnosis in children are available, such as [13C] urea breath test and stool antigen test[68] and different periods of administration of triple therapy showed a good efficacy in treating the infection[76,77]. Notwithstanding, close attention should be paid to the use of multiple antibacterial therapies during childhood, because of the possibility of *H. pylori* clarithromycine resistant strains development[68,78]. Hence, a good strategy to have a balance between the possibility of preventing and fighting against *H. pylori* and the necessity to bypass antibiotics resistance of some strains, may be represented by an healthy diet rich in cruciferous crops. Their intake starting from childhood may contrast possible infections, contributing to decrease infective potential of *H. pylori*. Then, good healthy habits acquired in young age may be helpful from beginning of their gaining and lifelong. A regular intake of cruciferous crops could help to impair both immediate and long term effects of *H. pylori* infection, reducing the consequent malnutrition and the possible accumulation of DNA modifications. Diet rich in cruciferous and, more generically, in vegetables, is a pivotal element of a healthy lifestyle (as it will be discussed in the next paragraph), hence it can be adopted from the early childhood, without a particular starting age.

A special topic is represented by the influence of *H. pylori* infection on aetiogenesis of Barrett's esophagus, a pathology consisting in the substitution of the normal squamous epithelium of the distal esophagus with columnar epithelium[79]. This condition predisposes to esophageal adenocarcinoma, since the characterizing columnar epithelium looks like a partial intestinal metaplasia, defined specialized intestinal metaplasia[79]. Gastroesophageal reflux is a well known cause of Barrett's esophagus, since an excess of acidic fluid accumulating in cardia after meals, can induce modifications of the squamous mucosa lining[80]. Therapy of this condition is based on the use of proton pump inhibitors, so as to control gastric fluid pH. The capability of *H. pylori* in neutralizing acidic pH of gastric environment[22] has been considered a possible explanation of the documented inverse correlation between *H. pylori* infection and Barrett's esophagus[81]. Yet, in a more recent paper, some authors showed that this correlation is tightly related to parameters used to perform the comparison. More specifically, if control samples are represented by endoscopic reports, *H. pylori* infection and Barrett's esophagus are inversely correlated, while if control samples are based on blood donors a clear association cannot be found[82]. Since both the papers cited represent a meta analysis, their results can be considered an effective overview on scientific literature focused on the topic under consideration. A concise conclusion cannot be gained, since further investigations should be performed and a clear mechanism explaining the relationship between H. pylori and Barrett's esophagus is not known[79].

PREVENTION OF GASTRIC CANCER INDUCED BY DIET

Stomach is one of the first organ contacting food, after oral mucosa and esophagus, performing the second step of chemical and mechanical digestion. The link between food and gastric cancer development has been largely studied. Various authors reported that reliable causes of stomach neoplasms are high intake of red meat[83-85], salted[20,86,87] and smoked food[88-90]. These diet habits are

source of compounds with high carcinogenic potential such as N-nitroso compounds, polycyclic aromatic hydrocarbons and heterocyclic amines. In countries with high incidence of gastric cancer, placed in South-East Asia, Maldives and South West America[91] typical dishes include fish and vegetables consumption, both fresh and salted, fermented and pickled. In 1990, Tsugane *et al*[92] published their results highlighting that Japan populations living in Hawaii showed a lower incidence rate of gastric cancer, if compared to Japanese resident in Sao Paulo, Brazil[92]. Brazilian diet habits include food with high N-nitrosation potential such as grilled red meat and fish, crustaceans and fried vegetables seasoned with large amount of salt. Other studies focused on the link between gastric cancer and salt intake analyzed salt excretion in 24 h-urine samples of subjects up to 75 years of age and it was found an almost linear correlation between the cumulative mortality rate for gastric cancer in five different area of Japan[93,94]. Moreover, Okinawa, the Japanese prefecture with the lowest mortality rate for gastric cancer, has diet habits including the lowest salt intake of the whole Japan[93,94]. Hence, the association between stomach tumours and salted food was confirmed by different ecological and epidemiological studies, but details of biological mechanisms involved have not been well clarified. An important role seems to be exerted if contemporaneous *H. pylori* infection occurs. In 2007, Loh *et al*[18] published an interesting paper in which they showed that high dietary salt intake may enhance CagA capability of moving toward gastric epithelium, potentiating *H. pylori* infection and, hence, transforming power. Previous experiments on *H. pylori* infected Mongolian gerbils showed that high levels of salt intake caused hypergastrinemia[95,96]. Others found that an increased gastrin secretion may contribute to epithelial cell growth with concurrent *H. pylori* infection[97,98]. Finally it was found that salt can determine alterations in gastric mucus viscosity, allowing N-nitroso compounds to better perform their mutation effects[21]. Hence, an effective prevention against gastric cancer development may be represented by low intake of salted food, avoiding to introduce a compound not mutagenic *per se*, but whose interaction with other predisposing factors may contribute significantly to the neoplastic pathology.

