

# *Helicobacter pylori* infection and gastric cancer

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Gastric cancer is the second most common fatal malignant neoplasm in the world. In mainland China, gastric cancer is now the second most common malignant neoplasm, while in Hong Kong the mortality rate ranked fourth of all cancers in 1995. Dietary factors seem to be involved in gastric carcinogenesis, and beta carotene, selenium, and vitamin E (tocopherols) have been shown to help reduce gastric cancer mortality. Prospective case-control studies have shown an increased risk for the development of gastric cancer of between 2.8 and 6.0 among carriers of *Helicobacter pylori*. In addition, *cagA*-positive strains of *Helicobacter pylori* have been found to be associated with gastric cancer and duodenal ulceration. The exact role of *Helicobacter pylori* in gastric carcinogenesis is still being investigated. *Helicobacter pylori* eradication programmes to help prevent gastric cancer are being conducted in China and other parts of the world. In high-risk areas such as China, a combination approach that includes *Helicobacter pylori* eradication and dietary supplementation may be necessary.

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## Introduction

In 1995, approximately 1 million new cases of gastric cancer were found worldwide. Currently, it is the fourth leading cause of death from cancer in Hong Kong. The cause of gastric cancer is still unclear but it is generally considered a multifactorial process that may include dietary factors, environmental factors, and bacterial and viral infections. Several large clinical trials are trying to address the causal relationship between *Helicobacter pylori* infection and gastric cancer. This article summarises the epidemiology of gastric cancer and the relationship between gastric cancer and *Helicobacter pylori* infection.

## The epidemiology of gastric cancer

Until recently, gastric cancer was the most frequently diagnosed cancer in the world. About 1 million new cases were diagnosed worldwide in 1995, of which 75% occurred in Asia. Countries in Asia with a high incidence include Japan, China, and South Korea; those with a low incidence include India, Pakistan, and Thailand. Other high-incidence areas include the former

Soviet Union, tropical South America, the Caribbean, and southern Europe. There is no consistent pattern. Furthermore, there are considerable differences in incidence within a country. Several regions of China such as Changde in Fujian have a very high incidence of gastric cancer, while in some parts, the incidence is quite low.<sup>1</sup> Even in small countries such as Japan, there is also considerable variation in the incidence and mortality rate.<sup>2</sup> An observation that is consistent in high- and low-risk areas, however, is that the incidence of gastric cancer increases with age. In Japan, the incidence of gastric cancer in 1981 was 82.8 per 100 000 for men aged 45 to 49 years but 572.1 per 100 000 for men aged 85 years or older.<sup>3</sup> The male to female ratio in terms of incidence is usually from 1.5:1 to 3.0:1 worldwide while in China, it varies from 1.6:1 to 3.9:1.<sup>4</sup>

Gastric cancer has been associated with low socio-economic status, based on family income,<sup>5</sup> education,<sup>6</sup> or occupation.<sup>7</sup> Generally, the risk of gastric cancer developing among individuals from the lower socio-economic class is up to two times that of those from the upper socio-economic class. There is also an association between *H pylori* infection and low socio-economic status.<sup>8</sup> Familial studies have found that the risk of gastric cancer developing in relatives of patients with gastric cancer is increased two- to three-fold.<sup>9</sup> Since family members usually share the same environment and have a similar socio-economic status, however, it is difficult to exclude environmental factors.

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### **H pylori and gastric cancer**

There is now evidence from epidemiological studies that *H pylori* carriers have a significantly greater risk for the development of gastric cancer. Results from three prospective epidemiological studies<sup>10-12</sup> estimate that *H pylori* carriers have a 2.8- to 6.0-fold increased risk of gastric cancer developing over mean follow-up periods of 6 to 16 years when compared with their *H pylori*-negative counterparts. The overall mean risk was calculated to be 3.8.<sup>13</sup> This odds ratio increased to 8.7 in those who were diagnosed 15 years or more after testing positive for *H pylori*. A significant trend towards an increased odds ratio arises with an increased length of follow-up.<sup>13</sup> Six of nine case-control studies from various countries have demonstrated a significantly increased risk for the development of gastric cancer among *H pylori* carriers while the remaining studies did not show any differences.<sup>14-22</sup> In addition, other studies have demonstrated a significant correlation between the *H pylori* infection rates and the incidence of gastric cancer.<sup>23-31</sup> Two studies from China<sup>27,30</sup> have shown an unequivocal association between gastric cancer mortality rates and *H pylori* infection rates. A previous study by us also showed that the prevalence of *H pylori* infection is higher in Changle province than in Hong Kong, with the gastric cancer mortality rate in Changle being about 10 times that of Hong Kong.<sup>28</sup>

