The American Journal of Medicine (2006) 119, 217-224

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

REVIEW

Smoking Increases the Treatment Failure for *Helicobacter pylori* Eradication

Takeshi Suzuki,[a,b] Keitaro Matsuo,[a] Hidemi Ito,[a] Akira Sawaki,[c] Kaoru Hirose,[a] Kenji Wakai,[a] Shigeki Sato,[b] Tsuneya Nakamura,[d] Kenji Yamao,[c] Ryuzo Ueda,[b] Kazuo Tajima[a]

[a]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan; [b]Department of Internal Medicine and Molecular Science, Nagoya City University Graduate School of Medical Science; [c]Department of Gastroenterology, Aichi Cancer Center Central Hospital; [d]Department of Endoscopy, Aichi Cancer Center Central Hospital, Nagoya, Japan

ABSTRACT

PURPOSE: Treatment failure for *Helicobacter pylori* (*H. pylori*) eradication is encountered in approximately 10-20% of patients, and many studies have pointed to a link with smoking. To investigate the effects of smoking on eradication outcome, we performed a meta-analysis.

METHODS: A PubMed search was performed to retrieve articles published up to August 2005. Pooled odds ratio (OR) and differences rate for *H. pylori* eradication failure in smokers compared with nonsmokers were used as summary statistics. Meta-regression was used for examining the source of heterogeneity.

RESULTS: Twenty-two published studies (5538 patients), which provided information on eradication failure according to smoking status, were included in the analysis. The summary OR for eradication failure among smokers relative to nonsmokers was 1.95 (95% confidence interval [CI]: 1.55-2.45; $P < .01$). It corresponds with the differences in eradication rates between smokers and nonsmokers (8.4% [95% CI: 3.3-13.5%, $P < .01$]). Meta-regression analysis demonstrated that a high proportion of nonulcer dyspepsia patients in studies revealed a higher failure rate among smokers, compared with a low proportion of nonulcer dyspepsia.

CONCLUSIONS: Our meta-analysis demonstrated that smoking increases the treatment failure rate for *H. pylori* eradication.

KEYWORDS: *Helicobacter pylori;* Smoking; Heterogeneity; Meta-analysis

Helicobacter pylori (*H. pylori*) infection is associated with chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphomas, and gastric cancer.[1-3] Triple drug therapies involving a proton pump inhibitor and 2 antibiotics for *H. pylori* eradication have been developed, and eradication rates of more than 80% have been reported with this approach.[4] However, treatment failure is encountered in approximately 10-20% of patients. Several factors such as poor compliance[5]; antibiotic resistance[5,6]; the disease of the patient, for example, peptic ulcer versus nonulcer dyspepsia[7]; coffee consumption[8]; and strain differences[9,10] have been reported to influence the response to *H. pylori* eradication therapy.

A number of studies have provided evidence that smoking is a potential risk factor for *H. pylori* eradication failure[11-20]; however, several articles found no association.[7,21]

The aim of the present study is to clarify the association between smoking and eradication failure for *H. pylori* by means of a systematic review of the literature, with a particular focus on heterogeneity in infection-related disease.

This work was supported in part by a Grant-in-Aid for Cancer Research (17-1) from the Ministry of Health, Labour and Welfare, Tokyo, Japan.

Correspondence should be addressed to Keitaro Matsuo, MD, PhD, MSc, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute 1-1 Kanokoden, Chikusa-ku Nagoya 464-8681, Japan Phone: +81-52-762-6111, Fax: +81-52-763-5233.

E-mail address: kmatsuo@aichi-cc.jp

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2005.10.003

MATERIALS AND METHODS

Selection of Studies

The initial literature search was conducted through PubMed by using the free text search term: (*helicobacter pylori*) AND (*smoking* OR *smoker* OR *tobacco*) AND (*eradication*), with the publication period limited up to August 2005. The inclusion criteria for our analysis were: 1) original articles published in English; 2) odds ratios (ORs) available as a measure of association or the number of succeeded and failed cases according to the smoking category; 3) use of the urea breath test or histological examination to define treatment success; 4) use of 3 or more drugs for *H. pylori* eradication therapy. Studies of second-line therapy for *H. pylori* eradication were excluded. All potentially relevant articles were reviewed by 2 investigators (T.S. and K.M.) independently, and disagreement was resolved by discussion. The reference lists of the studies identified through the search process also were checked in order to exhaustively identify candidate studies.

Data Abstraction

Two investigators (T.S. and K.M.) abstracted the data independently using a standard information extraction form. Characteristics abstracted from the articles included: the name of the first author, year of publication, country of study, disease of subjects, proportion of disease in each study, definition of eradication, study design, therapy regimen for eradication, and numbers of successful and failed eradications by smoking category.