High alcohol consumption and cigarette smoking may also be considered risk factors related to stomach tumours[1,98-100], although some contrasting data were published[101,102]. It can be inferred that since alcohol is able to induce chronic gastritis, and cigarette smoking contribute to absorb mutagenic compounds, both of them might be removed in a generally healthy lifestyle. Yet, it has to be specified that just high intake of alcohol showed a direct correlation with increased risk of gastric cancer, while it was not found in case of low, or moderate intake[98]. Preventive effects of a healthy lifestyle, with moderate physical activity, reduced intake of alcohol, fats, red meat and salted food are well established. But strategy of prevention has to include consumption of fresh fruits and vegetables, which seem to exert a protective role on gastric cancer development. Different authors focused their attention on tomatoes, broccoli, citrus fruit and pomegranate because of their antioxidant, cytostatic and anti-inflammatory properties[103-105]. Tomatoes intake decreases micronucleated polychromatic erythrocytes and lipid peroxidation, and enhances antioxidant status in Swiss mice treated by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)[106]. Micronucleated polychromic erythrocytes are a direct index of chromosomal damage, whereas final product of lipids peroxidation may be mutagenic and carcinogenic[107]. Hence, tomatoes intake showed a contrasting effect on some of the most carcinogenic compounds, namely MNNG. Besides, combination of lycopene, a carotenoid abundant in tomatoes, and S-allylcysteine, an organosulphur which can be found in garlic, is able to modulate the apoptosis pathway Bcl2-Bax-Bim, so as to reduce carcinogenic potential of MNNG and sodium chloride in stomach of Wistar rats[106]. Then it can be gathered that diet habits including tomatoes may help in prevention of gastric cancer development, because they can both decrease the overall levels of carcinogens and stimulate apoptotic pathways in gastric cancer cells.

Citrus fruits seem to perform a high level prevention because of their capability of inhibiting gastric endogenous N-nitrosation[108,109] and epidemiological studies corroborate this hypothesis[92,108-110]. The mechanism through which they exert this inhibition is still investigated, but it was supposed that they can be effective in blocking both acid-catalysed nitrosation (ACN), typical of high risk areas, and by biologically catalysed nitrosation (BCN)[109]. ACN occurs when intragastric environment has an acidic pH, whereas BCN occurs in nearly neutral pH[111], so N-nitrosation phenomenon shows independence from stomach pH, but a close relationship to quality of food intake. Yet, the preventive role of citrus fruits is not only limited to reduce this phenomenon, but also to induce G2/M cell cycle arrest in AGS gastric cancer cell line[112], to suppress CD74, an adhesion molecule of urease *H. pylori*, and to disrupt the related ERK1/2 activation pathway in NCI-N87 gastric cancer cell line[113,114]. Induction of apoptosis through caspase-3 activation was found too[115].

It is noteworthy to mention a paper published in 2004 describing an epidemiological investigation on Japanese males in which it was shown that chronic atrophic gastritis, often first step of gastric neoplastic transformation, was more frequent in men consuming broccoli once or more weekly, if compared to those who ate broccoli less frequently[116]. The same authors considered surprising the data obtained. They supposed that a more accurate diagnostic method for chronic atrophic gastritis, than serological determination of pepsinogen I and Ⅱ they used, and that a more accurate evaluation of amount of broccoli eaten would have to be performed, since they took account just of tines/weekly consumed, rather than precise amount. Moreover a study published in 2008

did not show a significant protective role from fruit and vegetable intake on gastric cancer development[117]. Yet, this study was performed in United States, where a generally well nourished population live. This comment was recently done also by Key in a recently published review[118], in which the author discussed the effective protective role of fresh fruit and vegetables on cancer development. He focused his attention on the importance of having at least a moderate intake of fresh fruits and vegetables, but also to pay attention to avoid overweight, high salted food and high alcohol consumption.

Contrasting papers on the usefulness of fresh fruits and vegetables intake in preventing gastric cancer, has not to be considered an advice of ignore consumption of this kind of food. Rather, experimental evidences suggesting that different compounds in fruits and vegetables may activate apoptotic and cytostatic pathways and inhibiting *H. pylori* adhesion, would have to encourage to change unhealthy lifestyle toward healthier habits.

PREVENTION OF GASTRIC CANCER IN FAMILIES CARRYING *E-CADHERIN* MUTATIONS

E-cadherin, also known as Cadherin type 1 (*CDH1*), is a cell-adhesion glycoprotein characterized for the first time in human cell lines by Shimoyama *et al*[119]. Its role in gastric cancer development was firstly defined by Guilford *et al*[8], who identified a G→T nucleotide substitution in the donor splice consensus sequence of exon 7 in a Maori kindred. This mutation produced a truncated protein whose final result was a reduced *E-cadherin* production. The family examined showed an early onset of gastric cancer characterized by diffuse histotype, as the other two families described who carried a frameshift mutation in exon 15 and a premature stop codon in exon 13, respectively. Successively, other authors identified other *E-cadherin* mutations in various worldwide families[120-123]. All these germline mutations are dominantly inherited, originating the so called Hereditary Diffuse Gastric Cancer (HDGC), a dominantly familial cancer syndrome. Updated criteria established by the International Gastric Cancer Linkage Consortium define that the syndrome of HDGC must be characterized by histological confirmation of diffuse gastric criteria only for one family member, inclusion of individuals with diffuse gastric cancer before the age of 40 years without a family history and inclusion of individuals and families with diagnoses of both diffuse gastric cancer (including one before the age of 50 years) and lobular breast cancer[124]. People belonging to families showing also just one of these features should undergo to genetic test to investigate on possible *CDH1* mutations. Although among familial gastric cases only 1%-3% are carriers of mutations in *CDH1,* positive results should be followed by well scheduled endoscopic surveillance so as to monitor the very first neoplastic lesions. Yet, the efficacy of this strategy may be invalidated in cases of small, or intramucosal, foci[125-127]. In scientific literature total gastrectomy is often performed as a prophylactic strategy and, as much often, it represents a therapeutic strategy[124-126], just because of frequent small foci undetectable by endoscopical techniques.

