ACTA GASTROENTEROL LATINOAM - Junio 2007;VOL 37:Nº2

Prevention of gastric cancer: a challenging but feasible task

Lucia C Fry, Klaus Mönkemüller, Peter Malfertheiner

Acta Gastroenterol Latinoam 2007;37:110-117

Summary

Despite its declining incidence gastric cancer still ranks as the second most common malignancy of the digestive tract, accounting for 10% of cancer deaths worldwide. At the time of the diagnosis less than 15% of the patients are in the stage of early cancer, the only stage in which a definite cure of gastric cancer is possible. Therefore the challenges are either early detection or even better prevention of gastric cancer. H. pylori has become recognized as the major risk factor for gastric adenocarcinoma. Epidemiological, biological, histomorphologic, molecular-genetic, epidemiological evidence and more recently few clinical trails have shown that H. pylori eradication has the potential to prevent the development of gastric cancer. Currently, H. pylori eradication is an indication for the prevention of gastric cancer in patients and groups of individuals with strongly increased risk, but further investigations are still required before an implementation of a general and global policy to eradicate H. pylori for the prevention of gastric cancer can be instituted. At present time, the main challenge remains to find out at what point mucosal abnormalities are no longer reversible and gastric cancer development cannot be prevented despite H. pylori eradication.

Key words: *H. pylori - gastric cancer - prevention*

Prevención del cáncer gástrico: una tarea difícil pero factible

Resumen

A pesar de la disminución en su incidencia, aún hoy el cáncer gástrico se presenta como la segunda causa más común de muerte por enfermedad maligna del tubo digestivo, siendo responsable del 10% de las muertes por cáncer a nivel mundial. Al momento del diagnóstico menos del 15% de los pacientes se encuentran en la etapa de cáncer gástrico temprano, el único estadío en el cual es posible su curación. Por lo tanto, el desafío está en la detección temprana o aún mejor, en la prevención del cáncer gástrico. H. pylori ha sido reconocido como el factor de riesgo más importante para el desarrollo del adenocarcinoma de estómago. Evidencia epidemiológica, biológica, histológica, molecular y más recientemente algunos estudios clínicos han demostrado que la erradicación del H. pylori tiene el potencial de prevenir el desarrollo de lesiones premalignas y del cáncer gástrico. Actualmente la erradicación del H. pylori está indicada para la prevención del cáncer gástrico en pacientes y grupos de individuos con alto riesgo, pero futuras investigaciones son aún necesarias antes de que sea establecida una política global para la erradicación del H. pylori en la prevención del cáncer gástrico. Actualmente el mayor desafío radica en encontrar en qué punto los cambios en la mucosa gástrica se tornan irreversibles, siendo el cáncer gástrico no prevenible a pesar de la erradicación del H. pylori.

Palabras clave: *H. pylori, cáncer gástrico, prevención.*

Division of Gastroenterology, Hepatology and Infectious Diseases. Otto-von-Guericke University. Magdeburg, Germany

Correspondencia: *Prof Peter Malfertheiner*
Department of Gastroenterology, Hepatology and Infectious Diseases. Universitätsklinikum Magdeburg, Otto-von-Guericke University, Leipziger Straße 44, 39120 Magdeburg, Germany
Tel:+49 391 6713100 - Fax:+ 49 391 6713105

E-mail: peter.malfertheiner@med.ovgu.de

Gastric cancer continuous to be a major challenge, largely because in the majority of cases it is recognized only in stages in which a curative therapy is no longer possible.[1] Therefore the efforts should be directed to early detection and prevention. *H. pylori* is the main risk factor for gastric cancer which offers the chance to battle against this disease by the preventive measure of *H. pylori*-eradication. The implication of a global gastric cancer prophylaxis strategy offers a unique chance against gastric cancer but should be evaluated taking health-economic aspects in consideration as well.