Statistical Analysis

Pooled odds ratios (OR) and rate difference were calculated to assess the eradication failure with smokers compared with nonsmokers using the inverse variance method. We calculated the between-study variation ($\tau 2$) from the Q statistic with the method described by DerSimonian and Laird.[22] Weights for each study were given by taking inverse variance estimates of each study and $\tau 2$ into consideration. Based on the significance of the Q statistics, we decided which model to use (random-effect or fixed-effect) in order to calculate summary ORs or summary rate differences and their 95% confidence intervals (CI). Heterogeneity among studies was further evaluated by meta-regression analysis.[23] The factors examined were the following: study conducted in Asian countries (yes/no); using omeprazole for eradication therapy (yes/no); using clarithromycin (yes/no); using metronidazole (yes/no); the proportion of nonulcer dyspepsia subjects in each study; using the urea breath test to define treatment success (yes/no); and published year. We defined a *P*-value of less than .05 as a statistically significant test result for a summary OR, rate difference and meta-regression analysis. Publication bias was assessed by Begg's funnel plots and Begg's test.[24] We used the STATA statistical package (Version 8; StataCorp LP, College Station, Tex) for all analyses in this study.

CLINICAL SIGNIFICANCE

- Treatment failure for *Helicobacter pylori* in smokers was about double compared to in non-smokers. The difference in eradication rates between smokers and non-smokers was 8.4%.
- Although the association was elucidated by means of a meta-analysis, a prospective intervention study is required to apply smoking cessation as a routine practice in *H. pylori* eradication.

RESULTS

Description of the Studies

The search yielded a total of 134 publications, 36 of which were excluded by screening of their titles. Abstracts of the remaining 98 articles were reviewed, and 59 were retrieved in full for further consideration. We examined all the candidate articles in detail, which resulted in further exclusion of 37 articles. They were excluded because 1) data for ORs or the number of eradication cases according to the smoking category could not be obtained (n = 26); 2) therapies were second line (n = 4); 3) use of two drugs for *H. pylori* eradication was performed (n = 4); 5) urea breath test or histological examination for definition of eradication was not performed (n = 1); or 6) studies covered the same data from the same investigators (n = 2). Finally, 22 studies were selected for the meta-analysis[7,11-21, 25-34] (Table 1). The selection process is summarized in Figure 1.

The geographical areas where studies were conducted varied: Europe (n = 15), Asia (n = 4), North America (n = 2), and Brazil (n = 1). Numbers of subjects ranged from 48 to 2313. The total number of subjects in these studies was 5538. Four studies concerned quadruple drug therapies. One was a randomized study comparing triple and quadruple therapies.[33] One was a randomized study comparing lansoprazole and ranitidine combining 3 antibiotics.[15] The other 2 were randomized studies comparing sequential and conventional therapy.[17,18]

Proton pump inhibitor was included in the eradication regimen in 19 studies, whereas clarithromycin and metronidazole were featured in 17 and 7 studies, respectively. Ten studies included patients with nonulcer dyspepsia as subjects. Descriptions concerning compliance with therapy were found in 19 of 22 studies. Information on the number of eradications in smoking and nonsmoking groups was available for 13 studies (Table 2).

We performed tests for homogeneity using all subject studies for the analysis using OR as a measure of association, and obtained a statistically significant result (Q = 40.8 with degrees of freedom = 24, P = .02, $\tau 2$ = 0.104), indicating the existence of between-study variability. A

