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Effect of smoking on failure of *H. pylori* therapy and gastric histology in a high gastric cancer risk area of Colombia

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Summary

It has been proposed that eradication of Helicobacter pylori infection is a sound strategy for gastric cancer prevention. Several factors including smoking have been associated to treatment failure rates. This study aimed to evaluate the smoking effect on the efficacy of H. pylori therapy, as well as on the histological parameters in the gastric mucosa from subjects from a high gastric cancer risk area. Two-hundred-sixty-four Colombian subjects with gastric precancerous lesions who participated in a chemoprevention trial, received anti-H. pylori treatment at baseline and had data recorded on cigarette use, were included in this study. A detailed histopathological assessment of the gastric mucosa was performed in biopsies taken before any intervention. H. pylori eradication was assessed in gastric biopsies at 36 months post-treatment. The overall eradication rate was 52.3%; rates of 41.3% and 57.1% were observed for active-smokers and non-smokers, respectively. Multivariate logistic regression analysis showed that smokers had a 2-fold higher probability of failure in Helicobacter pylori eradication than non-smokers (OR: 2.0; 95% CI: 1.01–3.95). At baseline, active-smokers had a higher score of intestinal metaplasia compared to non-smokers. In the corpus mucosa, active- smokers showed lower scores of H. pylori density, total inflammation, neutrophil infiltration, and mucus depletion than non-smokers. In the antrum, no significant differences were observed between active-smokers and non-smokers. In summary, in patients who smoked, H. pylori treatment was less effective. Smoking cessation may benefit H. pylori eradication rates.

Keywords

Helicobacter pylori eradication; gastric mucosa; intestinal metaplasia; smoking; Latin America

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Helicobacter pylori (H. pylori) infection is a well-recognized cause of gastric cancer.[1] The potential role of *H. pylori* eradication in preventing gastric adenocarcinoma is a focus of great public health interest. Although major improvements have been made in the efficacy of treatment regimes, virtually all of them result in some failures to eradicate the bacterial infection.[2] Several factors including smoking have been reported to influence this adverse outcome.[3–7] A recent meta-analysis evaluating mainly studies from Europe, Asia, and North America showed that smoking increases the treatment failure rate for *H. pylori* eradication.[6] Because limited and contrasting data from developing countries were available for the meta-analysis (one report from Brazil),[3] we believe that information from a high gastric cancer risk population from Latin America will complement the published findings. Additionally, the effects of smoking on gastric histopathology are of interest.

Both tobacco and tobacco smoke contain thousands of compounds, including a variety of carcinogens, [8] among which N-nitroso compounds have been associated to gastric carcinogenesis.[9] Tobacco smoking is a long-term known risk factor for development of gastric preneoplastic lesions and gastric cancer.[8,10–15] Furthermore, in subjects infected with *H. pylori*, smoking increases the risk of intestinal metaplasia[16] and gastric cancer.[17]

In the present study, including subjects from a high gastric cancer risk area in Colombia, we evaluated the smoking effect on the efficacy of *H. pylori* therapy and on the histological parameters in the gastric mucosa.

Methods

Study subjects, *H. pylori* treatment, and follow-up

Detailed description of characteristics of the subjects, interventions, follow-up, and results of this chemoprevention trial were reported previously.[18,19] Briefly, adults from two towns from a high risk gastric cancer area in Colombia were screened in 1991. The subjects underwent upper gastrointestinal endoscopy and gastric mucosa biopsies from antrum, incisura angularis and corpus. Individuals with gastric preneoplastic lesions were randomly assigned to receive anti-*H. pylori* treatment with or without vitamin supplementation (ascorbic acid and beta-carotene), and/or placebo in a 2 × 2 × 2 factorial design for 6 years.[18] Anti-*H. pylori* treatment consisted of amoxicillin (500 mg three times per day), metronidazole (375 mg three times per day), and bismuth subsalicylate (262 mg three times per day) for 14 days. As assessed by interviews and recorded pill counts every three months, the patients´ compliance with therapy protocol was satisfactory. The subjects included in this report represent patients who received anti-*H. pylori* treatment at entry, had a follow- up endoscopy at 36 months and provided information about cigarette use at enrollment. According to their smoking habit, subjects were classified into "non-smokers" (those who never smoked), "active-smokers" (smokers at the date of the recruitment, who had been smoking for at least one year), and "ex-smokers". The latter group was excluded from this analysis. The prevalence of smoking was 30.3%. Most of them were light smokers (median: 3 cigarettes per day); therefore, no dose-response was evaluated.

