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Review article

## Gastric cancer prevention strategies: a global perspective

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## **Abstract**

Gastric cancer (GC) is the fifth most common cancer worldwide, and mortality rates are still high. Primary preventive strategies, aimed to reduce risk factors and promote protective ones, will lead to a decrease in GC incidence. *Helicobacter pylori* infection is a well-established carcinogen for gastric cancer and its eradication is recommended as best strategy for the primary prevention. However, the role of other factors such as lifestyle, diet and drug use is still under debate in GC carcinogenesis.

Unfortunately, most patients with GC are diagnosed at late stages when treatment is often ineffective. Neoplastic transformation of the gastric mucosa is a multistep process, and appropriate diagnosis and management of preneoplastic conditions can reduce gastric cancer related mortality. Several screening strategies in relation to gastric cancer incidence have been proposed in order to detect neoplastic lesions at early stages. The efficacy of screening strategies in reducing gastric cancer mortality needs to be confirmed.

This review provides an overview of current international guidelines and recent literature on primary and secondary prevention strategies for gastric cancer.

## **Abbreviations:**

GC: gastric cancer

AG: atrophic gastritis

IM: intestinal metaplasia

RR: relative risk

OR: odds ratio

HR: hazard ratio

WLE: white light endoscopy

NBI: narrow band imaging

## **Epidemiology of gastric cancer**

The incidence of gastric cancer (GC) has been steadily declining worldwide in the last decades; nevertheless, GC still represents the fifth most common cancer with more than 1,000,000 cases in 2018, almost two-thirds occurring in developing countries <sup>1,2</sup>. The regions with highest incidence of GC are Eastern Asia, Central and Eastern Europe and several Central and South American countries, whereas North America, Australia and North Africa are considered to be low incidence areas. However, the distribution of GC does not follow a strict geographical pattern, since low rate countries have been reported within highest risk areas, such as India in Asia, while within low incidence populations there are sub-groups of subjects at higher risk, such as Koreans living in United States.

In all populations, the age-standardised risk is about 2-3-fold higher in males than in females <sup>1</sup>. Gastric cancer is a rare event before the age of 50 years; the risk steadily rises with increased age, with highest incidence rates occurring in the sixth and seventh decades of life.

Gastric cancer remains the third-most common cause of cancer-related death, after lung and colorectal cancers, responsible for more than 8% of deaths worldwide from cancer in 2018 <sup>1</sup>.

Mortality rates for GC continue to be high, with survival rates around 30% worldwide. Notably, the main factor influencing 5 years survival is the stage of disease at the diagnosis; indeed, GC detected at early stages leads to a 5 years survival rates of about 80%. Unfortunately, less than 20% of GCs are diagnosed in early stages in Europe <sup>3</sup>. This scenario does not account for Japan and Korea, where mass screening programs have led to diagnoses of GC in early stages increasing 5-years survival rates well above 60% <sup>4</sup>.

Primary preventive strategies aiming to reduce risk factors and promote protective ones, together with secondary strategies favouring early diagnosis of GC by identifying and surveying patients with precancerous conditions and lesions, such as atrophic gastritis (AG) and intestinal metaplasia (IM) and dysplasia will lead to a further decrease in GC incidence and mortality and reduce health care costs.

This review provides an overview of current international guidelines and reports recent evidence on primary and secondary prevention strategies for gastric cancer to guide physicians in the management of their patients.

## Primary prevention

Although the absolute number of GC remained stable in the last century due to the growth of the world population, the overall reduction of the incidence still supports the role of lifestyle, nutrition, drug use and other environmental factors in GC carcinogenesis (Figure 1) <sup>5</sup>.

Indeed, in the last century a decline in *Helicobacter (H.) pylori* prevalence, an improvement in food storage and hygiene, a decrease in smoking and an increase in antibiotic use have been related to the changing epidemiology of GC <sup>6</sup>.

### *Diet*

Dietary factors play a role in GC carcinogenesis. While some seem to increase the risk of developing the cancer, such as alcohol, coffee and meat consumption, others seem to have a protective role, in particular fruit, vegetables and vitamins intake.