Table 1 List of Studies Included in the Meta-analysis

Authors	Country	Categories of Therapies	% of NUD (No.)	Definition of Eradication	Treatment		Detail of the Study	% of Eradication (no.)	ORs[a] for Eradication Failure in Smokers
Cutler and Schubert[26] (1993)	US		29 (28/96)	UBT and histology	BIS	MET TC	One arm trial	83 (80/96)	3.10 (1.02–9.41)
O'Connor et al[27] (1995)	Ireland		0	Histology and urease test	BIS	MET TC	One arm trial	85 (72/85)	1.43 (0.43–4.80)
Bertoni et al[21] (1996)	Italy		NR[c]	Histology and urease test	OME	AMO AZI	RCT for 3- or 2- drug regimens[b]	92 (44/48)	0.58 (0.06–6.09)
Moayyedi et al[11] (1997)	UK		0	UBT	OME	CAM TIN	One arm trial	87 (238/273)	1.61 (1.09–2.38)
Kirstein et al[25] (1998)	Germany	BMT arm	45 (20/44)	UBT	BIS	MET TC	RCT for BMT, OMC and 2 drugs regimens[b]	91 (39/43)	0.95 (0.12–7.44)
		OMC arm	64 (28/44)		OME	CAM MET		90 (38/42)	0.33 (0.03–3.50)
Kamada et al[12] (1999)	Japan		42 (58/137)	UBT and histology	OME	AMO CAM	One arm trial	72 (98/137)	2.94 (1.27–6.82)
Fallone et al[28] (2000)	Canada		0	Histology and culture	BIS	AMO MET	RCT for 3, 2 or 1 drug regimens[b]	72 (63/87)	1.12 (0.42–2.97)
Gisbert et al[29] (2000)	Spain		75 (112/150)	UBT	PAN or RBC	AMO CAM	Mixture of PAN or RBC regimens	73 (109/150)	4.64 (2.16–9.98)
Kaushik and Vu[30] (2000)	Singapore		0	UBT, histology or urease test	LAN	AMO CAM	One arm trial	87 (98/113)	1.69 (0.38–7.69)
Maconi et al[13] (2001)	Italy		50 (71/142)	UBT	LAN	AMO CAM	Mixture of LAN 7 days or 14 days regimens	85 (110/129)	3.98 (1.00–15.00)
Perri et al[14] (2001)	Italy		0	UBT	PAN	AMO CAM	One arm trial	63 (89/142)	1.37 (1.01–1.87)
Treiber et al[15] (2002)	Germany		36 (87/243)	UBT	LAN or RAN	AMO CAM MET	Mixture of 5 days LAN, 5 Days RAN or 3 days LAN regimens	86 (202/234)	2.56 (1.09–5.88)
Baena et al[31] (2002)	Spain		0	UBT	OME	AMO CAM	One arm trial	76 (118/156)	1.33 (0.62–2.86)
Queiroz et al[32] (2002)	Brazil		0	UBT	PAN	CAM FUR	One arm trial	88 (85/97)	0.81 (0.20–3.29)
Mantzaris et al[33] (2002)	Greece		0	Histology, urease test and immunohistochemistry	OME	AMO CAM	Mixture of 3 or 4 drug regimens	72 (107/149)	3.75 (1.40–6.10)
					OME and BIS	MET TC			
Broutet et al[7] (2003)	France		61 (1400/2313)	UBT or histology and culture or PCR	PPI	AMO CAM etc.	One arm trial	73 (1699/2313)	1.20 (0.90–1.50)
Lee et al[16] (2003)	Korea		0	UBT	RAB	AMO CAM	One arm trial	84 (98/116)	4.11 (1.35–12.44)
De Francesco et al[17] (2004)	Italy		65 (224/342)	UBT, histology and urease test	RAB	AMO CAM TIN	RCT for sequential or conventional regimens	83 (285/342)	3.50 (1.50–7.70)
Wu et al[34] (2004)	Taiwan		0	UBT or histology and urease test	CET or PAN	AMO CAM	RCT for CET or PAN regimens	83 (48/58)	3.23 (0.71–10.00)

Table 1 List of Studies Included in the Meta-analysis

Authors	Country	Categories of Therapies	% of NUD (No.)	Definition of Eradication	Treatment		Detail of the Study	% of Eradication (no.)	ORs[a] for Eradication Failure in Smokers
Janssen et al[18] (2004)	Netherlands		51 (39/76)	Histology, urease test and culture	LAN and BIS	MET TC	RCT for LAN pretreated or nonpretreated	75 (57/76)	4.76 (1.25–10.00)
Koivisto et al[19] (2005)	Finland	LAM arm	0	UBT	LAN	AMO MET	RCT for LAM, LAC and RMT arm	78 (83/106)	1.08 (0.35–3.32)
		LAC arm	0		LAN	AMO CAM		91 (100/110)	4.50 (1.17–17.25)
		RMT arm	0		RBC	MET TC		81 (92/113)	0.90 (0.27–3.00)
Manes et al[20] (2005)	Italy		NR[d]	UBT	OME	CAM TIN	RCT for OME dose, 40 or 80 mg	83 (267/323)	2.68 (1.40–5.20)

OR = odds ratio; 95% CIs = 95% confidence Interval; BMT = bismuth citrate, metronidazole and tetracycline; OMC = omeprazole, metronidazole and clarithromycin; LAM = lansoprazole, amoxicillin and metronidazole; RMT = ranitidine bismuth citrate, metronidazole and tetracycline; NUD = nonulcer dyspepsia; UBT = urea breath test; BIS = bismuth citrate; OME = omeprazole; PAN = pantoprazole; RBC = ranitidine bismuth citrate; LAN = lansoprazole; RAN = ranitidine; PPI = proton pump inhibitor; RAB = rabeprazole; CET = cetraxate; TC = tetracycline; MET = metronidazole; AZI = azithromycin; AMO = amoxicillin; CAM = clarithromycin; TIN = tinidazole; FUR = furazolidone; RCT = randomized controlled trial; NR = no reference.

aReported odds ratios and 95% confidence intervals were used if available from literature and calculated if those were unavailable. Odds ratio >1.0 indicates that eradication failure rate in smokers is higher than in nonsmokers.

bData is only triple drugs study.

cProportion of NUD was not described.

dEligible diseases were not described.

similar result was obtained in the analysis using difference in percentage of failure as a measure of association (Q = 31.3 with degrees of freedom = 15, $P < .01$, $\tau 2 = 0.005$). Therefore, we decided to use a random-effect model to obtain summary statistics.