Histopathology

Gastric biopsy specimens taken at baseline and 36 months of follow-up were fixed in formalin and embedded in paraffin. Four-micron-thick sections were stained with haematoxylin and eosin for regular histology, with Alcian blue-periodic acid Schiff to detect intestinal metaplasia, and with the modified Steiner silver technique to detect *H. pylori*.[20] Histological diagnostic categories were: multifocal atrophic gastritis without metaplasia (MAG) and multifocal atrophic gastritis with intestinal metaplasia (IM). MAG, defined as loss of glands, was graded as mild, moderate, or marked.[21] IM was defined as replacement of the gastric epithelium by intestinal-type epithelium. It was further subclassified as complete (small intestine-type), defined by the presence of absorptive enterocytes with brush border alternating with goblet cells, or incomplete (colonic type), defined by the presence of columnar cells with foamy cytoplasm, lacking brush border. Based on the global diagnostic categories (3=MAG and 4=IM), a previously used histopathology score [19] that reflects the grade of atrophy and the type and extent of IM, was applied. Briefly, the MAG score was augmented according to the degree of atrophy: 0.25=indefinite for atrophy, 0.50=mild, 0.75=moderate, and 1.0=severe. The IM score was modified according to the type and extension. IM type was classified into four categories in an ordinal scale: 0.1=complete type, 0.2=mixed predominant complete type, 0.3=mixed predominant incomplete type, and 0.4=incomplete type. The average extension of the IM was grouped by tertiles. Each tertile was given a value: 0.2, 0.4, or 0.6, respectively. In order to obtain a total score of IM, values for type and extension were added to the original score for IM.

Infiltration of mononuclear (MN) cells, polymorphonuclear neutrophils (PMN), intraepithelial lymphocytes, mucus depletion, regenerative activity, and density of *H. pylori* colonization were graded in a semiquantitative scale 0–3 (absent, mild, moderate, and marked). MN, PMN, and *H. pylori* density were evaluated according to the updated Sydney system.[21] The number of lymphoid follicles observed in each biopsy sample was registered.

Statistical analysis

Average values of every histological parameter were estimated considering the total number of biopsies and separately by gastric subsite (corpus and antrum). Data obtained from transitional mucosa were combined with those from antrum. Total inflammation score was the average of the scores for PMN and MN inflammation.

H. pylori status at 36 months was used as the proxy variable for eradication (presence of infection was considered as failure, and lack of infection as success). Student's *t* tests were used to test associations between histological parameters and smoking status. Multivariate logistic regression models were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) to assess the risk of eradication failure. A linear regression model was used to assess the relationship of IM score and smoking status, known risk factors of IM, such as age and sex were considered. All analyses were performed using Stata 9.0 software (Stata Corporation, College Station, TX).

Results

Results of the analysis of *H. pylori* eradication by smoking status and baseline diagnosis are presented in table 1. The overall eradication rate was 52.3%. Eradication rates in active-smokers and non-smokers were 41.3% and 57.1%, respectively. These rates were not significantly influenced by age and sex. The adjusted OR for eradication failure for active-smokers was 2.0 (95% CI: 1.01–3.95), indicating a 2-fold higher probability of failure in *H. pylori* eradication. Subjects with IM had a decreased risk of eradication failure compared with those with MAG (OR: 0.48; 95% CI: 0.26–0.87).