The odds ratio of having gastric cancer is increased in young patients who are infected with *H pylori*. Kikuchi et al<sup>32</sup> have shown that at the average age of 34 years, the odds ratio for an *H pylori* carrier to have gastric cancer is 13.3.

There have been reports that gastric cancer mortality rates bear an inverse relationship to duodenal ulcer disease rates and to the duodenal ulcer to gastric ulcer ratio.<sup>33-35</sup> It remains a puzzle why the same organism could cause two diseases and yet one disease seems to protect against the other. The pathogenesis of the two diseases seems so different that each is likely to involve a mutually exclusive pathway. Hence, some factors in addition to *H pylori* are probably involved in the determination of ulcer or cancer formation.

In 1994, the Working Group of the International Agency for Research on Cancer, in affiliation with the World Health Organization, concluded that *H pylori* is carcinogenic to humans and classified it as a group 1 carcinogen.<sup>36</sup> It remains unclear at this stage what other factors are involved in *H pylori*-associated gastric carcinogenesis. Infection with the organism leads to changes in many factors that are important

in the pathogenesis of gastric cancer, including the vitamin C level in gastric juice, reactive oxygen metabolites, and epithelial cell proliferation. Specific pathogenic *H pylori* strains have been incriminated as responsible. Blaser et al<sup>37</sup> have demonstrated that *cagA*-positive *H pylori* patients have a greater risk for the development of intestinal metaplasia and gastric cancer. Furthermore, CagA-producing *H pylori* strains are consistently found to be more prevalent in patients with peptic ulceration<sup>38-42</sup> and, to a certain extent, in patients with gastric cancer.<sup>43,44</sup> In a controlled study, Parsonnet et al<sup>44</sup> found that subjects infected with *cagA*-positive strains had a nearly six-fold increase in the incidence of gastric cancer compared with uninfected individuals, whereas those who had been infected with *cagA*-negative strains had only a marginally (and insignificantly) increased risk of developing gastric cancer compared with the uninfected controls. Unfortunately, two other case-control studies that were performed in areas with high gastric cancer rates and high background prevalence of *cagA*-positive strains<sup>45,46</sup> did not support this finding. Thus, whether or not *cagA*-positive strains are relevant in the development of gastric cancer is still debatable.

### **Intervention trials investigating the prevention of gastric cancer**

Although diet is an important factor in gastric carcinogenesis, no intervention trials involving diet and gastric cancer are in progress and none are planned. There are, however, four micronutrient supplementation studies that have a cancer other than gastric cancer as the end-point that we can refer to. The Linxian chemoprevention trial on oesophageal cancer conducted in China showed a borderline significant reduction in the incidence of gastric cancer and mortality rates in a group that was given selenium, beta carotene, and vitamin E.<sup>47</sup> Another study in China showed a slightly higher incidence and mortality rate of gastric cancer in the group receiving 14 vitamins and 12 minerals compared with the placebo group.<sup>48</sup> A Finnish chemoprevention trial that investigated lung cancer gave participants either alpha tocopherol (alpha tocopheryl acetate), beta carotene, both, or a placebo. The investigators discovered that the incidence of gastric cancer was slightly greater among men who took beta carotene compared with those not receiving it, and likewise for those who took alpha tocopherol compared with those not receiving it; however, these differences were not statistically significant.<sup>49</sup> A fourth trial included 22 000 male physicians in the United States and involved supplementation with beta