There is substantial evidence supporting a carcinogenetic role of high salt intake in the development of GC. A meta-analysis reported a positive association, though not statistically significant, between intestinal metaplasia and urinary sodium excretion, which is directly related to salt intake <sup>7</sup>. More recently, an endoscopy based Asian study confirmed that high salt intake could be associated with an increased risk of atrophic gastritis with intestinal metaplasia <sup>8</sup>. In addition, a similar European study concluded that an increased risk of gastric dysplasia or gastric cancer in patients with *H. pylori* infection is further enhanced by high salt intake <sup>9</sup>.

As regards to alcohol consumption, a meta-analysis of twenty-two cohort studies concluded that moderate or large consumption is associated with a significantly increased risk of GC <sup>10</sup>. The effect of alcohol on gastric carcinogenesis A possible explanation for the carcinogenic effect of alcohol could be due to the local toxic effect of ethanol and of the alcohol metabolite acetaldehyde.

A possible correlation between coffee consumption and GC has been also investigated and summarized in several different metanalysis with inconclusive results <sup>11</sup>. Moreover, the mechanisms of the possible effect of coffee in the gastric carcinogenesis are not yet clear; therefore, the association between coffee and GC still needs to be clarified.

A recent meta-analysis aiming to assess whether meat consumption was associated with GC, concluded that red (RR 1.41) and processed (RR 1.57) meat consumers are associated with a higher risk of GC, whereas white meat consumption seems to have

a protective effect (RR 0.80) <sup>12</sup>. Processed meat often contains a high nitrite concentration, leading to the formation of highly carcinogenic N-nitroso compounds <sup>13</sup>. Among processed foods, smoked foods also seem to be involved in gastric carcinogenesis through the formation of polycyclic aromatic hydrocarbon.

Other specific dietary compounds, such as omega-3 and green tea consumption, did not show a clear correlation with the risk for GC <sup>14</sup>.

A large multicentric prospective study from Japan with 10-years follow-up of about 40,000 patients, highlighted an inverse correlation between GC and fruit and vegetables intake <sup>15</sup>. A meta-analysis of cohort studies on this topic confirmed an inverse association between fruit and vegetable intake, even though the results were too heterogeneous due to the great variability in the study designs <sup>16</sup>.

On the other hand, a pooled analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) study including a prospective cohort from 23 study centres in 10 European countries, revealed no significant association between total fruit or vegetable intake and GC, except for high intake of cereal fibre that was associated with a decreased risk of GC <sup>17</sup>. The discrepancies in the results of the different studies could be due to confounding factors such as the fibre composition, which might act as a protective factor alone, and the generalization of the fruit and vegetables category. A more focused pooled analysis from the stomach cancer pooling (StoP) project consortium, including 6,340 cases of GC and 14,490 controls from 15 case-control studies, reported a protective effect of citrus fruits on gastric cancer risk (OR 0.80) <sup>18</sup>. Citrus fruits seem to exert their anticancer effect through flavonoids which are contained almost exclusively in these fruits and their juices.

The beneficial effect of fruit and vegetables intake could be due to the presence of high levels of vitamins with antioxidant effects and with anti-cancer activities such as ascorbic acid, carotenoid, catechins <sup>19, 20</sup>. Several studies tried to find a potential beneficial role of vitamin supplementation in decreasing GC carcinogenesis rate with controversial results. Even when a beneficial effect was reported, this was time-dependent and linked to the continuous vitamin supplementation. More recently, a meta-analysis of randomized and observational studies on different types of vitamin intake showed that low-dose vitamin intake (vitamin A: 1.5 mg/day, vitamin C: 100 mg/day, vitamin E: 10 mg/day) was associated with a significant reduction of GC risk (29% for vitamin A, 26% for vitamin C and 24% for vitamin E, respectively) <sup>21</sup>. As part of the EPIC study, Buckland and colleagues reported that the Mediterranean diet, which is

based on high consumption of fruit, vegetables, fish and seafood, and low intake of red, processed meat and dairy products, with moderate use of red wine, was associated with a significant reduction of GC risk (hazard ratio: 0.67; 95% CI: 0.47, 0.94) <sup>22</sup>. Moreover, the EPIC study also showed that up to 20% of all Gastric Cancer cases could have been prevented if subjects in this population had followed healthy lifestyle behaviours related to smoking status (no smoking), Mediterranean diet and body mass index (normal weight) <sup>23</sup>.