Histopathological parameters in the gastric mucosa at baseline according to smoking status are shown in table 2. Although there was not a difference between active- smokers and non-smokers regarding the global histopathological diagnosis, the unadjusted mean of the IM score (which considers the type and extension) was significantly higher among active-smokers than among non-smokers (~13 percent difference; p=0.042). The difference remained statistically significant after adjustment for age, sex, and town (p=0.016). Stratified analysis by gastric subsite showed significantly lower scores of *H. pylori* density, PMN infiltrate, total inflammation, and mucus depletion in the corpus of active-smokers compared to non-smokers. There were no differences in any of the scores in the antrum between the two groups.

Interestingly, subjects who did not eradicate the bacterium had a significantly higher score of *H. pylori* density at baseline than those with a successful eradication (1.82 versus 1.61, p-value for mean difference=0.019).

Discussion

Increasing evidence supports that *H. pylori* eradication prevents the development of gastric adenocarcinoma. A prospective, randomized study in China found that eradication of *H. pylori* significantly decreased the incidence of gastric cancer in subjects without precancerous lesions.[14] In a retrospective, large-scale study in Japan, a significantly lower incidence of gastric cancer was observed in subjects with eradication compared to those in whom the infection persisted.[22] In addition, studies considering preneoplastic lesions as an end-point also support the benefits of *H. pylori* therapy.[19,23,24]

Our results indicate that smoking was associated with anti-*H. pylori* treatment failure. Although this association has been described previously and addressed in a recent meta-analysis,[6] limited and conflicting evidence from studies conducted in developing countries exist.[3]

Regarding the possible mechanisms involved in treatment failure, it is known that smoking decreases gastric mucosal blood flow and mucus secretion, [25,26] which may reduce the delivery of antibiotics to the gastric mucosa. In addition, smoking increases acid gastric secretion, which lowers the efficacy of some acid labile antibiotics, such as amoxicillin and clarithromycin.[27] These two effects seem to be supported by a recent large study that reports increase in the cure rate in smokers (but not in nonsmokers) who received increased doses of clarithromycin. [28]

Besides smoking, multiple other factors have been associated with *H. pylori* eradication failure: poor compliance,[29] antibiotic resistance,[5] low grades of inflammation in antrum and activity in the fundus,[4] H2-receptor antagonist pre-treatment,[30] genetic polymorphisms of *CYP2C19* (with different effects on the metabolism of PPIs),[31] excessive bacterial burden,[7] and infection with low-virulence *H. pylori* strains.[3,32,33]

Previous studies in Colombian patients reported higher prevalence of more virulent *H. pylori* strains (*vacA*s1m1, *cagA*-positive, and *cagE*-positive) in subjects with gastric cancer and IM in comparison with subjects with gastritis (atrophic and non-atrophic). [34,35] Assuming that in our study more advanced lesions (IM) may have been caused by strains with higher virulence, it is not surprising that the failure rate was higher in patients with MAG than in those with IM (table 1). It has been suggested that treatment may be more effective in eliminating more virulent strains, resulting in only partial and/or selective eradication of *H. pylori* in mixed infections. [32]

In the United States, the current recommended primary therapies for *H. pylori* infection include: a clarithromicyn-based triple therapy (a proton pump inhibitor [PPI], clarithromycin, and amoxicillin or metronidazole) for 14 days, or a bismuth quadruple therapy (a PPI or H_2-receptor antagonist, bismuth, metronidazole, and tetracycline) for 10–14 days.[2] Eradication rates are in the range of 70–90%.[2] Subjects in our chemoprevention trial were treated (in 1991) with bismuth subsalicylate, amoxicillin, and metronidazole for 2 weeks, reaching a cure rate of 52.3% at 36 months of follow-up. This relatively low rate may have been caused by the treatment protocol, which did not include clarithromycin or an antisecretory drug. It has been suggested that the eradication rates correlate positively with the degree of inhibition of gastric acid secretion.[36] *H. pylori* resistance against metronidazole may have also played a role in treatment failure. The prevalence of *H. pylori* resistance to nitroimidazoles has been reported to be about 80% in tropical regions, where these drugs are frequently used for diarrhea treatment.[37] In our chemoprevention study, subjects who tested positive for *H. pylori* at 36 months were treated again for 14 days with amoxicillin, clarithromycin, and a PPI. The eradication rate was 74% at 72 months of follow-up.[18] Finally, as previously reported, [7] we observed that excessive bacterial burden may have been also involved in failure to the initial treatment.