The knowledge of the effects exerted by inherited *CDH1* mutations, raises different ethical questions. Descendants of carrier families have often to choose if undergoing to preventive gastrectomy, or not. Some of them preferred right this option, while other did not. In both cases physicians have to show possible advantages and disadvantages deriving from each choice. The adoption of a healthy diet, in these cases, although advisable, is not sufficient to exert an active and effective prevention of gastric cancer, since *CDH1* loss of expression and/or function represent an important step towards carcinogenesis. Hence, people belonging to carrier families would have to join a constant endoscopic surveillance with a medical support, to plan the most suitable prevention strategy.

CONCLUSION

Up to date gastric cancer is one of the most lethal tumour, especially in South America and South-East Asia, where it shows the highest frequency and morbility. Rare cases of HDGC are caused by *CDH1* mutations and their prevention is above all based on continuous surveillance, generally following an actual mutational diagnosis. Non hereditary gastric cancer number among their predisposing factors both *H. pylori* infection, and unhealthy diet including high intake of salted and smoked food, red meat and alcohol and a reduced intake of vegetables and fresh fruit. Various studies have shown molecular bases related to preventive effects exerted by a healthy diet. More specifically it has been found that cruciferous crops helps to inhibit *H. pylori* infection and then its mutational power. On the other hand, tomatoes, garlic and citrus fruits are able to reduce N-nitrosation and to induce apoptosis and cell cycle arrest in G2/M phase, respectively. Hence, high consumption of vegetables helps to prevent and to block phenomena triggered both by salted and smoked food and red meat, and by *H. pylori* infection.

Future perspectives related to gastric cancer prevention are, above all, focused on improving strategy against *H. pylori* and discovering molecular mechanisms on which healthy diet may exert a function. Very recent papers highlight the possibility of alternative target to manage the bacterial infection[128] and to the different parameters to determine a really nutrient and balanced diet[129]. Again recently, a review written by Nagini[130] show an effective summary of all these last keypoints, giving useful hints for further research directions.

REFERENCES

1 **Asombang AW**, Kelly P. Gastric cancer in Africa: what do we know about incidence and risk factors? *Trans R Soc Trop Med Hyg* 2012; **106**: 69-74