Epidemiology of the *H. pylori* infection

H. pylori is one the most common chronic bacte-

rial infections in humans. Although the prevalence of *H. pylori* infection has decreased, the infection rate of the population over 50-years is still about 40%, which accounts to around 33 million people in Germany.[2] Most infections with *H. pylori* take place in childhood and adolescence, being infrequent as a new infection in adults. In addition, the prevalence of *H. pylori* infection varies in different populations, having a strong correlation with the socio-economic conditions, being more common in patients "from lower socio-economical status".[3,4] In Europe, there is a high prevalence of the infection throughout the population living in the Mediterranean and eastern European countries.[2,5,6] For example, in countries such as Romania or Turkey 60% of the children are already infected with *H. pylori*. In countries of the Western World the prevalence is around 10-20% in adults.[7] Current investigations show that the prevalence of *H. pylori* infection in people between 16 and 20 years-old in Germany is 7.1%.[2,8] Risk occupational groups represent an exception, such as physicians or nurses. An epidemiological study from Brazil showed a rise of *H. pylori* seroprevalence from 23.4% in students at the beginning of the medicine study to 38.6% for physicians in the hospital settings.[6]

H. pylori and gastric carcinoma

Adenocarcinoma of the stomach is divided in two main histological types according to the Lauren classification: a) well-differentiated or intestinal type and b) diffuse or signet ring cell type.[9,10] The intestinal type is associated with gastric atrophy and intestinal metaplasia and corpus-dominant gastritis, while the diffuse type frequently originates in pangastritis without atrophy. A decrease in the incidence of the intestinal type and an increase in the diffuse type of gastric carcinoma, especially the signet ring cell type have been noticed.[11] According to localization different etiology can be considered. In patients with distal gastric cancer, a chronic atrophic *H. pylori*-induced type B-gastritis is the main etiological factor. Also adenocarcinomas of the proximal stomach including cardia may be related with a *H. pylori* infection, but for this location there are other *H pylori*-independent factors which are not well known yet. In addition, there are other defined but uncommon conditions associated with gastric cancer: atrophic gastritis associated with pernicious anemia, hypertrophic gastropathy or Ménétrier's disease and gastric adenomatous polyps.[12] But nowadays it has been accepted that all these forms of gastritis are also linked with an *H. pylori* infection. At the present time, intestinal as well as diffuse type of gastric cancer are both considered strongly associated with chronic *H. pylori* infection.[13] The association between *H. pylori* infection and gastric cancer has been confirmed by epidemiological, cell-molecular, animal and interventional studies.[14-22]

Epidemiologic evidence

The association between *H. pylori* infection and the development of gastric cancer has been recognized in several epidemiological studies.[22-25] In retrospective case-control studies, patients with serologically confirmed *H. pylori* infection had an increased relative risk from 1.2 to 4.2 of developing gastric cancer.[2,19] In prospective studies, patients with gastric cancer and previous seropositivity for *H. pylori*, an increased relative risk from 2.8 to 6 was demonstrated.[2] In addition a meta-analysis performed in 2001 including only prospective cohort studies established the association between *H. pylori* infection and non-cardia gastric cancer (odds ratio 2.97).[26] Newer epidemiological investigations using immunological methods such as serum CagA antibodies showed that *H. pylori* infected patients have a 20-times higher risk to develop a gastric cancer.[2,19] In a study from Germany it was demonstrated that *H. pylori* infection is a sine qua non condition for the development of gastric cancer.[14]

From the imaginary perspective of an *H. pylori*-free-world, an 80% decrease of primary gastric MALT lymphomas and 70% of distal gastric cancers would be expected. Because of the proved relationship between *H. pylori* infection and the development of gastric malignant tumors, *H. pylori* was included in the category as a definite carcinogenic of the WHO guidelines.[2,5,10,27] Furthermore, *H. pylori* is the only bacterium so far which has been classified by the World Health Organization as a carcinogen. Although the pandemic spreading of the *H. pylori* infection contradicts with the relatively occasional occurrence of adenocarcinoma (0.5 to 1%) and lymphomas of the stomach, the role of the *H. pylori* as independent factor of risk for the tumorogenesis has been demonstrated. However, the final unequivocal demonstration of the association between *H. pylori* infection and the genesis of gastric cancer can be only revealed after performing long-

term follow-up prospective studies which also include a study arm with non-infected population.