Smoking is a risk factor for the development of gastric preneoplastic and neoplastic lesions [8,10–16] and *H. pylori* infection seems to increase this risk.[16,17] We did not find association between the histological diagnosis and the smoking status. It is likely that the presence of precancerous lesions in all the individuals influenced this result. However, active-smokers had significantly higher IM score (including extension and type) than non-smokers, indicating the presence of more advanced lesions.

Besides the carcinogenic effects of the N-nitroso compounds generated from the tobacco smoke components,[9] it is known that smoking impairs cell renewal process by several mechanisms, including reduced levels of epidermal growth factor, reduction of ornithine decarboxilase activity, and inhibition of constitutive nitric oxide synthesis.[38,39] In addition, smoking increases bile salt reflux rate and gastric bile salt concentration.[38,40] Several experimental studies have demonstrated that duodenogastric reflux (bile and/or

pancreaticoduodenal secretions) induces gastric adenocarcinoma.[41–43] *In vitro*, bile acid exposure has shown to promote intestinal differentiation in esophageal cell lines,[44] thereby starting the metaplasia-dysplasia-carcinoma sequence.

Regarding the histological parameters associated with inflammation and mucus depletion, we did not find differences in the antral mucosa between nonsmokers and active-smokers. It is likely that the effects of the *H. pylori* infection overlap those of the smoking, influencing the results. The lower scores in *H. pylori* density, total inflammation, and PMNs observed in the corpus mucosa of active-smokers compared to those of non-smokers may have a physiological explanation. Cigarette smoking increases gastric acid secretion by the parietal cells, located in the fundus and corpus of the stomach. The lower pH resultant may prevent *H. pylori* infection (which is predominantly antral) to disseminate to corpus and fundus, and therefore, lower scores of inflammation would be expected in these areas. The minor differences observed in histological parameters may be related to the low doses of tobacco smoke exposure (median: 3 cigarettes/day). Increased acid secretion has been observed in subjects who smoked at least 3 cigarettes per day compared to non-smokers.[45]

Despite its harmful effects on the gastric mucosa, cigarette smoking is consistently associated with lower incidence of ulcerative colitis and a lower relapse rate of the disease.[46,47] Studies have suggested that the beneficial effects of nicotine in ulcerative colitis are due to increased mucus secretion, and decreased production of proinflammatory cytokines and nitric oxide.[47] Future studies are needed to investigate these effects in the gastric mucosa.

A limitation of the present study was the assessment time of *H. pylori* eradication. The annual reinfection/ recrudescence rate of the cohort from which this sample was taken, was 5.4%.[19] Urea breath tests were performed on all subjects in the *H. pylori* treatment arm between the initial and the 3 year biopsies. Since the discrepancy in the infection status between the biopsy results and the breath tests was small, and because the breath tests had a significant variability in time, we favored the use of the biopsy results.

Considering that eradication of *H. pylori* infection may be a promising strategy to control gastric cancer, the observed adverse effect of smoking on eradication has an important public health implication. Particularly because while smoking rates have been decreasing for several decades in the United States and other industrialized countries, those in developing countries are increasing at around 3% per year.[48–50] While anti-smoking efforts are showing favorable results in developed countries, those efforts are far less effective in developing countries, where transnational tobacco companies have been increasingly promoting their products. This trend may result in poorer treatment outcomes in developing countries where *H. pylori* infection is highly prevalent.

In conclusion, on the basis of the findings of the published meta-analysis, and the additional information provided by our study, smoking increases the risk of *H. pylori* treatment failure. Smoking cessation may benefit *H. pylori* eradication rates. Therefore, infected smoker patients should be encouraged to quit their habit. Smoking also influences the gastric histopathologic parameters, decreasing the severity of the lesions in the corpus.