### *Smoking*

There is consistent evidence that smoking is a risk factor for gastric cancer. A meta-analysis of 42 studies reported a risk ratio of 1.7 in subjects smoking approximately 30 cigarettes per day <sup>24</sup>.

Other tobacco-related products were also found to be associated with GC: two Asian studies reported an association with tobacco chewing <sup>25</sup> and waterpipe tobacco smoking <sup>26</sup>.

Interestingly, vegetable and fruit consumption appears to have a more protective effect among smokers than non-smokers <sup>27</sup>.

### *Physical activity*

Physical activity seems to be a protective factor for GC development. A recent prospective cohort study from the UK showed a risk reduction of about 30% (HR 0.66) <sup>28</sup>. A meta-analysis of seven prospective cohort studies and four case-control studies, including almost 8000 cases of GC, reported a protective association, albeit modest, between regular physical activity (defined as 150 minutes of moderate intensity aerobics per week or 75 min of vigorous intensity physical activity or an equivalent combination of both) and GC (RR 0.81 in the prospective studies, RR 0.78 in the case-control studies) <sup>29</sup>. The protective effect of physical activity, could be due to the reduced circulating levels of insulin-like growth factor and leptin, which could favour pre-neoplastic changes in cell cycle <sup>30</sup>. Physical activity is also an important component of lifestyle interventions for weight loss and maintenance.

### *Drugs*

The association between long term proton pump inhibitors (PPIs) use and GC is still debated <sup>31</sup>. Recent large observational cohort studies carried out in China <sup>32</sup> and

Sweden<sup>33</sup> reported a significant association between long term PPIs use and GC. In the study by Cheung *et al.* among 63397 subjects, PPIs use was associated with an increased GC risk with an HR of 2.44 (95% CI 1.42 to 4.20), and the risk increased with duration of PPIs use (from HR 5.04 for  $\geq 1$  year to 8.34 for  $\geq 3$  years)<sup>32</sup>. On the contrary, a cohort study from the US did not confirm this finding<sup>34</sup>. A recent large placebo-controlled Randomized Clinical Trial (RCT), including 17,598 patients, reported that a 3-year chronic use of PPIs for did not increase the risk of developing precancerous atrophic conditions<sup>35</sup>. Long term RCTs are certainly needed to clarify if there is a causal link between PPI use and GC risk.

Non-steroidal anti-inflammatory drugs (NSAID), statins and metformin seem to have a protective effect for GC. A meta-analysis has shown an inverse association between NSAIDs and both cardia or non-cardia GC<sup>36</sup>. The results of another meta-analysis of 24 studies suggest that the protective effect of aspirin (RR 0.70) may be slightly higher than NSAIDs (RR 0.86), especially for non-cardia GC<sup>37</sup>. Aspirin and NSAID inhibit cell proliferation and induce apoptosis in various cancer cell lines, which is considered an important mechanism for their anti-tumour activity.

Two meta-analyses of observational and randomized controlled trials indicate that the use of statins reduce the risk of GC between 15% and 20%<sup>38, 39</sup>.

Finally, metformin has been shown to have in vitro an anti-tumorigenic effect inhibiting tumour growth by targeting gastric stem cells. A recent meta-analysis including 591,077 patients with type 2 diabetes, reported a lower risk of GC in patients receiving metformin therapy (HR 0.76) than in patients not receiving such treatment<sup>40</sup>.