Molecular studies

Cell biological investigations prove a direct influence of *H. pylori* on cellular signal cascades which are involved in the process of the carcinogenesis.[14-21] The cell biological phenomena which occur due to infection with *H. pylori* include the activation of growth factors, reduction of the apoptosis, induction of replication, increase of angiogenesis and disruption of cell-cell contacts (table 1). *H. pylori* regulates the activity of growth factor receptors promoting epithelial cell growth, survival, dissociation and motility.[18] These significant observations, documented under *in vitro* conditions, demonstrate that *H. pylori* affects cell physiology contributing to uncontrolled growth which leads to an aggressive behavior of the cell and promoting malignant transformation. The intracellular cascades, which lead to an increased and uncontrolled cell proliferation can regress after *H. pylori* eradication (table 2). Knowledge of the intracellular pathways related with malignant behavior is crucial to understand whether *H. pylori* eradication prevents the development of gastric cancer.

Table 1. *Preclinical evidence of the carcinogenic potential of H. pylori.*

Bacterial-related factors
- Influence *H. pylori* in cell biology
  - Activation of epidermal growth factor and their receptors
  - Enhancement of cell motility
  - Evasion of apoptosis
  - Increase of angiogenesis
  - Disruption of cell-cell contacts
- *H. pylori* virulence factors probably associated with gastric carcinogenesis
  - Pathogenicity island (PAI)
  - Genetic variations (recombination, point mutations, horizontal transfer of genetic elements)
  - Cag A+ strains
  - VacA s1, VacA m1 genotypes

Host-related factors
- Genetic factors
  - Functional polymorphisms in the interleukin IL-1 cluster
  - Functional polymorphisms in TNF-α genes
- Host response
  - Desintegration of gastric mucus
  - Production of free radicals
  - Damage of gastric mucosa

Environmental factors
- Dietary factors
  - Salt
  - Nitroso compounds
  - Meat
- Tobacco?
- Alcohol

Table 2. *Influence of H. pylori eradication on cellular events.*

- Reduction of free radicals
- Reduction of COX2 and expression of ornithine decarboxilase (in atrophic preneoplastic and malignant lesions)
- Reduction of epidermal growth factors and their receptors (EGF and EGFR)
- Improvement of metaplasia and genomic inestability
- Reversion of aberrant expression of cyclin D2 and p27 in intestinal metaplasia.
- Decrease of cell turn-over
- Elimination of DNA damage through free radicals
- Increase of gastric acid secretion
- Increase of ascorbic acid secretion

Animal experimental data

Gastric carcinogenesis has been evaluated in several animal models including ferrets, mice and mongolian gerbils.[28-31] In 1998, Watanabe et al presented evidence showing *H. pylori* as a gastric carcinogen in Mongolian gerbils. Further studies demonstrated that *H. pylori* alone is a weak carcinogenic factor, but the presence of nitrosamine together with *H. pylori* infection increases significantly the carcinogenic potential of *H. pylori*.[8,18] Furthermore, this carcinogenic potential has been shown to be increased in combination with a high-salt diet.[28] Histopathological studies in mongolian gerbils demonstrated that after *H. pylori* infection, gastric glands start to proliferate into the submucosa (named heterotopic proliferative glands) with a slightly dysplastic change of constituent cells.[30] After eradication, these heterotopic proliferative glands presented an evident reduction as well as an improvement of mucosal gastric lesions.[8,18,30] In the standard mouse model to assess the *H. pylori* infection, it was shown that male mice infected with *H. pylori* regularly developed atrophy, intestinal metaplasia, dysplasia and carcinoma.[31]

Interventional studies

Eradication of *H. pylori* is at present time accepted to heal gastritis and dramatically reduce the incidence and recurrence of peptic ulcer disease. Furthermore, the influence of *H. pylori* eradication on the development of gastric cancer has been demonstrated in observational as well as in interventional studies[32-37] (table 3). In a study from Japan which included 1526 patients (82% *H. pylori* positive) who were followed-up prospectively for 7.8 years, gastric cancer developed in 36 patients (2.9%) of the infected group but in none of the *H. pylori*-negative patients.[34] One study from China showed that gastric cancer development is preventable by *H. pylori* eradication only if gastritis has not yet reached the degree of atrophic changes or intestinal metaplasia (i.e. preneoplastic lesions)[35] (table 3). A recently published study followed 1131 patients with peptic ulcer disease who had received *H. pylori* eradication therapy. After a mean follow-up of 3.9 years, gastric cancer was developed in 9 of 953 (0.9%) patients cured of the infection and in 4 of 178 (2,2%) who had persistent *H. pylori* infection.[37] The risk of developing gastric cancer after receiving *H. pylori* eradication therapy was increased according to the grade of baseline gastric mucosal atrophy. The effect of *H. pylori* eradication on gastric preneoplastic lesions has been also evaluated in several studies (table 4).[38-46] In a study evaluating *H. pylori* positive patients with moderate and severe atrophic gastritis with a 5-years follow-up period Ito et al. demonstrated regression of gastric atrophy and intestinal metaplasia in some patients after *H. pylori* eradication.[47] Another randomized, controlled, chemopreventive study evaluating patients with increased risk for gastric cancer showed that *H. pylori* eradication led to a decrease of 15 to 30% of atrophic gastritis and intestinal metaplasia.[39] In another study it was demonstrated that