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Abbreviations

CI	confidence interval
H. pylori	*Helicobacter pylori*
IM	intestinal metaplasia
MAG	multifocal atrophic gastritis without metaplasia
MN	mononuclear cells
PMN	polymorphonuclear neutrophils
OR	odds ratio

References

1. IARC Monographs on the evaluation of carcinogenic risks to humans. Schistosomes, liver flukes and *Helicobacter pylori*. Lyon, France: International Agency for Research on Cancer. 1994; 61:177–240.
2. Chey WD, Wong BC. the Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol. 2007; 102:1808–1825. [PubMed: 17608775]
3. Queiroz DM, Dani R, Silva LD, Santos A, Moreira LS, Rocha GA, Correa PR, Reis LF, Nogueira AM, Alvares Cabral MM, Esteves AM, Tanure J. Factors associated with treatment failure of *Helicobacter pylori* infection in a developing country. J Clin Gastroenterol. 2002; 35:315–320. [PubMed: 12352294]
4. Kamada T, Haruma K, Komoto K, Mihara M, Chen X, Yoshihara M, Sumii K, Kajiyama G, Tahara K, Kawamura Y. Effect of smoking and histological gastritis severity on the rate of *H. pylori* eradication with omeprazole, amoxicillin, and clarithromycin. Helicobacter. 1999; 4:204–210. [PubMed: 10469195]
5. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. Aliment Pharmacol Ther. 2007; 26:343–357. [PubMed: 17635369]
6. Suzuki T, Matsuo K, Ito H, Sawaki A, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, Tajima K. Smoking increases the treatment failure for *Helicobacter pylori* eradication. Am J Med. 2006; 119:217–224. [PubMed: 16490464]
7. Moshkowitz M, Konikoff FM, Peled Y, Santo M, Hallak A, Bujanover Y, Tiomny E, Gilat T. High *Helicobacter pylori* numbers are associated with low eradication rate after triple therapy. Gut. 1995; 36:845–847. [PubMed: 7615271]
8. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans: Tobacco Smoke and Involuntary Smoking. Vol. 83. Lyon: International Agency for Research on Cancer; 2004.
9. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett. 1995; 93:17–48. [PubMed: 7600541]
10. Fontham E, Zavala D, Correa P, Rodriguez E, Hunter F, Haenszel W, Tannenbaum SR. Diet and chronic atrophic gastritis: a case-control study. J Natl Cancer Inst. 1986; 76:621–627. [PubMed: 3457199]
11. Kato I, Vivas J, Plummer M, Lopez G, Peraza S, Castro D, Sanchez V, Cano E, Andrade O, Garcia R, Franceschi S, Oliver W, Munoz N. Environmental factors in *Helicobacter pylori*-related gastric

precancerous lesions in Venezuela. Cancer Epidemiol Biomarkers Prev. 2004; 13:468–476. [PubMed: 15006925]