2 **Dikshit RP**, Mathur G, Mhatre S, Yeole BB. Epidemiological review of gastric cancer in India. *Indian J Med Paediatr Oncol* 2011; **32**: 3-11
3 **Hu J**, La Vecchia C, Morrison H, Negri E, Mery L. Salt, processed meat and the risk of cancer. *Eur J Cancer Prev* 2011; **20**: 132-139
4 **Dungal N**, Sigurjonsson J. Gastric cancer and diet. A pilot study on dietary habits in two districts differing markedly in respect of mortality from gastric cancer. *Br J Cancer* 1967; **21**: 270-276
5 **Matsuo T**, Ito M, Takata S, Tanaka S, Yoshihara M, Chayama K. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. *Helicobacter* 2011; **16**: 415-419
6 **González CA**, Agudo A. Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go. *Int J Cancer* 2012; **130**: 745-753
7 **Oda T**, Kanai Y, Oyama T, Yoshiura K, Shimoyama Y, Birchmeier W, Sugimura T, Hirohashi S. E-cadherin gene mutations in human gastric carcinoma cell lines. *Proc Natl Acad Sci USA* 1994; **91**: 1858-1862
8 **Guilford P**, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998; **392**: 402-405
9 **Kim TY**, Lee HJ, Hwang KS, Lee M, Kim JW, Bang YJ, Kang GH. Methylation of RUNX3 in various types of human cancers and premalignant stages of gastric carcinoma. *Lab Invest* 2004; **84**: 479-484
10 **Wei D**, Gong W, Oh SC, Li Q, Kim WD, Wang L, Le X, Yao J, Wu TT, Huang S, Xie K. Loss of RUNX3 expression significantly affects the clinical outcome of gastric cancer patients and its restoration causes drastic suppression of tumor growth and metastasis. *Cancer Res* 2005; **65**: 4809-4816
11 **Li WQ**, Pan KF, Zhang Y, Dong CX, Zhang L, Ma JL, Zhou T, Li JY, You WC. RUNX3 methylation and expression associated with advanced precancerous gastric lesions in a Chinese population. *Carcinogenesis* 2011; **32**: 406-410
12 **Duell EJ**, Travier N, Lujan-Barroso L, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Palli D, Krogh V, Panico S, Tumino R, Sacerdote C, Quirós JR, Sánchez-Cantalejo E, Navarro C, Gurrea AB, Dorronsoro M, Khaw KT, Allen NE, Key TJ, Bueno-de-Mesquita HB, Ros MM, Numans ME, Peeters PH, Trichopoulou A, Naska A, Dilis V, Teucher B, Kaaks R, Boeing H, Schütze M, Regner S, Lindkvist B, Johansson I, Hallmans G, Overvad K, Egeberg R, Tjønneland A, Lund E, Weiderpass E, Braaten T, Romieu I, Ferrari P, Jenab M, Stenling R, Aune D, Norat T, Riboli E, González CA. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Am J Clin Nutr* 2011; **94**: 1266-1275
13 **Mastoraki A**, Danias N, Arkadopoulos N, Sakorafas G, Vasiliou P, Smyrniotis V. Prophylactic total gastrectomy for hereditary diffuse gastric cancer. Review of the literature. *Surg Oncol* 2011; **20**: e223-e226
14 **Lynch HT**, Lynch JF. Hereditary diffuse gastric cancer: life-saving total gastrectomy for CDH1 mutation carriers. *J Med Genet* 2010; **47**: 433-435
15 **Maekita T**, Nakazawa K, Mihara M, Nakajima T, Yanaoka K, Iguchi M, Arii K, Kaneda A, Tsukamoto T, Tatematsu M, Tamura G, Saito D, Sugimura T, Ichinose M, Ushijima T. High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosae and its possible association with gastric cancer risk. *Clin Cancer Res* 2006; **12**: 989-995
16 **Ando T**, Yoshida T, Enomoto S, Asada K, Tatematsu M, Ichinose M, Sugiyama T, Ushijima T. DNA methylation of microRNA genes in gastric mucosae of gastric cancer patients: its possible involvement in the formation of epigenetic field defect. *Int J Cancer* 2009; **124**: 2367-2374
17 **Suzuki H**, Yamamoto E, Nojima M, Kai M, Yamano HO, Yoshikawa K, Kimura T, Kudo T, Harada E, Sugai T, Takamaru H, Niinuma T, Maruyama R, Yamamoto H, Tokino T, Imai K, Toyota M, Shinomura Y. Methylation-associated silencing of microRNA-34b/c in gastric cancer and its involvement in an epigenetic field defect. *Carcinogenesis* 2010; **31**: 2066-2073
18 **Loh JT**, Torres VJ, Cover TL. Regulation of Helicobacter pylori cagA expression in response to salt. *Cancer Res* 2007; **67**: 4709-4715
19 **Fox JG**, Dangler CA, Taylor NS, King A, Koh TJ, Wang TC. High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. *Cancer Res* 1999; **59**: 4823-4828
20 **Tsugane S**, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75-83
21 **Tsukamoto T**, Mizoshita T, Tatematsu M. Animal models of stomach carcinogenesis. *Toxicol Pathol* 2007; **35**: 636-648
22 **Konturek PC**, Konturek SJ, Brzozowski T. Helicobacter pylori infection in gastric cancerogenesis. *J Physiol Pharmacol* 2009; **60**: 3-21
23 **Tanih NF**, McMillan M, Naidoo N, Ndip LM, Weaver LT, Ndip RN. Prevalence of Helicobacter pylori vacA, cagA and iceA genotypes in South African patients with upper gastrointestinal diseases. *Acta Trop* 2010; **116**: 68-73
24 **Ramis IB**, Fonseca TL, de Moraes EP, Fernandes MS, Mendoza-Sassi R, Rodrigues O, Juliano CR, Scaini CJ, da Silva PE. Molecular Basis of pathogenicity in Helicobacter pylori clinical isolates. *J Clin Microbiol* 2010; **48**: 3776-3778
25 **van Doorn LJ**, Figueiredo C, Sanna R, Plaisier A, Schneeberger P, de Boer W, Quint W. Clinical relevance of the cagA, vacA, and iceA status of Helicobacter pylori. *Gastroenterology* 1998; **115**: 58-66
26 **Watada M**, Shiota S, Matsunari O, Suzuki R, Murakami K, Fujioka T, Yamaoka Y. Association between Helicobacter pylori cagA-related genes and clinical outcomes in Colombia and Japan. *BMC Gastroenterol* 2011; **11**: 141
27 **Wen S**, Moss SF. Helicobacter pylori virulence factors in gastric carcinogenesis. *Cancer Lett* 2009; **282**: 1-8
28 **Kumar Pachathundikandi S**, Brandt S, Madassery J, Backert S. Induction of TLR-2 and TLR-5 expression by Helicobacter pylori switches cagPAI-dependent signalling leading to the secretion of IL-8 and TNF-α. *PLoS One* 2011; **6**: e19614
29 **Vincent CD**, Buscher BA, Friedman JR, Williams LA, Bardill P, Vogel JP. Identification of non-dot/icm suppressors of the Legionella pneumophila DeltadotL lethality phenotype. *J Bacteriol* 2006; **188**: 8231-8243
30 **Hatakeyama M**. Deregulation of SHP-2 tyrosine phosphatase by the Helicobacter pylori virulence factor CagA. *Keio J Med* 2002; **51** Suppl 2: 26-32
31 **Hatakeyama M**. Oncogenic mechanisms of the Helicobacter pylori CagA protein. *Nat Rev Cancer* 2004; **4**: 688-694
32 **Buti L**, Spooner E, Van der Veen AG, Rappuoli R, Covacci A, Ploegh HL. Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. *Proc Natl Acad Sci USA* 2011; **108**: 9238-9243
33 **Rizzato C**, Torres J, Plummer M, Muñoz N, Franceschi S, Camorlinga-Ponce M, Fuentes-Pananá EM, Canzian F, Kato I. Variations in Helicobacter pylori cytotoxin-associated genes and their influence in progression to gastric cancer: implications for prevention. *PLoS One* 2012; **7**: e29605
34 **Ushijima T**, Hattori N. Molecular pathways: involvement of Helicobacter pylori-triggered inflammation in the formation of an epigenetic field defect, and its usefulness as cancer risk and exposure markers. *Clin Cancer Res* 2012; **18**: 923-929
35 **Aihara M**, Azuma A, Takizawa H, Tsuchimoto D, Funakoshi Y, Shindo Y, Ohmoto Y, Imagawa K, Kikuchi M, Mukaida N, Matsushima K. Molecular analysis of suppression of interleukin-8 production by rebamipide in Helicobacter pylori-stimulated gastric cancer cell lines. *Dig Dis Sci* 1998;