Table 3. *H. pylori eradication and gastric cancer incidence.*

Autor/ Jahr	Patients	Follow-up (years)	Study	End point	Incidence of gastric cancer
Uemura 1997	132	3	Prospective, placebo-controlled	Incidence of gastric cancer, reversibility of preneoplastic lesions	*Hp* neg: 0/65 (0%) *Hp* pos: 6/67 (9%) (p=0.011)
Saito 2000	64	2	Prospective, placebo-controlled	Progression of adenoma in *Hp* -positive patients	*Hp* neg: 0/32 (0%) *Hp* pos: 4/32 (12.5%) (p<0.05)
Uemura 2001	1526	7,8	Prospective, placebo-controlled	Development of gastric cancer in *Hp* -infected patients	*Hp* neg: 0/280 (0%) *Hp* pos: 36/1246 (2.9%) (p<0.001)
Wong 2004	1630	7	Population based, prospective, randomized, placebo-controlled	Incidence of gastric cancer after *Hp* eradication	Patients without preneoplastic lesions[1]: *Hp* neg: 0 vs *Hp* pos: 6 pts (p=0.02) No difference in pts with preneoplastic lesions.
Zhou 2005	1006	8	Population based, prospective, randomized, placebo-controlled	Incidence of gastric cancer after *Hp* eradication	*Hp* neg: 1/1968 (0.4%) *Hp* pos: 6/2448 (1.6%) After *Hp* eradication: significant reduction of atrophy in corpus (p=0.001)
Take 2007	1131	3,9 (mean)	Prospective, not randomized	Incidence of gastric cancer after *Hp* eradication	*Hp* neg: 9/953 (0.9%) *Hp* pos: 4/178 (2.2%) p=0,04

Hp: Helicobacter pylori

[1] preneoplastic lesions: gastric atrophy, intestinal metaplasia, dysplasia

Table 4. *Influence of H. pylori eradication on preneoplastic gastric lesions.*

Autor	Nº Patients	Follow-up (years)	Atrophy	Intestinal metaplasia
Tepes 1999	63	4	Regression	No change
Sung 2000	587	5	Prevents progression	Prevents progression
Rocco 2002	54	8	Improvement	Improvement
Ito 2002	22	5	Reversibility in some patients	Reversibility in some patients
Zhou 2003	552	5	No regression (antrum p=0.223) (corpus p=0.402)	Regression in Antrum p=0.032 no change in Corpus p=0.151
Lu 2005	179	3	Reduction P<0.01	Progression (p>0.05, NS)
Salih 2005	21	1	Improvement (NS)	Improvement (NS)
Mera 2005	795	12	Improvement	Improvement
Arkkila 2006	92	1	Regression in antrum (p<0,05) Regression in corpus (NS)	Not evaluated

NS: non-significant

improvement of gastritis and intestinal metaplasia was more apparent in patients with lower histological severity levels of gastritis.[42] An important cohort-study with a follow-up of 12 years evaluated 795 *H. pylori*-infected patients with gastric preneoplastic lesions who were randomized to either *H. pylori* eradication or antioxidants.[45] Participants without initial antibiotic therapy were offered *H. pylori* eradication 6 years after the start of the study. After 12 years follow-up, up to 66% of the *H. pylori*-negative patients showed an involution of preneoplastic lesions, in contrast to only 14% of the *H. pylori* positive patients. Healing of gastritis was most evident for patients with a lower grade of gastritis.[45] Nevertheless, even if these preneoplastic lesions are not fully reversible, it is possible that *H. pylori* eradication leads to a detention of further progression of the preneoplastic lesions already present.