Meta-analysis

The ORs for eradication failure among smokers relative to nonsmokers in each study are illustrated in Figure 2. The summary OR for eradication failure for smokers was 1.95 (95% CI: 1.55-2.45, $P < .01$), indicating an approximately 2-fold higher probability of failure in *H. pylori* eradication. A Begg's test did not support the existence of publication bias ($Z = -1.03$, $P = .30$), the symmetrical distribution of studies in the funnel plot being consistent with the test (Figure 3).

The summary of differences in probability of eradication success between smokers and nonsmokers was 8.4% (95% CI: 3.3-13.5, $P < .01$), indicating that smokers have an 8.4% higher probability of *H. pylori* eradication failure as compared with nonsmokers (Table 2). Again, publication bias was not detected in the analysis using difference as a measure of association (data not shown).

Evaluation of Source of Heterogeneity

The sources of heterogeneity examined by meta-regression analysis are shown in Table 3. Nonulcer dyspepsia proportion was statistically significant ($P < .01$ with a coefficient value of .013 for nonulcer dyspepsia proportion), indicating a larger OR in eradication failure of smoking. In contrast, Asian study, types of drug used, eradication assessment by urea breath test, and year of publication were not statistically significant.

DISCUSSION

This study shows that smoking increases risk of treatment failure for *H. pylori* eradication. We also found significant low rate of eradication among smokers. Of 22 studies we selected to examine, 12 studies observed a significant increase in ORs for eradication failure in smokers. Of 13 studies in which we could gain information about difference rate of eradication according to smoking category, 11 studies observed a higher rate of eradication failure in smokers compared with nonsmokers. The results of our study are consistent with these studies.

It is important to understand possible mechanisms behind the negative effects of cigarette smoking on eradication. Firstly, it is well known that smoking decreases gastric blood flow and mucus secretion[35,36] and, thus, might reduce the delivery of antibiotics to the gastric mucosa. Secondly, smoking stimulates acid secretion,[37] which has been associated with treatment failure.[38] Because amoxicillin is an acid-sensitive antibiotic, the efficacy of amoxicillin might be lowered in smokers.

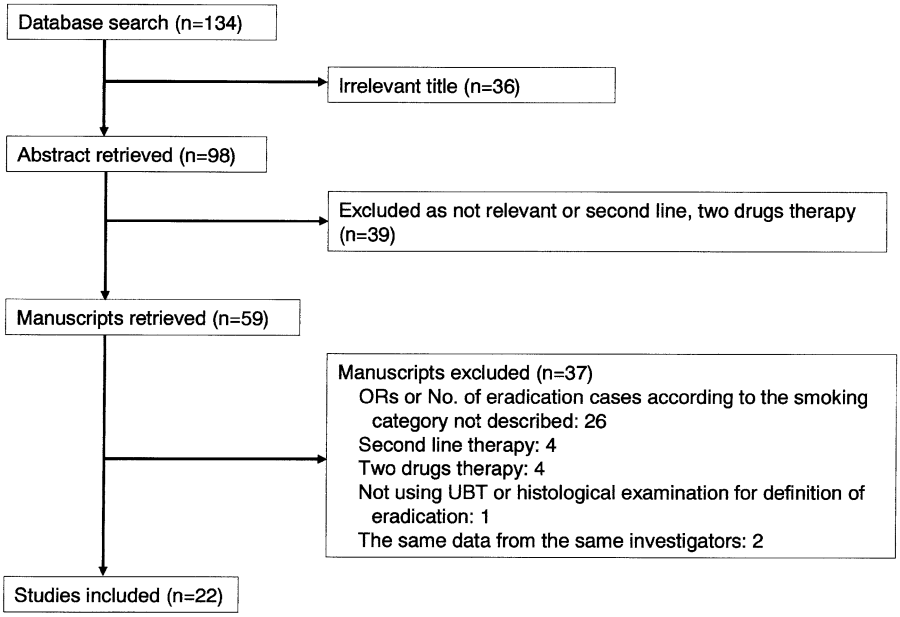

Figure 1 Study selection procedure. Of 134 publications identified by the initial literature search, 22 studies were finally selected for the meta-analysis. OR = odds ratio; UBT = urea breath test.

