PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroentero, 2001;7(2):243 - 247
World Journal of Gastroenterology
 ISSN 1007 - 9327

Helicobacter pylori and gastric cancer: current status of the Austrain Czech German gastric cancer prevention trial (PRISMA-Study)

S. Miehlke[1], C. Kirsch[1], B. Dragosics[2], M. Gschwantler[3], G. Oberhuber[4], D. Antos[5], P. Dite[6], J. L uter[7], J. Labenz[8], A. Leodolter[9], P. Malfertheiner[9], A. Neubauer[10], G. Ehninger[1], M. Stolte[11] and E. Bayerdörffer[1]

Subject headings *Helicobacter pylori*; Helicobacter infections/complications; Helicobacter infections/drug therapy; stomach neoplasms/microbiology; stomach neoplasms/drug therapy; gastritis/microbiology; gastritis/drug therapy

Miehlke S, Kirsch C, Dragosics B, Gschwantler M, Oberhuber G, Antos D, Dite P, L uter J, Labenz J, Leodolter A, Malfertheiner P, Neubauer A, Ehninger G, Stolte M, Bayerdörffer E. *Helicobacter pylori* and gastric cancer: current status of the Austrian Czech German gastric cancer prevention trial (PRISMA Study). ***World J Gastroenterol***, 2001;7(2):243-247

Abstract

AIM To test the hypothesis that *Helicobacter pylori* eradication alone can reduce the incidence of gastric cancer in a subgroup of individuals with an increased risk for this fatal disease.

METHODS It is a prospective, randomized, double blind, placebo controlled multinational multicenter trial. Men between 55 and 65 years of age with a gastric cancer phenotype of *Helicobacter pylori* gastritis are randomized to receive a 7 day course of omeprazole 2 × 20 mg, clarithromycin 2 × 500 mg, and amoxicillin 2 × 1 g for 7 days, or omeprazole 2 × 20 mg plus placebo. Follow-up endoscopy is scheduled 3 months after therapy, and thereafter in one-year intervals. Predefined study endpoints are gastric cancer, precancerous lesions (dysplasia, adenoma), other cancers, and death.

RESULTS Since March 1998, 1524 target patients have been screened, 279 patients (18.3%) had a corpus dominant type of *H. pylori* gastritis, and 167 of those were randomized (58.8%). In the active treatment group (n = 86), *H. pylori* infection infection was cured in 88.9% of patients. Currently, the cumulative follow-up time is 3046 months (253. 38 patient years, median follow up 16 months). So far, none of the patients developed gastric cancer or any precancerous lesion. Three (1.8%) patients reached study endpoints other than gastric cancer.

CONCLUSION Among men between 55 and 65 years of age, the gastric cancer phenotype of *H. pylori* gastritis appears to be more common than expected. Further follow up and continuing recruitment are necessary to fulfil the main aim of the study.

[1]Medical Department I, Gastroenterology, Hematology, Oncology, Pulmonology & Infectious Diseases, Technical University Hospital Carl Gustav Carus, Dresden, Germany
[2]Gesundheitszentrum Süd, Vienna, Austria
[3]Medical Department 4, Krankenanstalt Rudolfstiftung, Vienna, Austria
[4]Institute for Pathology, General Hospital, Vienna, Austria
[5]Surgical Department, Ludwig-Maximilians niversity Hospital Groβ hadern, Munich, Germany
[6]Univerzitni nemocnice Jihlavska, Brno-Bohunice, Czech Republic
[7]Institute for Medical Statistics, Otto-von-Guericke-University, Magdeburg, Germany
[8]Department of Medicine , Evang. Jung-Stilling Hospital, Siegen, Germany
[9]Department of Gastroenterology, Otto-v.-Guericke University Hospital, Magdeburg, Germany
[10]Department for Hematology, Oncology & Immunology, University Hospital Marburg, Germany
[11]Institute of Pathology, Klinikum Bayreuth, Bayreuth, Germany
Correspondence to: Ekkehard Bayerdörffer, M.D., Medical Department I, Technical University Hospital Carl Gustav Carus, Fetscherstraβe 74, D-01307 Dresden
Tel. 0049-351-458-5645, Fax. 0049-351-458-4394
Email. bayerdoerffer@t-online.de
Received 2001-02-06 **Accepted** 2001-03-01