12. Gonzalez CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Siman H, Nyren O, Agren A, Martinez C, Dorronsoro M, Barricarte A, Tormo MJ, Quiros JR, Allen N, Bingham S, Day N, Miller A, Nagel G, Boeing H, Overvad K, Tjonneland A, Bueno-De-Mesquita HB, Boshuizen HC, Peeters P, Numans M, Clavel-Chapelon F, Helen I, Agapitos E, Lund E, Fahey M, Saracci R, Kaaks R, Riboli E. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Int J Cancer. 2003; 107:629–634. [PubMed: 14520702]
13. You WC, Zhang L, Gail MH, Chang YS, Liu WD, Ma JL, Li JY, Jin ML, Hu YR, Yang CS, Blaser MJ, Correa P, Blot WJ, Fraumeni JF Jr, Xu GW. Gastric dysplasia and gastric cancer: *Helicobacter pylori* serum vitamin C, and other risk factors. J Natl Cancer Inst. 2000; 92:1607–1612. [PubMed: 11018097]
14. 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. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 2004; 291:187–194. [PubMed: 14722144]
15. Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsugane S. Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2006; 36:800–807. [PubMed: 17210611]
16. Peleteiro B, Lunet N, Figueiredo C, Carneiro F, David L, Barros H. Smoking, *Helicobacter pylori* virulence, and type of intestinal metaplasia in Portuguese males. Cancer Epidemiol Biomarkers Prev. 2007; 16:322–326. [PubMed: 17301266]
17. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. Cancer Causes Control. 2000; 11:363–371. [PubMed: 10843447]
18. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, Mera R. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti- *Helicobacter pylori* therapy. J Natl Cancer Inst. 2000; 92:1881–1888. [PubMed: 11106679]
19. 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. [PubMed: 15985559]
20. Garvey W, Fathi A, Bigelow F. Modified Steiner for the demonstration of spirochetes. J Histotechnol. 1985; 8:15–17.
21. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996; 20:1161–1181. [PubMed: 8827022]
22. Kato M, Asaka M, Nakamura T, Azuma T, Tomita E, Kamoshida T, Sato K, Inaba T, Shirasaka D, Okamoto S, Takahashi S, Terao S, Suwaki K, Isomoto H, Yamagata H, Nomura H, Yagi K, Sone Y, Urabe T, Akamatsu T, Ohara S, Takagi A, Miwa J, Inatsuchi S. *Helicobacter pylori* eradication prevents the development of gastric cancer - results of a long-term retrospective study in Japan. Aliment Pharmacol Ther. 2006; 24:S203–S206.
23. You WC, Brown LM, Zhang L, Li JY, Jin ML, Chang YS, Ma JL, Pan KF, Liu WD, Hu Y, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF Jr, Xu GW, Gail MH. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst. 2006; 98:974–983. [PubMed: 16849680]
24. Leung WK, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut. 2004; 53:1244–1249. [PubMed: 15306578]
25. Iwao T, Toyonaga A, Ikegami M, Oho K, Sumino M, Sakaki M, Shigemori H, Harada H, Sasaki E, Tanikawa K. Gastric mucosal blood flow after smoking in healthy human beings assessed by laser Doppler flowmetry. Gastrointest Endosc. 1993; 39:400–403. [PubMed: 8514074]