Thirdly, smoking might modulate the activity of specific cytochrome P450 isoenzymes involved in the metabolism of proton pump inhibitor.[39-41] Omeprazole and other proton pump inhibitors are mainly metabolized in the liver by a genetically determined enzyme, Smephenytoin 4'-hydroxylase (cytochrome P4502C19).[42,43] Fourthly, the effect of smoking might be attributable to other confounders such as reduced compliance. It is known that a major reason for treatment failure previously described is a lack of compliance with treatment[5] and smoking may simply be a marker of poor compliance.[44]

The interaction between smoking and *H. pylori* infection has been reported. It was found that the *H. pylori* infection was positively associated with smoking.[45,46]

Table 2 Summary Difference Rate of Eradication in Smokers and Nonsmokers

		Summary Different Rate[a] (%)	8.4	
		95% CI	3.3–13.5	
		P-value	<.01	
Authors	Categories of Therapies	Weights of Each Study[b] (%)	% Eradication in Smoker (No. of Subjects)	% Eradication in Nonsmoker (No. of Subjects)
Cutler and Schubert[26]		6	74 (28/38)	90 (52/58)
O'Connor et al[27]		6	83 (38/46)	87 (34/39)
Bertoni et al[21]		6	94 (16/17)	90 (28/31)
Kirstein et al[25]	BMT arm	5	91 (20/22)	90 (19/21)
	OMC arm	5	95 (19/20)	86 (19/22)
Kamada et al[12]		6	58 (30/52)	80 (68/85)
Fallone et al[28]		5	71 (22/31)	73 (41/56)
Gisbert et al[29]		7	54 (32/59)	85 (77/91)
Maconi et al[13]		8	78 (43/55)	91 (67/74)
Baena et al[31]		6	72 (36/50)	77 (82/106)
Broutet et al[7]		13	72 (612/854)	75 (1087/1459)
Lee et al[16]		7	75 (38/51	92 (60/65)
Wu et al[34]		3	67 (10/15)	88 (38/43)
Koivisto et al[19]	LAM arm	5	77 (17/22)	79 (66/84)
	LAC arm	7	81 (25/31)	95 (75/79)
	RMT arm	5	83 (19/23)	81 (73/90)

BMT = bismuth citrate, metronidazole and tetracycline; OMC = omeprazole, metronidazole and clarithromycin; LAM = lansoprazole, amoxicillin and metronidazole.

[a]Different rate >0 indicates that eradication success rate for nonsmokers was superior to that for smokers.

[b]Weight was converted to percentage of total weights in random effect model.

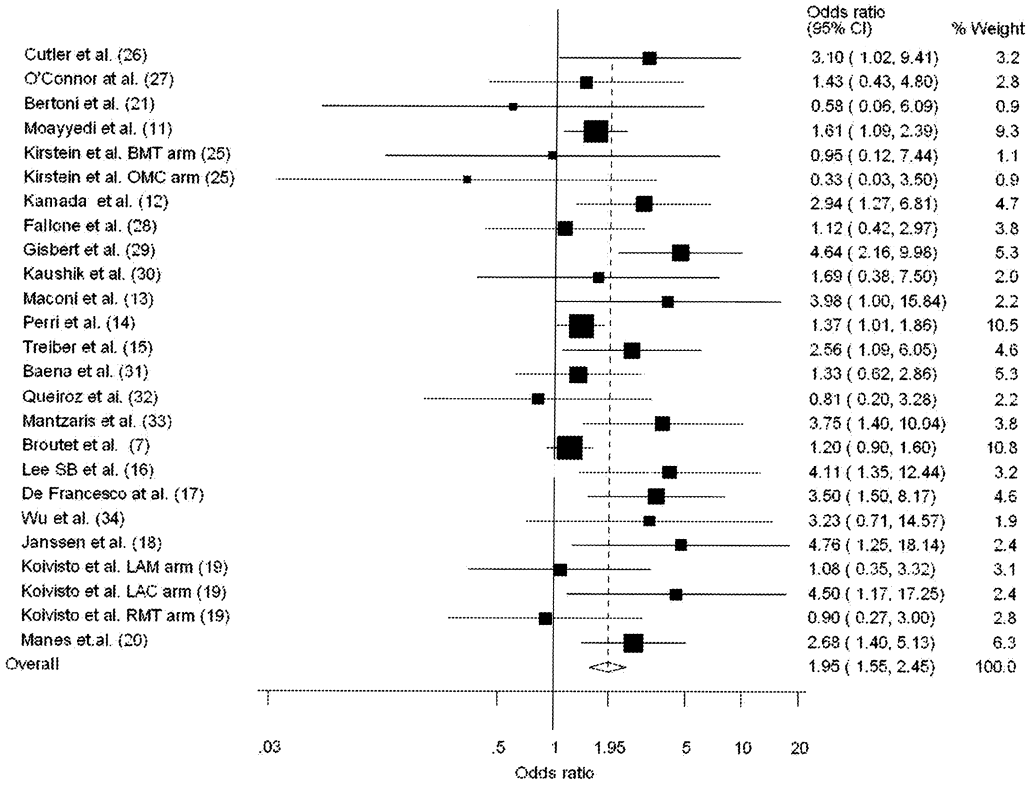

Figure 2 The result of meta-analysis for eradication failure in smokers. Odd ratios and their 95% confidence intervals for eradication failure in smokers are presented with weights in a random-effect model.[22]