INTRODUCTION

Gastric cancer is the second most common fatal malignancy in the world being responsible for at least 750 000 deaths annually[1]. Even though the incidence of gastric cancer is steadily decreasing in Western industrialized countries, the absolute number of diagnoses and deaths is likely to increase due to population growth and changing age structure of populations[2,3]. Following the first epidemiological reports of an association between *H. pylori* infection and gastric cancer in 1991[4-6], the International Agency for Research on Cancer, sponsored by the World Health Organization, categorized *H. pylori* infection as a definite human carcinogen in 1994[7]. Six years after that decision, the causal role of *H. pylori* in gastric carcinogenesis is still poorly understood, and the epidemiological data vary depending on the background prevalence of the infection and the design of the studies[8,9].

As suggested by an economical analysis based on the US data, a screen and treat strategy for *H. pylori* infection, even under conservative assumptions, may be a cost-effective strategy for gastric cancer prevention comparable to the costs of breast mammography screening programms[10]. This

strategy would become more cost-effective among populations at a higher background risk of gastric cancer [11]. However, valid prospective data on the benefit of *H. pylori* eradication for gastric cancer prevention are lacking. A non-randomized Japanese study on 132 *H. pylori* positive patients with early gastric cancer who had undergone endoscopic resection showed that after additional *H. pylori* eradication therapy there were no new occurrences of early gastric cancer during 2 years. However, among those who remained infected, there was a 9% recurrence rate of early gastric cancer[12]. Whether *H. pylori* eradication can lead to regression of gastric atrophy and intestinal metaplasia, histological risk markers for gastric cancer is still controversial[13]. The quality of endoscopic-bioptic follow-up studies of these parameters is often limited due to the confounding factor of sampling error, and due to a considerable lack of consensus among pathologists concerning the assessment of atrophy[14]. Decisive evidence that takes full account of all benefits and risks of preventive *H. pylori* eradication therapy could be derived only from adequately designed clinical trials with clearly defined study endpoints.

Recently, a corpus-dominant distribution of *H. pylori* gastritis has been recognized as a histological gastric cancer risk marker, which is frequently found not only in patients with gastric cancer at various clinical stages of disease[15,16], but also in healthy relatives of gastric cancer patients[17]. Based on histological studies, patients with a corpus-dominant *H. pylori* gastritis have an about 9-fold increased risk for gastric cancer[16]. This corpus-dominant gastritis has been termed as gastric cancer phenotype of *H. pylori* gastritis, and is the basis for the so-called "gastric cancer risk index" which has been suggested as a screening marker for *H. pylori* infected individuals in Germany being at an increasing risk for gastric cancer[18,19]. The major advantage of this screening marker is the homogenous distribution of the inflammatory response within antral or corpus mucosa which makes it less susceptible to sampling error.

In the present study, we are using this corpus-dominant phenotype of *H. pylori* gastritis as histological inclusion criteria to identify individuals with a clearly increased compared to the normal population. The aim of the present study is to investigate whether *H. pylori* eradication alone can reduce the incidence of gastric cancer in subjects with an individual high risk for gastric cancer.

PATIENTS AND METHODS

Recruitment and evaluation of patients

Gastroenterologists in hospitals and private practice in Austria, Czech Republic and Germany were asked to participate in the preparation of the study. Those who were interested were asked to obtain gastric biopsies for histological screening from all patients of the target age group who present for upper endoscopy, and to send these biopsies to one of the participating institutes of pathology.

At each endoscopic examination, two biopsies each from the antrum and the corpus were obtained according to the updated Sydney System[20]. In addition, one biopsy from the antrum and one from the corpus was taken for the rapid urease test (HUT-Test). At follow-up endoscopies, additional biopsies were obtained from macroscopically suspicious areas such as focal erythema, erosions or polyps.*H. pylori* colonization is detected by Warthin Starry. Hematoxilin & Eosin stain was used for assessment of gastritis according to the updated Sydney System[20], including the following parameters: grade and activity of gastritis, atrophy, intestinal metaplasia, lymphocytic aggregates, and degeneration of surface epithelium.

