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TOPIC HIGHLIGHT

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# Gastric cancer, *Helicobacter pylori* infection and other risk factors

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## Abstract

Gastric cancer incidence is declining. However, it is too early to consider this neoplastic disease as rare and the worldwide mortality rate still remains high. Several risk factors have been identified for non-cardia gastric cancer and primary prevention is feasible since most of the risk factors can be removed. *Helicobacter pylori* eradication treatment reduces but does not abolish gastric cancer risk. Indeed, gastric cancer is a multifactorial disease and removing one factor does not therefore prevent all cases. Endoscopic surveillance is still needed, especially in subjects at higher risk. The definition of high-risk patients will be the future challenge as well as identifying the best surveillance strategy for such patients.



**Key words:** *Helicobacter pylori*; Eradication treatment; Diet; Gastric cancer

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## INTRODUCTION

Worldwide, cancer still represents the third leading cause of death after cardiovascular and infectious diseases.

In 2002, stomach cancer was the fourth most common cancer worldwide, with more than 900 000 new cases[1] and almost two-thirds occurring in developing countries[2]. However, the distribution of gastric cancer does not follow a strict geographical pattern. Indeed, low rate countries (e.g. India) are also reported within areas at highest risk (e.g. Asia). Similarly, within populations at low risk, there are sub-groups at higher risk (e.g. Koreans living in U.S.)[3,4].

In all populations, the age-standardised risk is about 2-fold higher in males than in females. In addition, the female incidence rate at any age is equivalent to the male incidence rates for 10 years lower age[5].

Except for Japan, where mass screening programs increased the 5-year survival rate up to approximately 60%, in most areas of the world only 1 out of 5 patients with gastric cancer is still alive after 5 years[5-7].

Mortality is influenced by several factors: cancer incidence, stage at diagnosis, individual biological factors and response to the available treatment. Therefore, any intervention acting to reduce the cancer incidence (i.e. elimination/correction of potential risk factors and/or promotion of protective factors), to favour an early diagnosis (i.e. identification and surveillance of patients at increased risk) or to improve the health care access, will result in reduced cancers mortality.

## RISK FACTORS FOR GASTRIC CANCER

Several risk factors have been identified for non-cardia gastric cancer: *Helicobacter pylori* (*H. pylori*) infection[8], low socioeconomic status[9], smoking[10], salty and smoked food intake and low consumption of fruits and vegetables[11,12] and familiarity for gastric cancer[13].

### *Helicobacter pylori*

*H. pylori* represents one of the most common human infections, although its prevalence varies widely across different countries. A progressive decrease has been reported, at least in high socio-economic regions[14]. Since its discovery in 1984, *H. pylori* has been recognised as a major cause of several upper gastrointestinal diseases, such as peptic ulcer disease, gastric adenocarcinoma and primary gastric B-cell lymphoma[15].

*H. pylori* infection is a strong and well-established risk factor for gastric cancer and has been classified as a group I carcinogen by the International Agency for Research on Cancer (IARC)[16]. Several pathogenic pathways suggesting how the infection could increase the risk of gastric cancer have been proposed, but it is thought that long-term chronic inflammation represents the primary mechanism[17,18].

*H. pylori* is specifically adapted to survive in the hostile acidic gastric environment and the colonization of the stomach by *H. pylori* results in the development of gastritis in virtually all infected subjects. The attachment of the bacteria to the epithelial cells induces an inflammatory response resulting in the recruitment of neutrophils followed by B and T lymphocytes, macrophages and plasma cells, most of which generate large amounts of reactive oxygen or nitrogen species[19], implicated in epithelial cell damage and carcinogenesis[20,21].

Gastric mucosal damage induced by *H. pylori* infection is also due to the bacterial virulence factors encoded by the *cag* pathogenicity island, such as the vacuolating cytotoxin A (VacA) and the CagA protein (CagA). The first is a secreted toxin that enters the epithelial cell membrane, induces vacuole formation and affects mitochondria leading to apoptosis[22,23]. On the other hand, CagA, upon entering the epithelial cell, induces proliferation and motility signals, as well as production of cytokines[24]. Several mechanisms by which CagA induces the transformational changes in a host cell have been described, such as its interaction with SHP-2 protein, a cytoplasmic tyrosine phosphatase[25]. Indeed, following its injection into the cell, CagA is firstly tyrosine-phosphorylated by Src family kinases and secondly binds the SHP-2. As SHP-2 is known to play an important role in transduction events induced by a variety of different receptor tyrosine kinases, CagA perturbs cellular functions by the deregulation of SHP-2, inducing cytoskeletal rearrangements, proliferation and increased motility of gastric epithelial cells[25,26].