Furthermore, it was suggested that smoking might exacerbate disease progression in *H. pylori*-positive subjects. Smoking might lead to progression of atrophic gastritis and intestinal metaplasia in patients infected with *H. pylori*.[47] Nicotine was found to have the ability to potentiate the vacuolating toxin activity of *H. pylori* in gastric cells.[48] On the other hand, smoking cessation during therapy may lead to better eradication rate among smokers.[49] Thus, smokers who stopped smoking during eradication therapy showed the same efficacy as nonsmokers, whereas those who continued smoking experienced a worse result on average.

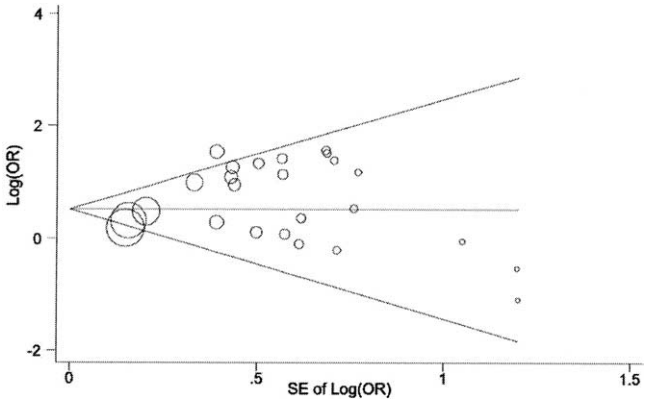

Figure 3 Begg's funnel plot for publication bias in the overall analysis. Each circle represents the log-transformed odds ratios (ORs) for *H. pylori* eradication failure among smokers relative to nonsmokers according to the standard error (SE) of each log-transformed OR. The diameter of each circle represents the inverse variance of the treatment effect by which the weight in the meta-analysis was defined.

In meta-regression analysis, we found that studies including a high percentage of nonulcer dyspepsia subjects were associated with a higher eradication failure rate in smokers. One article reported that in patients with nonulcer dyspepsia, a double dose of proton pump inhibitor is more effective than a single dose.[50] Considering that the intra-

Table 3 Source of Heterogeneity by Multivariate Meta-Regression Analysis

	Coefficient[a]	SE	*P*-value
Asia	0.368	0.33	.27
Omeprazole	−0.002	0.27	1.00
Clarithromycin	0.204	0.46	.66
Metronidazole	−0.090	0.35	.80
% of NUD	0.013	<0.01	<.01
UBT using eradication assessment	−0.389	0.37	.29
Published year	0.009	0.04	.83

SE = standard error; NUD = nonulcer dyspepsia; UBT = urea breath test.

[a]Coefficient in meta-regression analysis denotes to what extent the existence of a certain factor or one unit increase changes the OR in overall analysis by meta-analysis.

gastric pH is decreased by smoking, it might be reasonable to again hypothesize that relatively lower doses of proton pump inhibitor for nonulcer dyspepsia patients contributed to our result.

The present study has several limitations. Firstly, it was not possible to assess smoking status (former or current) and dose in detail. Secondly, compliance with therapy could not be evaluated because of lack of information or differences in definition. As compliance of smokers can be assumed to be worse, we could not rule out that eradication failure of *H. pylori* in smokers might be simply caused by this factor. Thirdly, therapy regimen and eradication definitions differed with the study, although our analyses exploring source of heterogeneity did not point to significant effects. Fourthly, the studies we selected in our meta-analysis were conducted in various countries where the common *H. pylori* strain types may differ. For example, east Asian cytotoxin-associated gene A (CagA) protein possesses stronger activity than the western CagA,[51] so that drug's effect for eradication might be different. Therefore, results in this study must be carefully interpreted.

Eradication therapy for *H. pylori* has been recognized as a standard treatment for diseases such as peptic ulcer and mucosa-associated lymphoid tissue lymphomas, and effects can be expected for prevention of gastric cancer. Therefore, eradication of the *H. pylori* infection has become an important treatment goal in clinical practice. The results of the present study indicate that eradication rates could be potentially improved by smoking cessation. We should be more proactive and look out for treatment failure in smoking patients with *H. pylori*.