At present time it is not clear in which stage of gastric carcinogenesis (atrophy, metaplasia and dysplasia) it is still possible to interrupt the development of gastric cancer. Progression of atrophic gastritis and intestinal metaplasia into gastric cancer can also occur despite a successful *H. pylori* eradication, pointing to the existence of a "point of no return" in the model of gastric carcinogenesis. Obviously, specific molecular-biological and cell genetic events are already present at this time, which perpetuate themselves so that *H. pylori* elimination does not result in regression of the carcinogenic process. Therefore, it is very important that the implementation of any interventional and preventive strategies which lead to a reduction of the incidence of gastric cancer are applied before this irreversible "point of no return" has occurred.

Perspective

Nowadays it is unquestionable that *H. pylori*-induced chronic gastritis represents a critical predisposition for the emergence of the gastric cancer. Nonetheless, at current time the general prevention of gastric cancer is not yet feasible due to the high prevalence of the infection in the asymptomatic population. The first reason why this strategy cannot be implemented is the costs associated with antibiotic therapy. Nevertheless, there are several studies which show that the economic impact of a generalized *H. pylori* eradication would be favorable.[48,49] These studies show that *H. pylori* eradication would lead to a

reduction of long-term health-costs for the treatment of dyspepsia and ulcer-associated disorders and a lower incidence of gastric cancer would be expected.[48,49] The second reason why a generalized *H. pylori* eradication has not yet been implemented is the lack of the final and undisputed proof that *H. pylori* eradication significantly reduces the incidence of gastric cancer. But in order to evaluate the influence of *H. pylori* eradication on the incidence of gastric cancer, a very large multicentric, multinational, prospective, double-blinded, placebo-controlled study with long-term follow-up needs to be performed. But such a study, with todays knowledge regarding *H. pylori* infection and its consequences is nearly impossible to accomplish. First of all, many patients must be recruited; secondly, the follow-up must be 10 or more years; and thirdly, it becomes difficulty (and unethical?) for physicians to recruit patients who remain untreated for many decades infected with a bacterium that they know is a proven carcinogen. At the present time, according to the Maastricht recommendations a pro-active eradication of *H. pylori* is indicated for first -degree relatives of patients with gastric cancer, patients with dyspepsia and patients with corpus-predominant gastritis.[5,12,18,21]

Conclusion

Gastric cancer is recognized as the second cause of cancer death world-wide. With todays level of knowledge, *H. pylori* infection can be accepted as the main risk factor in the pathogenesis of gastric cancer. Apart from epidemiological, biological, histomorphologic and molecular-genetic references we can rely on various clinical studies which show that *H. pylori* eradication can prevent the development of preneoplastic lesions and gastric cancer. Groups at risk for the development of gastric cancer should be systematically evaluated and searched for *H. pylori* infection, and if positive preventively treated. Because most gastric precancerous lesions do not progress or even regress after *H. pylori* eradication, we recommend *H. pylori* eradication for *H. pylori*-positive patients. The chance of success is more feasible if no preneoplastic lesions are present at the time of treatment. The treatment of the gastric cancer is still very unsatisfactory, thus prevention is an important task. The fight against gastric cancer by the preventive measure of *H. pylori* eradication brings an immense chance to clearly lower the incidence of this deadly disease worldwide.