Furthermore, it has been hypothesized that polymorphisms in *cag*, which lie in the tyrosine residue encoding sequence, could be essential variables for the clinical outcome upon the infection by different *cag*+ *H. pylori* strains. Indeed, *H. pylori* can be divided into 2 major subpopulations based on distinctly structured tyrosine phosphorylation/SHP-2 binding sites: the East Asian CagA-positive strain and the Western CagA-positive strain[27]. Notably, patients infected with East Asian stains show increased inflammatory response, higher degrees of preneoplastic gastric lesion and may be at greater risk for gastric cancer than those infected by Western strains[27,28].

Moreover, CagA-positive *H. pylori* infection up-regulates COX-2 expression in gastric mucosa and cancer[29]. COX-2 is usually undetectable in normal tissue and becomes abundant at sites of inflammation and can also be overexpressed in gastric carcinomas. The overexpression of COX-2 leads to an increased synthesis and release of prostaglandins, such as $PGE_2$. This COX-2-induced prostaglandin pathway promotes carcinogenesis by increasing cell proliferation, inhibiting apoptosis and by enhancing the invasiveness of malignant cells[30]. The expression of COX-2 decreases significantly after *H. pylori* eradication in patients with atrophic gastritis, confirming the pivotal role of the bacteria in the COX-2-PG pathway[31].

Increasing evidence has confirmed the importance of genetic variability in the pathogenesis of gastric cancer and its precursor lesions. Functional polymorphisms of TLR4, a cell-surface lipopolysaccharide (LPS) receptor involved in *H. pylori* recognition and host response, have been associated with an increased degree of inflammation with severe tissue damage in *H. pylori*-infected subjects. Specifically, carriers of TLR4+896A>G polymorphism are associated with more severe gastric atrophy and inflammation and also with increased risk of noncardia gastric cancer[32].

Finally, polymorphisms and genetic diversity of essential pathogenic elements such as the cagA, TRL4 and SHP2 genes appears to influence the oncogenic potential of *H. pylori* strains[32,33]. Therefore, it is important to recognize and differentiate the more oncogenic *H. pylori* strains and to identify the high-risk populations that are genetically more susceptible to gastric cancer.

However, although many molecular pathways confirm the role of *H. pylori* in gastric cancer carcinogenesis, *H. pylori* infection is not considered a sufficient cause for cancer development[28]. Indeed, only a minority of subjects carrying the infection develop gastric cancer, since many host and environmental factors act synergistically in this multifactorial disease.

### *Diet*

Diet has undoubtedly a pivotal role in cancer development, as observed by the change in the incidence patterns among immigrants according to where they live. In particular, several lines of evidence (ecological, case-control and cohort studies) suggest that a high intake of salt-preserved foods, salt *per se* as well as nitrosamines present in smoked fish and pickled vegetables, "probably" increase the risk of gastric cancer, as stated by the World Health Organization (WHO)/Food and Agriculture Organization (FAO)[34]. Indeed, worldwide geographic variation in gastric cancer mortality, particularly in Japan, has been correlated with the level of daily salt intake[35]. Furthermore, the decline in

**Table 1 Randomized controlled trial with gastric cancer incidence as primary outcome measure**

| Study | Province, Country | Gastric cancer incidence in the general population | No. of patients randomized (treatment/control) | Follow up | No. of patients with gastric cancer (treatment/control) |
|---|---|---|---|---|---|
| Wong *et al*[56] | Fujian, China | 99 cases per 100 000 persons per year | 817/813 | 7.5 yr | 7/11 (0.9%/1.4%) |
| Fukase *et al*[57] | Japan | 62 cases per 100 000 persons per year | 272/272 | 3 yr | 9/24 (3.3%/8.8%) |

gastric cancer incidence in the USA and Europe has been associated with the spread of refrigeration, that could have favoured the transition to methods of food preservation other than salting and to the increased consumption of fresh fruits and vegetables[36].

However, it has not yet been demonstrated which active components of fruit and vegetables are responsible for this protective action. Oxidative stress can induce gene mutation, modulate the apoptotic programme and promote gastrointestinal carcinogenesis[37]. Therefore, antioxidant supplements (e.g. β-carotene, α-tocopherol and vitamin C) have been widely investigated but the best available data have failed to show any beneficial effect and role in gastric cancer prevention[38].