26. Wu WK, Cho CH. The pharmacological actions of nicotine on the gastrointestinal tract. J Pharmacol Sci. 2004; 94:348–358. [PubMed: 15107574]
27. Gisbert JP, Gonzalez L, Calvet X. Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in *Helicobacter pylori* eradication. Helicobacter. 2005; 10:157–171. [PubMed: 15904473]
28. Ishioka H, Mizuno M, Take S, Ishiki K, Nagahara Y, Yoshida T, Okada H, Yokota K, Oguma KA. Better cure rate with 800 mg than with 400 mg clarithromycin regimens in one-week triple therapy for *Helicobacter pylori* infection in cigarette-smoking peptic ulcer patients. Digestion. 2007; 75:63–68. [PubMed: 17476101]
29. Wolle K, Malfertheiner P. Treatment of *Helicobacter pylori*. Best Pract Res Clin Gastroenterol. 2007; 21:315–324. [PubMed: 17382279]
30. Moayyedi P, Chalmers DM, Axon AT. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate *Helicobacter pylori*. J Gastroenterol. 1997; 32:24–27. [PubMed: 9058291]
31. Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol. 2006; 101:1467–1475. [PubMed: 16863547]
32. Correa P, van Doorn LJ, Bravo JC, Ruiz B, Bravo LE, Realpe JL. Unsuccessful treatment results in survival of less virulent genotypes of *Helicobacter pylori* in Colombian patients. Am J Gastroenterol. 2000; 95:564–566. [PubMed: 10685783]
33. Suzuki T, Matsuo K, Sawaki A, Ito H, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, Tajima K. Systematic review and meta-analysis: importance of CagA status for successful eradication of *Helicobacter pylori* infection. Aliment Pharmacol Ther. 2006; 24:273–280. [PubMed: 16842453]
34. Cittelly DM, Huertas MG, Martinez JD, Oliveros R, Posso H, Bravo MM, Orozco O. *Helicobacter pylori* genotypes in non atrophic gastritis are different of the found in peptic ulcer, premalignant lesions and gastric cancer in Colombia. Rev Med Chil. 2002; 130:143–151. [PubMed: 11974526]
35. Quiroga AJ, Cittelly DM, Bravo MM. BabA2, oipA and cagE *Helicobacter pylori* genotypes in Colombian patients with gastroduodenal diseases. Biomedica. 2005; 25:325–334. [PubMed: 16276680]
36. Murakami K, Sato R, Kubota T, Fujioka T, Nasu M. Effects of new triple therapy regimens on inhibition ofgastric acid secretion and eradication of *Helicobacter pylori* in a randomized trial [Abstract]. Gastroenterology. 1999; 116:A260.
37. Peitz U, Hackelsberger A, Malfertheiner P. A practical approach to patients with refractory *Helicobacter pylori* infection, or who are re-infected after standard therapy. Drugs. 1999; 57:905–920. [PubMed: 10400404]
38. Maity P, Biswas K, Roy S, Banerjee RK, Bandyopadhyay U. Smoking and the pathogenesis of gastroduodenal ulcer - recent mechanistic update. Mol Cell Biochem. 2003; 253:329–338. [PubMed: 14619984]
39. Ma L, Wang WP, Chow JY, Lam SK, Cho CH. The role of polyamines in gastric mucus synthesis inhibited by cigarette smoke or its extract. Gut. 2000; 47:170–177. [PubMed: 10896906]
40. Muller-Lissner SA. Bile reflux is increased in cigarette smokers. Gastroenterology. 1986; 90:1205–1209. [PubMed: 3956939]
41. Miwa K, Hasegawa H, Fujimura T, Matsumoto H, Miyata R, Kosaka T, Miyazaki I, Hattori T. Duodenal reflux through the pylorus induces gastric adenocarcinoma in the rat. Carcinogenesis. 1992; 13:2313–2316. [PubMed: 1473239]
42. Miwa K, Fujimura T, Hasegawa H, Kosaka T, Miyata R, Miyazaki I, Hattori T. Is bile or are pancreaticoduodenal secretions related to gastric carcinogenesis in rats with reflux through the pylorus? J Cancer Res Clin Oncol. 1992; 118:570–574. [PubMed: 1517278]
43. Taylor PR, Mason RC, Filipe MI, Vaja S, Hanley DC, Murphy GM, Dowling RH, McColl I. Gastric carcinogenesis in the rat induced by duodenogastric reflux without carcinogens: morphology, mucin histochemistry, polyamine metabolism, and labelling index. Gut. 1991; 32:1447–1454. [PubMed: 1773947]

44. Hu Y, Jones C, Gellersen O, Williams VA, Watson TJ, Peters JH. Pathogenesis of Barrett esophagus: deoxycholic acid up-regulates goblet-specific gene MUC2 in concert with CDX2 in human esophageal cells. Arch Surg. 2007; 142:540–545. [PubMed: 17576890]
45. Derakhshan MH, El-Omar E, Oien K, Gillen D, Fyfe V, Crabtree JE, McColl KE. Gastric histology, serological markers and age as predictors of gastric acid secretion in patients infected with *Helicobacter pylori*. J Clin Pathol. 2006; 59:1293–1299. [PubMed: 16644877]
46. Höie O, Wolters F, Riis L, Aamodt G, Solberg C, Bernklev T, Odes S, Mouzas IA, Beltrami M, Langholz E, Stockbrügger R, Vatn M, Moum B. on behalf of the European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD). Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. Am J Gastroenterol. 2007; 102:1692–1701. [PubMed: 17555460]
47. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007; 369:1627–1640. [PubMed: 17499605]
48. Chelala C. Tobacco corporations step up invasion of developing countries. Lancet. 1998; 35:889. [PubMed: 9525381]
49. Gajalakshmi, CK.; Jha, P.; Ranson, K.; Nguyen, S. Global patterns of smoking and smoking attributable mortality: Section I. In: Jha, P.; Chaloupka, FJ., editors. Tobacco use and its consequences in tobacco control in developing countries. New York: Oxford University Press; 2000.
50. National Center for Health Statistics. Health, United States, 2006 with chartbook on trends in the health of Americans. Washington, DC, Hyattsville, MD: U.S. Government Printing Office; 2006.