The first follow-up endoscopy was performed 3 months after treatment to determine successful eradication, and to increase the probability to detect preneoplastic changes or early gastric cancer which may have been overseen at the screening examination. Thereafter, follow-up endoscopies are scheduled in one-year intervals.

Inclusion criteria

Men between 55 and 65 years of age are eligible for inclusion in the study if they give informed consent to participate, if *H. pylori* is detected, and if the following histological criteria are present: ① grade of gastritis in the corpus $\geqslant$ grade of gastritis in the antrum; ② grade of activity of gastritis in the corpus $\geqslant$ grade of activity of gastritis in the antrum[18]. The grade and activity of gastritis in the corpus is required to be at least moderate or high according to the updated Sydney System[20].

Patients are not eligible for participation if one of the follwing criteria is present: *H. pylori*-associated diseases with strongly recommended indication for anti *H. pylori* therapy[21], type-A gastritis, a history of partial stomach resection, contraindications for biopsy sampling, present or history of malignant disease, expected residency in Germany, Austria or Czech Republic for the following five years, severe chronic disease with a survival expectancy of less than five years, benigne neoplastic lesions (adenoma, dysplasia) or early gastric cancer at the 3-month endoscopy, known allergy against the study medication.

Randomization and intervention

The randomization was carried out by the study secretariats at the University Hospitals in Dresden, Vienna and Brno. Patients receive either omeprazole 2 × 20 mg, clarithromycin 2 × 500 mg, and amoxicillin 2 × 1000 mg given for 7 days with meals[22], or omeprazole 2 × 20 mg and identically looking placebos. In case of allergy against penicilline, patients received either omeprazole 2 × 20 mg, clarithromycin 2 × 250 mg, and metronidazole 2 × 400 mg, or omeprazole plus

placebo. The trial was conducted in a double-blind fashion. Patients who did not agree to randomization received open anti *H. pylori* therapy, and were asked to return to regular follow-up endoscopies.

Statistics and ethics

The main study end points are benign neoplastic lesions (dysplasia, adenoma) in two subsequent examinations, gastric cancer, cancer of other origin, and death. The analysis is based on the intention-to-treat principle. *Chi*-square tests were used to compare categorial variables. The study was approved by the Ethics Committee of the University of Magdeburg, and by all Regional Ethics Committees in Germany, Austria and Czech Republic where patients were recruited.

RESULTS

In preparation of the trial, about 1300 gastroenterologists in Germany were informed by mail and invited to participate in the study. In addition, multiple information seminars were held in various regions of the country to explain organisatory matters, and to discuss critical questions. At initiation of the study in Germany, 500 gastroenterologists (232 in hospitals, 268 in private practice) and 201 pathologists stated interest and announced to participate in the study. However, during the first two years only 239 (47.8%) gastroenterologists became active by screening and recruiting at least one patient. Among those were 157 gastroenterologists in hospitals, and 82 doctors in private practice. Thus, between April 1998 and Dezember 2000, 1526 men at the age between 55 and 65 years were endoscopic-histologically screened, 749 in hospitals and 777 in private practice. The histological inclusion criteria was identified in 279 (18.3%) patients. Of these patients, 167 (58.8%) agreed to participate in the study, 86 were randomized to receive therapy to eradicate *H. pylori* (omeprazole plus antibiotics), while 81 were assigned to receive omeprazole plus placebo. One patient (1.2%) of the active treatment group prematurely discontinued treatment due to severe allergy. Otherwise no adverse side effects occurred leading to discontinuation of therapy. Of the 112 patients who declined randomisation and received open anti-*H. pylori* therapy, 109 stated to return to follow-up endoscopies in one to two-year intervals. Thus, 276 patients are currently under follow-up.

In the active treatment group, 54 (62.8%) patients have returned to control examinations so far. Among those, *H. pylori* infection has been cured in 48 (88.9%) patients. Those patients who did not become *H. pylori* negative did not receive a second course of anti-*H. pylori* therapy so far.