43: 174S-180S
36 **Komoto K**, Haruma K, Kamada T, Tanaka S, Yoshihara M, Sumii K, Kajiyama G, Talley NJ. Helicobacter pylori infection and gastric neoplasia: correlations with histological gastritis and tumor histology. *Am J Gastroenterol* 1998; **93**: 1271-1276
37 **El-Omar EM**. The importance of interleukin 1beta in Helicobacter pylori associated disease. *Gut* 2001; **48**: 743-747
38 **Raghavan S**, Quiding-Järbrink M. Immune modulation by regulatory T cells in Helicobacter pylori-associated diseases. *Endocr Metab Immune Disord Drug Targets* 2012; **12**: 71-85
39 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781
40 **Graham DY**, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153
41 **Gisbert JP**, Pajares R, Pajares JM. Evolution of Helicobacter pylori therapy from a meta-analytical perspective. *Helicobacter* 2007; **12** Suppl 2: 50-58
42 **Gumurdulu Y**, Serin E, Ozer B, Kayaselcuk F, Ozsahin K, Cosar AM, Gursoy M, Gur G, Yilmaz U, Boyacioglu S. Low eradication rate of Helicobacter pylori with triple 7-14 days and quadriple therapy in Turkey. *World J Gastroenterol* 2004; **10**: 668-671
43 **Bigard MA**, Delchier JC, Riachi G, Thibault P, Barthelemy P. One-week triple therapy using omeprazole, amoxycillin and clarithromycin for the eradication of Helicobacter pylori in patients with non-ulcer dyspepsia: influence of dosage of omeprazole and clarithromycin. *Aliment Pharmacol Ther* 1998; **12**: 383-388
44 **Cianci R**, Montalto M, Pandolfi F, Gasbarrini GB, Cammarota G. Third-line rescue therapy for Helicobacter pylori infection. *World J Gastroenterol* 2006; **12**: 2313-2319
45 **Mégraud F**. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384
46 **Chuah SK**, Tsay FW, Hsu PI, Wu DC. A new look at anti-Helicobacter pylori therapy. *World J Gastroenterol* 2011; **17**: 3971-3975
47 **Vaira D**, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, Hassan C, Bernabucci V, Tampieri A, Morini S. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. *Ann Intern Med* 2007; **146**: 556-563
48 **Gatta L**, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069-3079; quiz 1080
49 **Hsu PI**, Wu DC, Wu JY, Graham DY. Is there a benefit to extending the duration of Helicobacter pylori sequential therapy to 14 days? *Helicobacter* 2011; **16**: 146-152
50 **Essa AS**, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. *Helicobacter* 2009; **14**: 109-118
51 **Wu DC**, Hsu PI, Wu JY, Opekun AR, Kuo CH, Wu IC, Wang SS, Chen A, Hung WC, Graham DY. Sequential and concomitant therapy with four drugs is equally effective for eradication of H pylori infection. *Clin Gastroenterol Hepatol* 2010; **8**: 36-41.e1
52 **Shiotani A**, Nishi R, Uedo N, Iishi H, Tsutsui H, Ishii M, Imamura H, Kamada T, Hata J, Haruma K. Helicobacter pylori eradication prevents extension of intestinalization even in the high-risk group for gastric cancer. *Digestion* 2010; **81**: 223-230
53 **Fuccio L**, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, Grilli D, Bazzoli F. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009; **151**: 121-128
54 **Wu CY**, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009; **137**: 1641-1648.e1-2
55 **Mabe K**, Takahashi M, Oizumi H, Tsukuma H, Shibata A, Fukase K, Matsuda T, Takeda H, Kawata S. Does Helicobacter pylori eradication therapy for peptic ulcer prevent gastric cancer? *World J Gastroenterol* 2009; **15**: 4290-4297
56 **Kosunen TU**, Pukkala E, Sarna S, Seppälä K, Aromaa A, Knekt P, Rautelin H. Gastric cancers in Finnish patients after cure of Helicobacter pylori infection: A cohort study. *Int J Cancer* 2011; **128**: 433-439
57 **Maehata Y**, Nakamura S, Fujisawa K, Esaki M, Moriyama T, Asano K, Fuyuno Y, Yamaguchi K, Egashira I, Kim H, Kanda M, Hirahashi M, Matsumoto T. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. *Gastrointest Endosc* 2012; **75**: 39-46
58 **Yamamoto K**, Kato M, Takahashi M, Haneda M, Shinada K, Nishida U, Yoshida T, Sonoda N, Ono S, Nakagawa M, Mori Y, Nakagawa S, Mabe K, Shimizu Y, Moriya J, Kubota K, Matsuno Y, Shimoda T, Watanabe H, Asaka M. Clinicopathological analysis of early-stage gastric cancers detected after successful eradication of Helicobacter pylori. *Helicobacter* 2011; **16**: 210-216
59 **Matsuo T**, Ito M, Tatsugami M, Boda T, Takata S, Tanaka S, Chayama K. Gastric cancer development after Helicobacter pylori eradication therapy: a new form of gastric neoplasia. *Digestion* 2012; **85**: 61-67
60 Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241
61 **Shin SH**, Park SY, Ko JS, Kim N, Kang GH. Aberrant CpG island hypermethylation in pediatric gastric mucosa in association with Helicobacter pylori infection. *Arch Pathol Lab Med* 2011; **135**: 759-765
62 **Nakajima T**, Yamashita S, Maekita T, Niwa T, Nakazawa K, Ushijima T. The presence of a methylation fingerprint of Helicobacter pylori infection in human gastric mucosae. *Int J Cancer* 2009; **124**: 905-910
63 **Fahey JW**, Haristoy X, Dolan PM, Kensler TW, Scholtus I, Stephenson KK, Talalay P, Lozniewski A. Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of Helicobacter pylori and prevents benzo[a]pyrene-induced stomach tumors. *Proc Natl Acad Sci USA* 2002; **99**: 7610-7615
64 **Oijen AH**, Verhulst ML, Roelofs HM, Peters WH, de Boer WA, Jansen JB. Eradication of Helicobacter pylori restores glutathione S-transferase activity and glutathione levels in antral mucosa. *Jpn J Cancer Res* 2001; **92**: 1329-1334
65 **Tripathi S**, Ghoshal U, Mittal B, Chourasia D, Kumar S, Ghoshal UC. Association between gastric mucosal glutathione-S-transferase activity, glutathione-S-transferase gene polymorphisms and Helicobacter pylori infection in gastric cancer. *Indian J Gastroenterol* 2011; **30**: 257-263
66 **Yanaka A**, Fahey JW, Fukumoto A, Nakayama M, Inoue S, Zhang S, Tauchi M, Suzuki H, Hyodo I, Yamamoto M. Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in Helicobacter pylori-infected mice and humans. *Cancer Prev Res* (Phila) 2009; **2**: 353-360
67 **Blaser MJ**. Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Rep* 2006; **7**: 956-960
68 **Wewer V**, Kalach N. Helicobacter pylori infection in pediatrics. *Helicobacter* 2003; **8** Suppl 1: 61-67
69 **Bakka AS**, Salih BA. Prevalence of Helicobacter pylori infection in asymptomatic subjects in Libya. *Diagn Microbiol Infect Dis* 2002; **43**: 265-268