It is very likely that *H. pylori* infection and dietary factors act synergistically to promote gastric cancer development. Prospective human studies encounter methodological and logistical difficulties when multiple concurrent causes of the disease are investigated simultaneously. Indeed, to maintain a tight control of dietary intake and of *H. pylori* status is virtually impossible in whole population studies. Therefore, several experimental animal models have been developed[39-42]. More recent evidence, based on studies performed in primates, suggests that long-term infection or nitrosamine intake alone can cause gastric mucosal inflammation but not cancer. although cancer develops when both factors are present[43].

### *Family history and inherited genetic syndromes*

Familial clustering is observed in approximately 10% of gastric cancers, and hereditary gastric cancer accounts for only 1%-3% of cases[13,44]. Most studies report an increase in the risk of developing the disease from 1.5- to 3.5-fold among the first-degree relatives of gastric cancer patients[13,45]. Moreover, in the study by Brenner *et al*[46], a family history of gastric cancer showed a relative risk of 2.9 (95%CI: 1.3-6.5) and the development of the disease was also associated with an increased prevalence of *H. pylori* infection. Interestingly, the presence of both gastric cancer family history and *H. pylori* infection increased the risk for the disease development eight times. Infrequently, gastric cancer is described as part of several inherited cancer syndromes, such as familial adenomatous polyposis[47], Peutz-Jeghers[48] and hereditary nonpolyposis colon cancer syndrome[49].

In 1998, Guilford *et al*[50] reported the first cases of hereditary diffuse gastric cancer (HDGC)[51]. The authors described three families showing early onset, multigenerational, diffuse gastric cancer. On a molecular level, germline mutations of E-cadherin (*CDH1*) gene were found in these families[50]. Therefore, in families with at least two members with diffuse gastric cancer, and with at least one case with early onset (diagnosed before age of 50 years), mutational analysis should be recommended[52]. Furthermore, *H. pylori* infection is not considered a prerequisite for HDGC development although, its role in the distribution of the lesions is still unclear[53]. Finally, in carriers of germline *CDH1* deleterious mutations, intensive endoscopic surveillance may not be sufficient and total prophylactic gastrectomy is being currently offered as a curative strategy to prevent the development of a lethal cancer.

## HELICOBACTER PYLORI ERADICATION AND GASTRIC CANCER RISK

*H. pylori* infection has been clearly correlated with gastric carcinogenesis. The strongest support for the link between *H. pylori* infection and gastric cancer development has come from prospective cohort studies. A pooled analysis of data from 12 prospective cohort studies demonstrated a 6-fold increase in risk after 10 years of follow-up[8].

Nevertheless, whether the eradication of *H. pylori* infection can represent an effective chemo-preventive strategy to reduce gastric cancer risk has not been firmly established[54,55]. In particular, there are only two randomized controlled interventional studies[56,57] with gastric cancer development as primary outcome measure (Table 1). Both studies were performed in areas at high-risk of gastric cancer, China[56] and Japan[57]. However, the two studies substantially differed in the design. The study by Wong and coworkers[56] was placebo-controlled and included patients with or without gastric preneoplastic lesions (e.g. atrophy, intestinal metaplasia or dysplasia), but excluded those with early gastric cancer (Table 2). On the other hand, Fukase *et al*[57] performed an open-label study including patients with early gastric cancer, either recently diagnosed and scheduled to have endoscopic treatment or in post-resection follow-up (Table 2). These patients were randomly assigned to eradication treatment or to no treatment.

In the study of Wong *et al*[56], 1630 *H. pylori*-positive patients were enrolled and during a 7-year follow-up period, 7 of 817 (0.9%) subjects from the eradication group and 11 out of 813 (1.3%) from the placebo group developed gastric cancer ($P = 0.33$). However, the most interesting finding was provided by the post hoc analysis. None of the patients enrolled within the active group of treatment without pre-cancerous gastric lesions at baseline histopathology developed cancer. On the other hand, all of the patients who

**Table 2 Baseline histology of RCTs with gastric cancer incidence as primary outcome measure**

| Study | Baseline histology | | | | |
|---|---|---|---|---|---|
| | Gastritis | Atrophy | Intestinal metaplasia | Dysplasia | Early gastric cancer[a] |
| Wong *et al*[56] | + | + | + | + | - |
| Fukase *et al*[57] | - | + | + | - | + |

[a]Early gastric cancer either newly diagnosed and planning to have endoscopic treatment or in post-resection follow-up. +: Included; -: Not included.

developed gastric cancer presented pre-neoplastic lesions at study entry. Wong *et al*[56] concluded that the chemo-preventive effect of eradication is achieved only during the earlier phases of carcinogenesis, before preneoplastic lesions have developed and they suggested a "point of no return" in the sequence of events leading to gastric cancer.