### ***Helicobacter pylori* eradication for gastric cancer prevention**

*H. pylori* has been classified as class I carcinogen by IARC (international Agency for Research on Cancer)<sup>2</sup>. There is strong evidence that *H. pylori* is a risk factor for GC development; its action is exerted through virulence factors mainly expressed by cagA strains.

The key mechanisms for *H. pylori* carcinogenesis are related to the development of gastritis; the inflammation of the gastric mucosa induces oxidative damage and nitrosation of DNA. The progressive inflammation leads to atrophy, intestinal metaplasia, dysplasia and cancer following the so-called Correa's cascade. The risk of developing GC is directly linked to the severity and extent of gastric atrophy and intestinal metaplasia.

A recent large retrospective cohort study that included more than 370,000 patients in the US with a diagnosis of *H. pylori* infection, reported a cumulative incidence of cancer at 5, 10, and 20 years after detection of infection of 0.37%, 0.5%, and 0.65%, respectively; the risk of gastric cancer was significantly higher in racial and ethnic minorities and smokers.<sup>41</sup> Moreover, the study showed that treatment of *H. pylori* infection decreased risk only if eradication was successful.<sup>41</sup> This data is also confirmed by several meta-analyses, the most recent by Lee *et al.* in 2016, that reported a reduction of GC risk after *H. pylori* eradication of about 35%<sup>42-45</sup>; this effect was more relevant in patients without intestinal metaplasia with a risk reduction of about 75%.

*H. pylori* eradication treatment should also be offered to persons with the infection who have a family history of gastric cancer in first-degree relatives, as it appears to effectively reduce the risk of GC.<sup>46</sup>

A recent trial reported that in patients with early GC *H. pylori* eradication reduced the risk of metachronous GC, reducing gastric atrophy<sup>47</sup>.

Thus, International guidelines recommend *H. pylori* eradication as best strategy for the primary prevention of GC, in particular, in subjects without intestinal metaplasia<sup>48</sup>.

### **Diagnostic tests for detecting preneoplastic conditions (endoscopy vs non-invasive tests)**

Neoplastic transformation of the gastric mucosa is a multistep process described in the Correa's cascade. In this model, atrophic gastritis and IM precede the development of dysplasia and gastric cancer. Early diagnosis and appropriate management of these preneoplastic conditions can reduce gastric cancer related mortality; therefore, several screening strategies have been proposed and vary in relation to gastric cancer incidence.

At present, white light endoscopy (WLE) with mapping biopsies remains the most informative and accurate test for gastric mucosa assessment; enhancing techniques such as dye chromoendoscopy (CE) with acetic acid or indigo can also be used to increase the sensitivity and guide mucosal biopsies. A meta-analysis including a total of 902 lesions from 10 studies, the majority of which from Asia, showed an overall accuracy of CE vs WLE of 86.6% vs 54.9% for gastric cancer, and for preneoplastic lesions of 98.4% and 81.0%, respectively<sup>49</sup>. However, procedures including CE are time consuming and require additional resources; to overcome this issue several

studies have investigated the usefulness of virtual chromoendoscopy, such as narrow band imaging (NBI). The effectiveness of this technique is related to the endoscopists experience and requires additional training. A prospective multicentre study involving five centres in Western countries showed a higher sensitivity of NBI for diagnosis of IM compared to WLE (87% vs 53%  $P < 0.001$ ) with higher overall accuracy (94% vs 83%  $P < 0.001$ ); the specificity was higher than 95% for both techniques <sup>50</sup>. The diagnostic accuracy of NBI for preneoplastic lesions has been further evaluated in a meta-analysis including 31 studies; the pooled sensitivity for IM and dysplasia was 86% and 90% respectively, the specificity showed similar results (77% and 83%) with a diagnostic odds ratio of 17 for intestinal metaplasia and 47 for dysplasia/early gastric cancer <sup>51</sup>.

These results were confirmed in a multicentre prospective randomized study involving a total of 579 patients aged older than 50 years from five tertiary institutions in the Asia-Pacific region. NBI compared to HD-WLE showed higher sensitivity for IM and malignancy (92.3% vs 59.1% and 100% vs 28.6%) <sup>52</sup>.