70 **Vitale G**, Barbaro F, Ianiro G, Cesario V, Gasbarrini G, Franceschi F, Gasbarrini A. Nutritional aspects of Helicobacter pylori infection. *Minerva Gastroenterol Dietol* 2011; **57**: 369-377

71 **Akcam M**. Helicobacter pylori and micronutrients. *Indian Pediatr* 2010; **47**: 119-126

72 **Thomas JE**, Dale A, Bunn JE, Harding M, Coward WA, Cole TJ, Weaver LT. Early Helicobacter pylori colonisation: the association with growth faltering in The Gambia. *Arch Dis Child* 2004; **89**: 1149-1154

73 **Windle HJ**, Kelleher D, Crabtree JE. Childhood Helicobacter pylori infection and growth impairment in developing countries: a vicious cycle? *Pediatrics* 2007; **119**: e754-e759

74 **Gulcan M**, Ozen A, Karatepe HO, Gulcu D, Vitrinel A. Impact of H. pylori on growth: is the infection or mucosal disease related to growth impairment? *Dig Dis Sci* 2010; **55**: 2878-2886

75 **Bourke B**. Will treatment of Helicobacter pylori infection in childhood alter the risk of developing gastric cancer? *Can J Gastroenterol* 2005; **19**: 409-411

76 **Malaty HM**. Helicobacter pylori infection and eradication in paediatric patients. *Paediatr Drugs* 2000; **2**: 357-365

77 **Yang YJ**, Sheu BS. Sequential therapy in childhood Helicobacter pylori eradication: emphasis on drug compliance. *J Pediatr* 2011; **159**: 700; author reply 700-701

78 **Yang YJ**, Yang JC, Jeng YM, Chang MH, Ni YH. Prevalence and rapid identification of clarithromycin-resistant Helicobacter pylori isolates in children. *Pediatr Infect Dis J* 2001; **20**: 662-666

79 **Appelman HD**, Umar A, Orlando RC, Sontag SJ, Nandurkar S, El-Zimaity H, Lanas A, Parise P, Lambert R, Shields HM. Barrett's esophagus: natural history. *Ann N Y Acad Sci* 2011; **1232**: 292-308

80 **Tytgat GN**. Recent developments in gastroesophageal reflux disease and Barrett's esophagus: ANNO 2012. *J Dig Dis* 2012; **13**: 291-295

81 **Rokkas T**, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis. *Clin Gastroenterol Hepatol* 2007; **5**: 1413-1417

82 **Wang C**, Yuan Y, Hunt RH. Helicobacter pylori infection and Barrett's esophagus: a systematic review and meta-analysis. *Am J Gastroenterol* 2009; **104**: 492-500; quiz 491, 501

83 **Jakszyn P**, Agudo A, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Navarro C, Palli D, Boeing H, Manjer J, Numans ME, Igali L, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Grioni S, Panico c, Tumino R, Sacerdote C, Quirós JR, Molina-Montes E, Huerta Castaño JM, Barricarte A, Amiano P, Khaw KT, Wareham N, Allen NE, Key TJ, Jeurnink SM, Peeters PH, Bamia C, Valanou E, Trichopoulou A, Kaaks R, Lukanova A, Bergmann MM, Lindkvist B, Stenling R, Johansson I, Dahm CC, Overvad K, Olsen A, Tjonneland A, Skeie G, Broderstad AR, Lund E, Michaud DS, Mouw T, Riboli E, González CA. Dietary intake of heme iron and risk of gastric cancer in the European prospective investigation into cancer and nutrition study. *Int J Cancer* 2012; **130**: 2654-2663

84 **Babaei M**, Pourfarzi F, Yazdanbod A, Chiniforush MM, Derakhshan MH, Mousavi SM, Samadi F, Rahimi G. Gastric cancer in Ardabil, Iran--a review and update on cancer registry data. *Asian Pac J Cancer Prev* 2010; **11**: 595-599

85 **González CA**, Jakszyn P, Pera G, Agudo A, Bingham S, Palli D, Ferrari P, Boeing H, del Giudice G, Plebani M, Carneiro F, Nesi G, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Nyrén O, Hallmans G, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quirós JR, Allen N, Key TJ, Day NE, Linseisen J, Nagel G, Bergmann MM, Overvad K, Jensen MK, Tjonneland A, Olsen A, Bueno-de-Mesquita HB, Ocke M, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Trichopoulou A, Psaltopoulou T, Roukos 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