At present, 105, 50 and 24 patients have passed the 3-month, one-year, and two-year control endoscopy. Until January 2001, the cumulative follow-up time of all randomized patients was 3046 months (253.8 patient years). The median follow-up period of these patients was currently 16 months (range 3-35 months). So far, none of the patients developed gastric cancer or any preneoplastic lesion in the stomach. Three (1.8%) patients reached study endpoints other than gastric cancer. One patient of the active treatment group developed malignant melanoma 8 months after anti-*H. pylori* therapy. Two patients who were randomized to the placebo group died of myocardial infarction 6 and 7 months after therapy, respectively. Both patients had known coronary heart disease but were in stable condition at randomisation. Two patients of the placebo group received anti-*H. pylori* therapy, one of them due to active duodenal ulcer, the other patient due to persistent functional dyspepsia. Both patients, however, will continue the follow-up. Another 2 patients received cardiac surgery, one aortic valve replacement and one coronary bypass. Both patients will continue follow-up.

Table 1 Current status of the PRISMA study (initiation April 1998)

Endoscopy-histologically screened men between 55 and 65 years of age	Cases (n = 1526)	%
Presence of histological inclusion criteria	n = 279	18.3
Patients randomized	n = 167	58.8[a]
Non-randomized patients continuing follow-up	n = 109	39.1[a]
Patients with study endpoints	3	1.8[b]
Cumulative follow-up (months / years)	3046 / 253.8	

[a]Percentage of those who meet all inclusion criteria
[b]Percentage of all randomized patients.

Table 2 Currently conducted *H. pylori*-gastric cancer intervention trials with cancer endpoints

Name	Country	Target group	Age group	Sample size	Main endpoints
SCISC	China	Population	30-65	2400	Gastric cancer
NCI	China	Population	35-69	3400	Gastric cancer , dysplasia
JITHP	Japan	Population	20-59	5000	Gastric cancer
BUPA	U.K.	Population	35-69	56000	Gastric cancer
PRISMA	Germany Austria Tchech Republic	Male subjects with Corpus dominant gastritis	55-65	3000	Gastric cancer dysplasia,adenoma

DISCUSSION

Reliable epidemiological evidence on *H. pylori* and gastric cancer is still relatively sparse. Until today, only 10 seroepidemiological prospective have investigated the prevalence of *H. pylori* in a total of 800 gastric cancer cases. A combined analysis of these studies yielded a risk ratio of 2.5 for gastric cancer in people seropositive for *H. pylori* antibodies[9]. It may well be that the role of *H. pylori* in gastric cancer has been underestimated by these studies due to methodological reasons, such as poor sensitivity and specificity of serological tests available in the late 80s, or geographic variation of *H. pylori* antigens. In contrast, more recent studies indicate a much higher risk for gastric cancer in *H. pylori* infected individuals[23,24]. For example, a histology-based prevalence study in our patient

population has shown a *H. pylori* prevalence of more than 90% in patients with early gastric cancer, and a much higher relative risk for gastric cancer calculated after exclusion of other precancerous conditions such as type A gastritis[23]. Moreover, histological studies of our group have described a corpus-dominant pattern of mucosal inflammation, which is found in most *H.pylori* infected gastric cancer patients irrespective of the clinical stage[15,16], and also significantly higher in healthy relatives of gastric cancer patients compared to individuals without of family history of gastric cancer[17]: the so-called "gastric cancer risk index" which was developed on the basis of this gastric cancer phenotype of *H. pylori* gastritis[18] serves as histological inclusion criteria for the present study. A major advantage of this inclusion criteria is that it can be used to identify individuals with an increased gastric cancer risk independent of the presence of intestinal metaplasia which is always prone to sampling error. This gastric cancer risk index has recently been investigated in a Japanese patient population. In this study, a high prevalence of the gastric cancer phenotype of *H. pylori* gastritis was found in gastric cancer patients, but also with a similar frequency in control subjects[25]. In the study by Meining *et al*[18] duodenal ulcer patients were chosen as control group, because these patients rarely develop gastric carcinoma, and therefore probably would show histopathological features different from those of gastric cancer patients. In contrast, the Japanese study used gastritis patients without clinical relevant disease as control group, and were therefore unable to reproduce our previous findings.