References

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8-31,1.
2. Malfertheiner P, Peitz U, Wolle K, Treiber G. *Helicobacter pylori* Infektion--ein Update 2004 Dtsch Med Wochenschr 2004;129:1821-1826.
3. Glynn MK, Friedman CR, Gold BD, Khanna B, Hutwagner L, Iihoshi N, Revollo C, Quick R. Seroincidence of *Helicobacter pylori* infection in a cohort of rural Bolivian children: acquisition and analysis of possible risk factors. Clin Infect Dis 2002;35:1059-1065.
4. Aguemon BD, Struelens MJ, Massougbodji A, Ouendo EM. Prevalence and risk-factors for *Helicobacter pylori* infection in urban and rural Beninese populations. Clin Microbiol Infect 2005;11:611-617.
5. Nardone G, Morgner A. *Helicobacter pylori* and gastric malignancies. Helicobacter 2003;8:44-52.
6. Melo ET, Lopes EP, Almeida JR, Albuquerque HF, Moura IM. Seroprevalence of *H. pylori* antibodies in medical students and residents in Recife, Brazil. Clin Gastroenterol 2003;36:134-138.
7. Grimm W, Fischbach W. *Helicobacter pylori* infection in children and juveniles: an epidemiological study on prevalence, socio-economic factors and symptoms. Dtsch Med Wochenschr 2003;128:1878-1883.
8. Malfertheiner P, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G; European Helicobacter Pylori Study Group (EHPSG). Current concepts in the management of *Helicobacter pylori* infection - The Maastricht 2 - 2000 Consensus Report. Aliment Pharmacol Ther 2002;16:167-180.
9. Lauren P. the two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64:31-49.
10. Nardone G, Rocco A, Malfertheiner P. Review article: *Helicobacter pylori* and molecular events in precancerous gastric lesions. Aliment Pharmacol Ther 2004;20:261-70.
11. Henson DE, Dittus C, Younes M et al. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med 2004;128:765-770.
12. Ebert MPA, Malfertheiner P. Review article: pathogenesis of sporadic and familial gastric cancer - implications for clinical management and cancer prevention. Aliment Pharmacol Ther 2002;16:1059-1066.
13. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. Gastroenterology 1998;114:1169-79.
14. Brenner H, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D. Is H.p. infection a necessary condition for noncardia gastric cancer? Am J Epidemiol 2004;159:252-258.
15. Churin Y, Al-Ghoul L, Kepp O, Meyer TF, Birchmeier W, Naumann M. *Helicobacter pylori* CagA protein targets the c-Met receptor and enhances the mitogenic response. J Cell Biol 2003;28:249-255.
16. Ekström M, Held M, Hansson LE, Engstrand L, Nyrén O. Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. Gastroenterology 2001;121:784-791