Fukase *et al*[57] in a multi-centre study, enrolled 544 patients and at a 3-year follow-up observed that 9 of 272 patients in the eradication group and 24 of 272 patients in the no treatment group developed metachronous gastric cancer. Eradication treatment significantly reduced the risk of developing cancer after endoscopic treatment with an OR of 0.353 (95%CI: 0.161-0.775, $P = 0.009$). This study provided evidence of a preventive effect of *H. pylori* eradication even in later phases of carcinogenesis, apparently in contrast to the conclusion drawn by Wong *et al*[56]. Several reasons could explain this discrepancy: study design, sample size, endoscopic assessment technique, histological definitions and length of follow-up.

Furthermore, another important conclusion that can be drawn from both studies[56,57] is that gastric cancer can still develop despite *H. pylori* eradication and endoscopic surveillance is mandatory for early diagnosis. This latter conclusion has been further strengthened by a recently published meta-analysis of randomized controlled trials that compared an eradication treatment group with a placebo or an untreated group, providing data on the number of gastric cancer cases developed during the study follow-up[58]. At histopathology baseline most of the subjects presented a diagnosis of gastric atrophy, intestinal metaplasia or dysplasia. Over a follow-up period ranging from 4 to 10 years, 33 out of 3112 patients (1.0%) who received eradication treatment developed gastric cancer, compared with 50 of 3031 controls (1.6%); this difference yielded a relative risk of 0.65 (95% CI: 0.42-1.01, $P = 0.05$). Thus, *H.pylori* eradication treatment modestly reduces gastric cancer risk even in subjects with already established preneoplastic lesions, although the risk is not abolished[59].

According to the current guidelines, *H. pylori* infection should be test and treated in patients with a family history of gastric cancer, with atrophic gastritis and after gastric resection[60]. Furthermore, in communities with high incidence of gastric cancer, a screen-and-treat strategy should be adopted.

Future multicenter RCTs are needed to confirm the preventive effect of *H. pylori* eradication on gastric cancer risk. However, such interventional studies are unrealistic because of ethical, methodological, and financial problems.

## GASTRIC CANCER DEVELOPMENT AFTER HELICOBACTER PYLORI ERADICATION

It has been shown that 1.0% of patients still develop gastric cancer despite successful *H. pylori* eradication[58]. More recently, it has been reported that tumors can develop several years after eradication[61]. It should not be forgotten that gastric cancer, as other tumors, is a multifactorial disease and removing one factor does not prevent all gastric cancer cases. Endoscopic surveillance is still needed, especially in subjects at higher risk. However, a clear definition of "high risk" subjects is still the subject of debate. It is well known that the gastric cancer risk varies according to the type of baseline preneoplastic lesion. Indeed, a nationwide cohort study performed in the Netherlands[61] showed that, within the first 5 years of follow-up, patients with a diagnosis of low- or high-grade dysplasia, carry a 0.6% and 6.0% annual risk for cancer, respectively. On the other hand, patients with atrophic gastritis and intestinal metaplasia present 0.1% and 0.25% gastric cancer risk per year, respectively, within the first 5 years of follow-up[61].

Therefore, patients with a baseline diagnosis of dysplasia should be carefully managed and scheduled for a more intensive endoscopic surveillance program than patients with atrophic gastritis or intestinal metaplasia. However, there are currently no international guidelines in Western countries suggesting how, how often and for how many years endoscopic surveillance should be performed in patients with preneoplastic gastric lesions after *H. pylori* eradication treatment[62,63].

In the future, the routine use of recently proposed histological staging system (e.g. OLGA)[64,65] and a better identification of host and bacterial risk factors could help to further stratify patients needing endoscopic surveillance.

## CONCLUSION

Although gastric cancer incidence is declining, it is too early to consider this neoplastic disease as rare and the worldwide mortality rate remains high. Primary prevention is feasible since most of the risk factors can be removed. However, gastric cancer is a multifactorial disease therefore removing one factor (e.g. *H. pylori* infection) does not prevent all cases. Endoscopic surveillance is still needed, especially in subjects at higher risk. Although the definition of patients at increased risk is far from clearly defined, it is reasonable to consider at those patients with a family histo-

ry of gastric cancer, with baseline preneoplastic lesions and those with previous diagnosis of gastric cancer to be at increased risk. All the risk factors that can be easily managed, such us giving up smoking, increasing fruit and vegetable intake and *H. pylori* eradication, should be considered as preventive strategy. The definition of high-risk patients is challenge for the future as well as identification of the best surveillance strategy for such patients.

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