References

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1:1311-1315.
2. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet*. 1991;338:1175-1176.
3. 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.
4. 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.
5. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of Helicobacter pylori with triple therapy. *Gastroenterology*. 1992;102:493-496.
6. Lind T, Megraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of Helicobacter pylori with 1-week triple therapies. *Gastroenterology*. 1999;116:248-253.
7. Broutet N, Tchamgoue S, Pereira E, et al. Risk factors for failure of Helicobacter pylori therapy—results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther*. 2003;17:99-109.
8. Lin CK, Hsu PI, Lai KH, et al. One-week quadruple therapy is an effective salvage regimen for Helicobacter pylori infection in patients after failure of standard triple therapy. *J Clin Gastroenterol*. 2002;34:547-551.
9. van Doorn LJ, Schneeberger PM, Nouhan N, et al. Importance of Helicobacter pylori cagA and vacA status for the efficacy of antibiotic treatment. *Gut*. 2000;46:321-326.
10. Broutet N, Marais A, Lamouliatte H, et al. cagA Status and eradication treatment outcome of anti-Helicobacter pylori triple therapies in patients with nonulcer dyspepsia. *J Clin Microbiol*. 2001;39:1319-1322.
11. 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.
12. Kamada T, Haruma K, Komoto K, et al. Effect of smoking and histological gastritis severity on the rate of H. pylori eradication with omeprazole, amoxicillin, and clarithromycin. *Helicobacter*. 1999;4:204-210.
13. Maconi G, Parente F, Russo A, et al. Do some patients with Helicobacter pylori infection benefit from an extension to 2 weeks of a proton pump inhibitor-based triple eradication therapy? *Am J Gastroenterol*. 2001;96:359-366.
14. Perri F, Villani MR, Festa V, et al. Predictors of failure of Helicobacter pylori eradication with the standard 'Maastricht triple therapy'. *Aliment Pharmacol Ther*. 2001;15:1023-1029.
15. Treiber G, Wittig J, Ammon S, et al. Clinical outcome and influencing factors of a new short-term quadruple therapy for Helicobacter pylori eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med*. 2002;162:153-160.
16. Lee SB, Park SJ, Ryu JK, et al. Efficacy of triple therapy with rabeprazole for Helicobacter pylori infection in relation to CYP2C19 genotype. *Korean J Gastroenterol*. 2003;42:468-475.
17. De Francesco V, Zullo A, Hassan C, et al. The prolongation of triple therapy for Helicobacter pylori does not allow reaching therapeutic outcome of sequential scheme: a prospective, randomised study. *Dig Liver Dis*. 2004;36:322-326.
18. Janssen MJ, Laheij RJ, Jansen JB, de Boer WA. The influence of pretreatment on cure rates of Helicobacter pylori eradication. *Neth J Med*. 2004;62:192-196.
19. Koivisto TT, Rautelin HI, Voutilainen ME, et al. First-line eradication therapy for Helicobacter pylori in primary health care based on antibiotic resistance: results of three eradication regimens. *Aliment Pharmacol Ther*. 2005;21:773-782.
20. Manes G, Pieramico O, Perri F, et al. Twice-daily standard dose of omeprazole achieves the necessary level of acid inhibition for Helicobacter pylori eradication. A randomized controlled trial using standard and double doses of omeprazole in triple therapy. *Dig Dis Sci*. 2005;50:443-448.
21. Bertoni G, Sassatelli R, Nigrisoli E, et al. Triple therapy with azithromycin, omeprazole, and amoxicillin is highly effective in the eradication of Helicobacter pylori: a controlled trial versus omeprazole plus amoxicillin. *Am J Gastroenterol*. 1996;91:258-263.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Prognostic role of antibody reactivity to melanoma. *Control Clin Trials*. 1986;7:177-188.
23. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med*. 1999;18:2693-2708.
24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.
25. Kirstein FW, Epple HJ, Bojarski C, et al. Dual versus triple therapy: comparison of five antibiotic regimens for eradication of Helicobacter pylori in a prospective, randomized study. *Z Gastroenterol*. 1998;36:803-809.
26. Cutler AF, Schubert TT. Patient factors affecting Helicobacter pylori eradication with triple therapy. *Am J Gastroenterol*. 1993;88:505-509.
27. O'Connor HJ, Kanduru C, Bhutta AS, et al. Effect of Helicobacter pylori eradication on peptic ulcer healing. *Postgrad Med J*. 1995;71:90-93.
28. Fallone CA, Barkun AN, Friedman G, et al. Is Helicobacter pylori eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol*. 2000;95:914-920.
29. Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitor, clarithromycin and either amoxycillin or nitroimidazole: a meta-analysis of eradication of Helicobacter pylori. *Aliment Pharmacol Ther*. 2000;14:1319-1328.