To calculate the gastric cancer risk for target group in our study, we started from an average incidence of gastric cancer of about 62/100 000 per year in men aged 55 to 65 years[26]. Based on our data in patients with early gastric cancer[23], we calculated an incidence of 143/100 000 for *H. pylori*-positive men in this age group can be calculated. Under consideration of the histological inclusion criteria used in the present study which are found in 72% of early gastric cancer patients and in only 9% of *H. pylori* infected individuals without disease, we expect an incidence of gastric cancer as high as 1200/100 000 in our target patient group. In the present study, we observed that at least in men in the age group 55 to 65 years, the prevalence of a corpus-dominant pattern of *H. pylori* gastritis was higher than in the average population of infected individuals. By the selection of this high risk group for gastric cancer, we hope to be able to decrease the follow-up time of the study population and the number of recruited patients.

The key question is whether gastric cancer can be prevented by *H. pylori* eradication. It is worth mentioning that development of gastric cancer several years after *H. pylori* eradication has already been reported. For example, patients of the German MALT Lymphoma Trial which started in 1993 still remain under long-term endoscopic-histological follow-up[27,28]. Until today, 3 of these patients have developed early gastric cancer approximately 4 years after *H. pylori* eradication and complete remission of their lymphoma[29]. In addition, the extended follow-up of Japanese early gastric cancer patients who were treated with endoscopic mucosal resection and *H. pylori* eradication has shown that a metachronous gastric cancer may be inhibited to a great extent. However, one of these patients so far has developed a second gastric cancer four years after *H. pylori* eradication[30]. Although these reports suggest that gastric cancer may still occur after *H. pylori* eradication, they can not be transferred to the general population since those patients already had a gastric malignancy.

Relevant studies addressing the question of gastric cancer prevention by *H. pylori* eradication can be divided into those with precancerous lesions and those with gastric cancer as major study endpoint[13]. The latter studies vary considerably in their study design, but have in common that they require a much larger number of recruited patients and a longer follow-up compared with the studies using precancerous lesions as endpoints. Three of these trials are being conducted in Asian populations, while two studies, Including ours, are conducted in European populations (Table 2). The Asian studies are recruiting subjects from the general population in an area with a high population risk of gastric cancer following an endoscopy. One of the Chinese studies is also recruiting subjects to receive antioxidant micronutrients such as vitamins C and E, and therefore will be able to investigate the interaction between *H. pylori* eradication and dietary intervention in reducing the cancer risk. The British study aims to recruit the largest number of subjects with the longest follow-up, since the study is performed in a population with a relatively low gastric cancer risk. Men and women undergoing routine medical examination are randomized to testing for *H. pylori* and subsequent treatment if positive, or no testing. In contrast, the PRISMA study will assess the benefit of *H. pylori* eradication in patients with a high individual risk within a population of relatively low gastric cancer risk. By selection of a particular high-risk group it was expected to be able to reduce the necessary samplesize and the follow-up time. During the first two years of the study, however, we had to learn that at least in Germany the recruitment of subjects for this particular study-despite tremendous efforts by the principlal investigators[31-34] is extremely affected by the concerns of both patients and doctors regarding the possibility of being randomized to the control group. In our opinion, these concerns are mainly caused by the relatively broad knowledge about the association of *H. pylori* and gastric

cancer which has already been distributed by both professional and general media. Therefore, many patients expect and receive antimicrobial therapy if the infection has been diagnosed, despite the absence of strongly recommended indications for anti *H. pylori* therapy[21], and although the effect on cancer prevention is unproven. On the other hand, the certain benefit of regular control endoscopies which is the only measure to detect malignancy at a curable stage, and which would be provided by participation in the PRISMA study seems to be regarded as not acceptable or inconvenient for many patients and physicians. Due to these obvious difficulties in the recruitment of patients, it is currently planned to modify the study design and to continue without a placebo group. Although this measure will reduce the power of the study to a certain extent, it is believed that the key question can still be answered.

ACKNOWLEDGEMENTS The PRISMA Studies are supported by the Deutsche Krebshilfe e.V. (Project Nr. 70-2345-Ba I), and by the Onkologischer Arbeitskreis Bayreuth e. V. We thank the following pharmaceutical companies for providing the study medication: AstraZeneca, Wedel, Germany; Abbott GmbH, Wiesbaden, Germany, Ratiopharm GmbH, Ulm, Germany. We also thank our study secretary assistant Ms. R. Beckmann for her valuable support.

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Edited by Ma JY