Table 1

Odds ratios and 95% confidence intervals of eradication failure by smoking status and baseline histological diagnosis.

	***H. pylori* eradication**[a]		
	Success n=138	**Failure n=126**	***Adjusted OR (95% CI)***
Smoking status, n(%)			
Non-smoker	105(57.1)	79(42.9)	1.0
Active-smoker	33(41.3)	47(58.7)	2.0(1.01 – 3.95)[b]
Histopathological diagnosis, n(%)			
Multifocal atrophic gastritis	23(37.7)	38(62.3)	1.0
Intestinal metaplasia	115(56.6)	88(43.4)	0.48(0.26 – 0.87)[c]

Abbreviations: OR, Odds ratio; CI, confidence interval

[a] Status based on *H. pylori* status at 36 months of follow-up

[b] Adjusted by age, sex, town, intervention (consumption of ascorbic acid and beta-carotene), and baseline histological diagnosis

[c] Adjusted by age, sex, town, intervention (consumption of ascorbic acid and beta-carotene), and smoking status

Table 2

Histological parameters by smoking status at baseline

Histological parameters at baseline	Smoking status at baseline		
	Non-smoker n=184	**Active-smoker n=80**	***Two-sided p-value***
Histopathological diagnosis, n(%)			
Multifocal atrophic gastritis	43(23.4)	18(22.5)	0.878
Intestinal metaplasia	141(76.6)	62(77.5)	
Histopathological score, mean (SD)	4.26(0.43)	4.33(0.44)	0.251
Total score of Intestinal metaplasia, mean (SD)	0.48(0.19)	0.54(0.22)	0.042
Density of *H. pylori* colonization, mean (SD)			
Total	1.69(0.74)	1.75(0.67)	0.516
Antrum	1.58(0.78)	1.71(0.76)	0.186
Corpus	2.10(0.77)	1.88(0.72)	0.050
Polymorphonuclears, mean (SD)			
Total	1.91(0.66)	1.97(0.58)	0.484
Antrum	1.87(0.71)	2.00(0.63)	0.165
Corpus	2.08(0.74)	1.78(0.87)	0.011
Mononuclears, mean (SD)			
Total	1.93(0.26)	1.92(0.22)	0.740
Antrum	1.94(0.29)	1.93(0.23)	0.764
Corpus	1.93(0.35)	1.86(0.42)	0.230
Total inflammation, mean (SD)			
Total	1.92(0.44)	1.95(0.37)	0.662
Antrum	1.91(0.47)	1.97(0.40)	0.334
Corpus	2.00(0.50)	1.83(0.59)	0.020
Intraepithelial lymphocytes, mean (SD)			
Total	0.31(0.32)	0.37(0.37)	0.195
Antrum	0.36(0.39)	0.45(0.43)	0.112
Corpus	0.16(0.36)	0.10(0.28)	0.255
Mucus depletion, mean (SD)			
Total	2.11(0.97)	2.13(0.92)	0.917
Antrum	2.11(1.02)	2.20(0.98)	0.511
Corpus	2.19(1.09)	1.87(1.14)	0.050
Lymphoid follicles, mean (SD)			
Total	0.33(0.30)	0.33(0.31)	0.937
Antrum	0.37(0.36)	0.34(0.35)	0.598
Corpus	0.22(0.47)	0.22(0.43)	0.963
Regenerative activity, mean (SD)			
Total	0.60(0.52)	0.66(0.53)	0.405
Antrum	0.68(0.59)	0.75(0.62)	0.358
Corpus	0.43(0.63)	0.32(0.61)	0.204

Abbreviation: SD: Standard deviation