30. Kaushik SP, Vu C. Helicobacter pylori eradication with lansoprazole, amoxycillin and clarithromycin: testing an ideal regimen in a multicultural south east Asian population and examining factors potentially influencing eradication. *Aust N Z J Med*. 2000;30:231-235.
31. Baena JM, Lopez C, Hidalgo A, et al. Relation between alcohol consumption and the success of Helicobacter pylori eradication therapy using omeprazole, clarithromycin and amoxicillin for 1 week. *Eur J Gastroenterol Hepatol*. 2002;14:291-296.
32. Queiroz DM, Dani R, Silva LD, et al. Factors associated with treatment failure of Helicobacter pylori infection in a developing country. *J Clin Gastroenterol*. 2002;35:315-320.
33. Mantzaris GJ, Petraki K, Archavlis E, et al. Omeprazole triple therapy versus omeprazole quadruple therapy for healing duodenal ulcer and eradication of Helicobacter pylori infection: a 24-month follow-up study. *Eur J Gastroenterol Hepatol*. 2002;14:1237-1243.
34. Wu CJ, Hsu PI, Lo GH, et al. Comparison of cetraxate-based and pantoprazole-based triple therapies in the treatment of Helicobacter pylori infection. *J Chin Med Assoc*. 2004;67:161-167.
35. Endoh K, Kauffman GL Jr, Leung FW. Mechanism of aggravation of mucosal injury by intravenous nicotine in rat stomach. *Am J Physiol*. 1991;261:G1037-G1042.
36. Holm L, Perry MA. Role of blood flow in gastric acid secretion. *Am J Physiol*. 1988;254:G281-G293.
37. Parente F, Lazzaroni M, Sangaletti O, et al. Cigarette smoking, gastric acid secretion, and serum pepsinogen I concentrations in duodenal ulcer patients. *Gut*. 1985;26:1327-1332.
38. Labenz J, Stolte M, Blum AL, et al. Intragastric acidity as a predictor of the success of Helicobacter pylori eradication: a study in peptic ulcer patients with omeprazole and amoxicillin. *Gut*. 1995;37:39-43.
39. van der Weide J, Steijns LS. Cytochrome P450 enzyme system: genetic polymorphisms and impact on clinical pharmacology. *Ann Clin Biochem*. 1999;36:722-729.
40. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36:425-438.
41. Villard PH, Seree EM, Re JL, et al. Effects of tobacco smoke on the gene expression of the Cyp1a, Cyp2b, Cyp2e, and Cyp3a subfamilies in mouse liver and lung: relation to single strand breaks of DNA. *Toxicol Appl Pharmacol*. 1998;148:195-204.
42. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. *Ann Intern Med*. 1998;129:1027-1030.
43. Sagar M, Tybring G, Dahl ML, et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. *Gastroenterology*. 2000;119:670-676.
44. Degoulet P, Menard J, Vu HA, et al. Factors predictive of attendance at clinic and blood pressure control in hypertensive patients. *Br Med J* (Clin Res Ed). 1983;287:88-93.
45. Konturek SJ, Bielanski W, Plonka M, et al. Helicobacter pylori, non-steroidal anti-inflammatory drugs and smoking in risk pattern of gastroduodenal ulcers. *Scand J Gastroenterol*. 2003;38:923-930.
46. Hamajima N, Matsuo K, Saito T, et al. Interleukin 1 polymorphisms, lifestyle factors, and Helicobacter pylori infection. *Jpn J Cancer Res*. 2001;92:383-389.
47. Nakamura M, Haruma K, Kamada T, et al. Cigarette smoking promotes atrophic gastritis in Helicobacter pylori-positive subjects. *Dig Dis Sci*. 2002;47:675-681.
48. Endoh K, Leung FW. Effects of smoking and nicotine on the gastric mucosa: a review of clinical and experimental evidence. *Gastroenterology*. 1994;107:864-878.
49. Matsuo K, Hamajima N, Ikehara Y, et al. Smoking and polymorphisms of fucosyltransferase gene Le affect success of H. pylori eradication with lansoprazole, amoxicillin, and clarithromycin. *Epidemiol Infect*. 2003;130:227-233.
50. Lamouliatte H, Samoyeau R, De Mascarel A, Megraud F. Double vs. single dose of pantoprazole in combination with clarithromycin and amoxycillin for 7 days, in eradication of Helicobacter pylori in patients with non-ulcer dyspepsia. *Aliment Pharmacol Ther*. 1999;13:1523-1530.
51. Azuma T. Helicobacter pylori CagA protein variation associated with gastric cancer in Asia. *J Gastroenterol*. 2004;39:97-103.