Mucosal patterns seen using NBI have been described for identification and characterisation of abnormal gastric mucosa; the light blue crest sign is highly suggestive of IM with 91% accuracy <sup>53</sup>. Other authors have proposed and validated a simplified NBI classification showing accuracy of 84% for IM and 95% for dysplasia <sup>54</sup>; this classification does not require a long learning curve and can be useful to minimize sampling errors and guide mucosal biopsies.

The OLGA and OLGIM scores, combining staging and extension of gastric atrophy and intestinal metaplasia, have been developed to stratify the risk of progression and to identify high-risk patients that could benefit from close follow-up with repeated endoscopic examination. These scores were validated in both Western and Eastern cohorts; moreover, a meta-analysis by Yue and colleagues has proven its reliability in daily clinical practice <sup>55</sup>, and their use is currently recommended by the European guidelines for the management of preneoplastic condition <sup>56</sup>. Interestingly, a recent prospective multicentre study evaluated an NBI-based endoscopic grading system for gastric metaplasia avoiding the need for biopsies showing high diagnostic performance when compared with OLGIM <sup>57</sup>. Other less invasive techniques have been proposed for the screening of gastric lesions. A large multicentre study conducted in China suggested that magnetically controlled capsule endoscopy could

be evaluated as a promising screening modality presenting good safety and feasibility characteristics <sup>58</sup>.

Non-invasive tests have been proposed for prediction of preneoplastic conditions in order to minimise the need of invasive procedures. Pepsinogen, pepsinogen I/II ratio and gastrin serum levels have been used to identify subjects with a higher risk for gastric preneoplastic lesions that could benefit from endoscopic evaluation. A meta-analysis on pepsinogen tests in gastric atrophic gastritis suggested a good correlation between decreased pepsinogen serum levels and atrophy. In this meta-analysis, the summary sensitivity and specificity for atrophic gastritis diagnosis were 0.69 (95%CI 0.55–0.80) and 0.88 (95%CI 0.77–0.94), respectively <sup>59</sup>. Another meta-analysis focused on the combination of pepsinogen I/II, gastrin-17, and anti-Helicobacter antibodies showing that this serological assay could be a useful tool for the diagnosis of atrophic gastritis. This meta-analysis, including 20 studies with a total of 4241 subjects, showed a summary sensitivity of 74.7% (95%CI, 62.0-84.3) and the specificity of 95.6% (95%CI, 92.6-97.4) for diagnosing atrophic gastritis <sup>60</sup>.

Other non-invasive markers for the assessment of gastric precancerous lesions have also been proposed but not implemented routinely, such as decreased serum ghrelin, evaluation of trefoil factors and panels of MicroRNAs (miRNA) <sup>61</sup>. MicroRNAs are noncoding RNAs regulating gene expression playing a crucial role in the neoplastic process. Their expression can potentially provide diagnostic and prognostic information. Several miRNAs have been evaluated for gastric cancer both circulating and in the gastric juice, such as miR-21, miR-106a, and the combination of multiple miRNAs appears to be more accurate than a single miRNA measurement <sup>61</sup>. These markers are promising and would benefit from further studies to evaluate their role in clinical practice.

### **Current nationwide screening programs**

Population screening is recommended in regions with high-incidence of GC, whereas individual screening is recommended for high-risk subjects in low-incidence regions <sup>56</sup>.

National population screening programs have currently been implemented in Japan and South Korea. At present, the Japanese guidelines recommend radiographic (X-ray) examination screening or gastroscopy for 50-year-old individuals <sup>62</sup>. Similarly, the

Korean guidelines recommend endoscopy or radiographic examination to all 40-year-old individuals every two years <sup>63</sup>.

The participation to these programs and the screening rate with endoscopy have been increasing since their introduction, and both Japanese and Korean programs have shown to be effective in reducing gastric cancer mortality. Patients attending screening programs are more likely to be diagnosed an early gastric cancer, with a consequent improved survival and a higher percentage of successful endoscopic resection.