17. El-Omar EM, Rabkin CS, Gammon MD, Voughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF, Chow W. Increased risk of noncardiogastric cancer associated with proinflammatory cytokine polymorphismus. Gastroenterology 2003;124: 1193-1201
18. Malfertheiner P, Sipponen P, Naumann M, Moayyedi P, Megraud F, Xiao SD, Sugano K, Nyren O; Lejondal *H. pylori*-Gastric Cancer Task Force. *Helicobacter pylori* eradication has the potential to prevent gastric cancer: a state-of-the-art critique. Am J Gastroenterol 2005;100:2100-2115.
19. Malfertheiner P, Fry LC, Mönkemüller K. Can gastric cancer be prevented by *Helicobacter pylori* eradication? Ballieres Clin Gastroenterol 2006;20:709-719.
20. Meining AG, Bayerdorffer E, Stolte M. *Helicobacter pylori* gastritis of the gastric cancer phenotype in relatives of gastric carcinoma patients. Eur J Gastroenterol Hepatol 1999;11:717-720.
21. Peek RM Jr, Blaser MJ, Mays DJ, Forsyth MH, Cover TL, Song SY, Krishna U, Pietenpol JA. *Helicobacter pylori* strain-specific genotypes and modulation of the gastric epithelial cell cycle. Cancer Res 1999;59:6124-6431.
22. Fuccio L, Zagari RM, Minardi ME, Bazzoli F. Systematic review: *Helicobacter pylori* eradication for the prevention of gastric cancer. Aliment Pharmacol Ther 2007;25:133-141.
23. Parsonnet J, Friedman GD, Vandersteen DP et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-1131.
24. Forman D, Newell DG, Fullerton F et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. BMJ 1991;302:1302-1305.
25. Hansen S, Melby KK, Aase S et al. *Helicobacter pylori* infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study. Scand J Gastroenterol 1999; 34:353-360.
26. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49:347-353.
27. Fischbach W, Goebeler-Kolve ME, Dragosics B, Greiner A, Stolte M. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive *Helicobacter pylori* eradication therapy: experience from a large prospective series. Gut 2004;53:34-37.
28. Tatematsu M, Tsukamoto T, Toyoda T. Effects of eradication of *Helicobacter pylori* on gastric carcinogenesis in experimental models. J Gastroenterol 2007;42 (Suppl 17):7-9.
29. Watanabe T, Tada M, Nagai H, Sasaki S, Nakao M. *Helicobacter pylori* infection induces gastric cancer in mongolian gerbils. Gastroenterology 1998;115:642–648.
30. Nozaki K, Shimizu N, Tsukamoto T, Inada K, Cao X, Ikehara Y, Kaminishi M, Sugiyama A, Tatematsu M. Reversibility of heterotopic proliferative glands in glandular stomach of *Helicobacter pylori*-infected Mongolian gerbils on eradication. Jpn J Cancer Res 2002;93:374-381.
31. Fox JG, Wang TC, Rogers AB et al. Host and microbial constituents influence *Helicobacter pylori*-induced cancer in a murine model of hypergastrinemia. Gastroenterology 2003;124:1879-1890.
32. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, Sasaki N, Haruma K, Sumii K, Kajiyama G. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997; 6:639-642.
33. Saito K, Arai K, Mori M, Kobayashi R, Ohki I. Effect of *Helicobacter pylori* eradication on malignant transformation of gastric adenoma. Gastrointest Endosc 2000;52:27-32
34. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. H.p. infection and the development of gastric cancer. N Engl J Med 2001;345:784-789.
35. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS; China Gastric Cancer Study Group. H.p. eradication to prevent gastric cancer in a high-risk region of China. J Amer Med Assoc 2004;291:187-194.
36. Zhou LY, Lin SR, Ding SG, Huang XB, Zhang L, Meng LM, Cui RL, Zhu J. The changing trends of the incidence of gastric cancer after *Helicobacter pylori* eradication in Shandong area. Chin J Dig Dis 2005;6:114-115.
37. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, Oguma K. Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases. J Gastroenterol 2007;42 Suppl 17:21-27.
38. Tepes B, Kavcic B, Zaletel LK, Gubina M, Ihan A, Poljak M, Krizman I. Two- to four-year histological follow-up of gastric mucosa after *Helicobacter pylori* eradication. J Pathol. 1999;188:24-29.
39. Sung JJ, Lin SR, Ching JY, Zhou LY, To KF, Wang RT, Leung WK, Ng EK, Lau JY, Lee YT, Yeung CK, Chao W, Chung SC. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. Gastroenterology 2000;119:7-14.
40. Rocco A, Suriani R, Cardesi E, Venturini I, Mazzucco D, Nardone G. Gastric atrophy and intestinal metaplasia changes 8 years after *Helicobacter pylori* eradication. A blind, randomised study. Minerva Gastroenterol Dietol 2002;48:175-178.
41. Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, Sumii M, Tanaka S, Yoshihara M, Chayama K. *Helicobacter pylori* eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002;16:1449-1456.
42. Zhou L, Sung JJ, Lin S, Jin Z, Ding S, Huang X, Xia Z, Guo H, Liu J, Chao W. A five-year follow-up study on the pathological changes of gastric mucosa after *H. pylori* eradication. Chin Med J 2003;116:11-14.
43. Lu B, Chen MT, Fan YH, Liu Y, Meng LN. Effects of *Helicobacter pylori* eradication on atrophic gastritis and intestinal metaplasia: a 3-year follow-up study. World J Gastroenterol 2005;11:6518-6520.
44. Salih BA, Abasiyanik MF, Saribasak H, Huten O, Sander E. A follow-up study on the effect of *Helicobacter pylori* eradication on the severity of gastric histology. Dig Dis Sci 2005;50:1517-1522.

45. Mera R, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, Correa P. Long term follow up of patients treated for *Helicobacter pylori* infection. Gut 2005; 54:1536-1540.
46. Arkkila PE, Seppala K, Farkkila MA, Veijola L, Sipponen P. *Helicobacter pylori* eradication in the healing of atrophic gastritis: a one-year prospective study. Scand J Gastroenterol 2006;41:782-790.
47. Ito M, Tanaka S, Kamada T, Haruma K, Chayama K. Causal role of *Helicobacter pylori* infection and eradication therapy in gastric carcinogenesis. World J Gastroenterol 2006;12:10-16.
48. Roderick P, Davies R, Raftery J et al. Cost-effectiveness of population screening for *Helicobacter pylori* in preventing gastric cancer and peptic ulcer disease, using simulation. J Med Screen 2003;10:148-156.
49. Ford AC, Forman D, Bailey AG et al. A community screening program for *Helicobacter pylori* saves money: 10-year follow-up of a randomized controlled trial. Gastroenterology 2005;129:1910-1917.