86 **Strumylaite L**, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina* (Kaunas) 2006; **42**: 164-170

87 **Shikata K**, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, Tanizaki Y, Doi Y, Tanaka K, Oishi Y, Matsumoto T, Iida M. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer* 2006; **119**: 196-201

88 **Pakseresht M**, Forman D, Malekzadeh R, Yazdanbod A, West RM, Greenwood DC, Crabtree JE, Cade JE. Dietary habits and gastric cancer risk in north-west Iran. *Cancer Causes Control* 2011; **22**: 725-736

89 **Sumathi B**, Ramalingam S, Navaneethan U, Jayanthi V. Risk factors for gastric cancer in South India. *Singapore Med J* 2009; **50**: 147-151

90 **Ramón JM**, Serra L, Cerdó C, Oromí J. Dietary factors and gastric cancer risk. A case-control study in Spain. *Cancer* 1993; **71**: 1731-1735

91 WHO Disease and injury country estimates. World Health Organization. 2009.

92 **Tsugane S**, de Souza JM, Costa ML, Mirra AP, Gotlieb SL, Laurenti R, Watanabe S. Cancer incidence rates among Japanese immigrants in the city of São Paulo, Brazil, 1969-78. *Cancer Causes Control* 1990; **1**: 189-193

93 **Tsugane S**, Gey F, Ichinowatari Y, Miyajima Y, Ishibashi T, Matsushima S, Hirota Y, Inami T, Yamaguchi M, Karita K, Kabuto M, Takashima Y, Todoriki H, Tsuda M, Akabane M, Furuichi Y, Hamada G, Watanabe S. Cross-sectional Epidemiologic Study for Assessing Cancer Risks at the Population Level I. Study Design and Participation Rate. *J Epidemiol* 1992; **2**: 75-81

94 **Watanabe H**, Hirayama T. [Stomach cancer mortality and life styles in Niigata Prefecture]. *Gan No Rinsho* 1990; Spec No: 285-291

95 **Peek RM**, Wirth HP, Moss SF, Yang M, Abdalla AM, Tham KT, Zhang T, Tang LH, Modlin IM, Blaser MJ. Helicobacter pylori alters gastric epithelial cell cycle events and gastrin secretion in Mongolian gerbils. *Gastroenterology* 2000; **118**: 48-59

96 **Kato S**, Tsukamoto T, Mizoshita T, Tanaka H, Kumagai T, Ota H, Katsuyama T, Asaka M, Tatematsu M. High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer* 2006; **119**: 1558-1566

97 **Wang TC**, Dangler CA, Chen D, Goldenring JR, Koh T, Raychowdhury R, Coffey RJ, Ito S, Varro A, Dockray GJ, Fox JG. Synergistic interaction between hypergastrinemia and Helicobacter infection in a mouse model of gastric cancer. *Gastroenterology* 2000; **118**: 36-47

98 **Tramacere I**, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, Corrao G, La Vecchia C, Boffetta P. A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 2012; **23**: 28-36

99 **Kim J**, Cho YA, Choi IJ, Lee YS, Kim SY, Shin A, Cho SJ, Kook MC, Nam JH, Ryu KW, Lee JH, Kim YW. Effects of interleukin-10 polymorphisms, Helicobacter pylori infection, and smoking on the risk of noncardia gastric cancer. *PLoS One* 2012; **7**: e29643

100 **Shin A**, Kim J, Park S. Gastric cancer epidemiology in Korea. *J Gastric Cancer* 2011; **11**: 135-140

101 **Gao Y**, Hu N, Han XY, Ding T, Giffen C, Goldstein AM, Taylor PR. Risk factors for esophageal and gastric cancers in Shanxi Province, China: a case-control study. *Cancer Epidemiol* 2011; **35**: e91-e99