Table 1. Intervention trials in progress that include follow-up of precancerous lesions

Country/region	Disease present	No. of participants	Study design	Treatment	Length of follow-up
Columbia (Correa,* 1991)	CAG <sup>†</sup> , IM <sup>‡</sup> , dysplasia	700	2x2; placebo	(1) Triple therapy (2) beta carotene + vitamin C	6 years
Venezuela (Munoz et al, <sup>51</sup> 1992)	CAG, IM, dysplasia	2200	Double-blind; placebo	Vitamin C + vitamin E +beta carotene	3 years
Europe (Read and Johnston, <sup>52</sup> 1993)	IM	1200	Double-blind; placebo	(1) Triple therapy (2) Vitamin C	3 years

\* Correa P, written communication, 1999

<sup>†</sup> CAG chronic atrophic gastritis

<sup>‡</sup> IM intestinal metaplasia

Table 2. Intervention trials in progress that have the development of cancer as their end-point

Country/region	<i>H pylori</i> status	No. of participants	Study design	Treatment	Length of follow-up
Changle (Wong et al, <sup>28</sup> 1994)	+ve	1600	Placebo	Triple therapy	5 years
Shandong (Sung et al, <sup>53</sup> 1996)	+ve	1000	Placebo	Triple therapy	5 years
Shandong (Gail et al, <sup>54</sup> 1995)	+ve	3411	Placebo	2 <sup>3</sup> factorial of: (1) Triple therapy (2) Vitamin and mineral supplement (3) Garlic supplement	5 years

carotene or placebo. No difference in the incidence of gastric cancer was found.<sup>50</sup>

The initial chemoprevention trials were all based on high-risk subjects—namely, those with precancerous lesions in the stomach. The end-point used was regression or progression of the precancerous lesions. There have been three large-scale chemoprevention trials of this type (Table 1). The Columbian study was designed so that subjects (with chronic atrophic gastritis, intestinal metaplasia, or dysplasia) were given *H pylori* eradication therapy and then randomised to receive either beta carotene and vitamin C (ascorbic acid) or placebo (Correa P, written communication, 1999). Another study in Venezuela randomised subjects (with chronic atrophic gastritis, intestinal metaplasia, or dysplasia) to receive either vitamin C, beta carotene, and vitamin E, or placebo.<sup>51</sup> The European Cancer Prevention/Intestinal Metaplasia Study Group randomised patients who had intestinal metaplasia to receive *H pylori* eradication therapy, followed by vitamin C supplementation or placebo.<sup>52</sup>

Other chemoprevention trials follow asymptomatic subjects to see if the eradication of *H pylori* reduces the overall incidence of gastric cancer. The end-point will be cancer incidence among the cohort. There are currently three chemoprevention trials using this approach to study asymptomatic *H pylori* carriers (Table 2). Our group was the first to use such a study design.<sup>28</sup>

A total of 1600 asymptomatic carriers are part of a study being conducted in Changle, Fujian province, China. Participants were randomised to receive *H pylori* eradication therapy or placebo in 1994 without micronutrient supplements.<sup>28</sup> The effect on cancer incidence and any precancerous lesions will be investigated by a second upper endoscopy in late 1999 in Changle. Two other studies in Shandong, China also have a similar design and aim to establish whether or not cancer is prevented by the eradication of *H pylori*.<sup>53,54</sup>

There are now at least two more intervention trials looking at precancerous lesions and another trial using cancer incidence as an end-point. Scrutinising cancer incidence in this way will give conclusive evidence that *H pylori* causes gastric cancer, assuming that the results of these trials are positive. Unfortunately, all of these trials are conducted in areas with high incidences of gastric cancer. It is possible that apart from *H pylori*, there are important dietary and environmental factors that also contribute to gastric carcinogenesis. It would thus be reasonable to add micronutrient supplementation to *H pylori* eradication therapy to maximise the protective effect, although supplementation will almost certainly require more than one micronutrient. With the results of these trials becoming available in the next few years, we may be able to devise some strategies to prevent the world's second most common cancer.

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