102 **Shin CM**, Kim N, Cho SI, Kim JS, Jung HC, Song IS. As-

sociation between alcohol intake and risk for gastric cancer with regard to ALDH2 genotype in the Korean population. *Int J Epidemiol* 2011; **40**: 1047-1055
103 **Velmurugan B**, Bhuvaneswari V, Abraham SK, Nagini S. Protective effect of tomato against N-methyl-N'-nitro-N-nitrosoguanidine-induced in vivo clastogenicity and oxidative stress. *Nutrition* 2004; **20**: 812-816
104 **Bae JM**, Lee EJ, Guyatt G. Citrus fruit intake and stomach cancer risk: a quantitative systematic review. *Gastric Cancer* 2008; **11**: 23-32
105 **Hajimahmoodi M**, Shams-Ardakani M, Saniee P, Siavoshi F, Mehrabani M, Hosseinzadeh H, Foroumadi P, Safavi M, Khanavi M, Akbarzadeh T, Shafiee A, Foroumadi A. In vitro antibacterial activity of some Iranian medicinal plant extracts against Helicobacter pylori. *Nat Prod Res* 2011; **25**: 1059-1066
106 **Velmurugan B**, Mani A, Nagini S. Combination of S-allylcysteine and lycopene induces apoptosis by modulating Bcl-2, Bax, Bim and caspases during experimental gastric carcinogenesis. *Eur J Cancer Prev* 2005; **14**: 387-393
107 **Marnett LJ**. Lipid peroxidation-DNA damage by malondialdehyde. *Mutat Res* 1999; **424**: 83-95
108 **Stähelin HB**, Rösel F, Buess E, Brubacher G. Cancer, vitamins, and plasma lipids: prospective Basel study. *J Natl Cancer Inst* 1984; **73**: 1463-1468
109 **Xu GP**, Song PJ, Reed PI. Effects of fruit juices, processed vegetable juice, orange peel and green tea on endogenous formation of N-nitrosoproline in subjects from a high-risk area for gastric cancer in Moping County, China. *Eur J Cancer Prev* 1993; **2**: 327-335
110 **La Vecchia C**, Negri E, Decarli A, D'Avanzo B, Franceschi S. A case-control study of diet and gastric cancer in northern Italy. *Int J Cancer* 1987; **40**: 484-489
111 **Steevens J**, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Int J Cancer* 2011; **129**: 2681-2693
112 **Lee DH**, Park KI, Park HS, Kang SR, Nagappan A, Kim JA, Kim EH, Lee WS, Hah YS, Chung HJ, An SJ, Kim GS. Flavonoids Isolated from Korea Citrus aurantium L. Induce G2/M Phase Arrest and Apoptosis in Human Gastric Cancer AGS Cells. *Evid Based Complement Alternat Med* 2012; **2012**: 515901
113 **Sekiguchi H**, Washida K, Murakami A. Suppressive Effects of Selected Food Phytochemicals on CD74 Expression in NCI-N87 Gastric Carcinoma Cells. *J Clin Biochem Nutr* 2008; **43**: 109-117
114 **Sekiguchi H**, Irie K, Murakami A. Suppression of CD74 expression and Helicobacter pylori adhesion by auraptene targeting serum starvation-activated ERK1/2 in NCI-N87 gastric carcinoma cells. *Biosci Biotechnol Biochem* 2010; **74**: 1018-1024
115 **Kim MJ**, Park HJ, Hong MS, Park HJ, Kim MS, Leem KH, Kim JB, Kim YJ, Kim HK. Citrus Reticulata blanco induces apoptosis in human gastric cancer cells SNU-668. *Nutr Cancer* 2005; **51**: 78-82
116 **Sato K**, Kawakami N, Ohtsu T, Tsutsumi A, Miyazaki S, Masumoto T, Horie S, Haratani T, Kobayashi F, Araki S. Broccoli consumption and chronic atrophic gastritis among Japanese males: an epidemiological investigation. *Acta Med Okayama* 2004; **58**: 127-133
117 **Freedman ND**, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. *Cancer Causes Control* 2008; **19**: 459-467
118 **Key TJ**. Fruit and vegetables and cancer risk. *Br J Cancer* 2011; **104**: 6-11
119 **Shimoyama Y**, Hirohashi S, Hirano S, Noguchi M, Shimosato Y, Takeichi M, Abe O. Cadherin cell-adhesion molecules in human epithelial tissues and carcinomas. *Cancer Res* 1989; **49**: 2128-2133
120 **Gayther SA**, Gorringe KL, Ramus SJ, Huntsman D, Roviello F, Grehan N, Machado JC, Pinto E, Seruca R, Halling K, MacLeod P, Powell SM, Jackson CE, Ponder BA, Caldas C. Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Res* 1998; **58**: 4086-4089
121 **Yoon KA**, Ku JL, Yang HK, Kim WH, Park SY, Park JG. Germline mutations of E-cadherin gene in Korean familial gastric cancer patients. *J Hum Genet* 1999; **44**: 177-180
122 **Yamada H**, Shinmura K, Ito H, Kasami M, Sasaki N, Shima H, Ikeda M, Tao H, Goto M, Ozawa T, Tsuneyoshi T, Taniока F, Sugimura H. Germline alterations in the CDH1 gene in familial gastric cancer in the Japanese population. *Cancer Sci* 2011; **102**: 1782-1788
123 **Corso G**, Marrelli D, Pascale V, Vindigni C, Roviello F. Frequency of CDH1 germline mutations in gastric carcinoma coming from high- and low-risk areas: metanalysis and systematic review of the literature. *BMC Cancer* 2012; **12**: 8
124 **Fitzgerald RC**, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, Chung DC, Norton J, Ragunath K, Van Krieken JH, Dwerryhouse S, Caldas C. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 2010; **47**: 436-444
125 **Cisco RM**, Ford JM, Norton JA. Hereditary diffuse gastric cancer: implications of genetic testing for screening and prophylactic surgery. *Cancer* 2008; **113**: 1850-1856
126 **Chen Y**, Kingham K, Ford JM, Rosing J, Van Dam J, Jeffrey RB, Longacre TA, Chun N, Kurian A, Norton JA. A prospective study of total gastrectomy for CDH1-positive hereditary diffuse gastric cancer. *Ann Surg Oncol* 2011; **18**: 2594-2598
127 **Terdiman JP**. Hereditary diffuse gastric cancer: surveillance endoscopy is not enough to save lives. *Gastroenterology* 2007; **133**: 1730-1732; discussion 1732-1733
128 **Mori J**, Vranac T, Smrekar B, Cernilec M, Serbec VČ, Horvat S, Ihan A, Benčina M, Jerala R. Chimeric flagellin as the self-adjuvanting antigen for the activation of immune response against Helicobacter pylori. *Vaccine* 2012; **30**: 5856-5863
129 **Lim H**, Cho G, Kim S. Evaluation of nutrient intake and diet quality of gastric cancer patients in Korea. *Nutr Res Pract* 2012; **6**: 213-220
130 **Nagini S**. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol* 2012; **4**: 156-169

S- Editor Jiang L **L- Editor** A **E- Editor** Li JY