In this scenario, gastroscopy is the most cost-effective screening strategy with a higher sensitivity and a greater likelihood of early diagnosis when compared to radiological investigations. The benefit of gastroscopy have been registered up to 3-5 years, and a recent meta-analysis confirmed the overall effectiveness of endoscopic screening in Asian countries reporting a 40% RR reduction in gastric cancer mortality <sup>64</sup>.

The benefit of mass-screening remains difficult to confirm with population-based prospective studies, since such studies may be challenging and unethical to perform due to the lack of a control population not undergoing screening. Additional factors need to be considered such as the local applicability and the mortality of gastric cancer. A cost-utility analysis showed that gastric cancer screening with gastroscopy could be cost-effective if combined with colonoscopy for colorectal cancer screening if the risk of gastric cancer is equal or superior to 10 cases per 100,000 <sup>65</sup>.

Two nation-wide screening programs were conducted in Matsu Island (Taiwan), a high incidence area for gastric cancer, where gastroscopy was offered after a positive non-invasive test. The first screening program offered gastroscopy to screen individuals with low serum pepsinogen; the second offered gastroscopy to patient positive for *H. pylori* infection <sup>66</sup>. In this context, a cost-effective analysis showed that testing for *H. pylori* and early eradication might be more cost-effective than surveillance with serum pepsinogen followed by endoscopy <sup>67</sup>.

The introduction of national screening programs has been debated in other high-incidence regions. Singapore is a multi-ethnic country presenting individuals with different risks for gastric cancer, two studies showed that biannual endoscopic surveillance might be cost-effective for Singaporean Chinese aged from 50 to 70 years <sup>68</sup>. The introduction of a prevention program has also been proposed in China, however endoscopic screening studies in this region have shown contrasting results <sup>69</sup>.

In conclusion, endoscopic screening appears to be a valid option in those regions that have a considerably increased risk of GC compared to others, and serological screening can be used to identify subjects who are at a much higher risk of developing GC in order to offer endoscopic surveillance<sup>48, 56</sup>.

### **Prevention of metachronous cancer after endoscopic resection**

Endoscopic resection is the recommended treatment for early gastric cancer without nodal involvement<sup>63, 70, 71</sup>. In these cases, endoscopic techniques may present a non-inferior overall survival compared to surgical gastrectomy; in addition, these minimally invasive procedures allow anatomical and functional preservation of the stomach and present several advantages including less adverse events and complications, shorter hospitalisation, lower costs. However, the preservation of the stomach can expose patients to the development of metachronous lesions arising from the remaining gastric mucosa that is still potentially subject to field cancerisation. The incidence of these lesions following endoscopic resection varies from 2.7% to 15.6% and, in most cases, they can be treated endoscopically without affecting the overall mortality<sup>72</sup>.

The prevention of metachronous gastric lesions following endoscopic resection is based on reduction of risk factors and endoscopic surveillance. Several risk factors have been associated with an increased risk of developing metachronous lesions including old age, male sex, family history of gastric cancer, number and features of the lesions at the initial diagnosis, including the presence of IM and high grade dysplasia and *H. pylori* status.

Other authors found no significant association between the characteristics of the initially resected lesions including number, location, gross and histological type, and development of secondary multiple tumours, whereas *H. pylori* negative status, location in the lower third of the stomach and presence of intestinal metaplasia have shown to be risk factors for the development of further multiple gastric lesions. Prevention of a metachronous lesion through *H. pylori* eradication has been debated. Several studies including open-label randomised controlled trials and meta-analysis of prospective and retrospective studies have shown reduction of the risk even in later phases of gastric cancerogenesis and high-risk patients after *H. pylori* eradication<sup>43</sup>. Moreover, a recent double-blind randomised control trial confirmed the reduction of metachronous lesions and the improvement of histological changes<sup>73</sup>. This paper was discussed in an opinion paper which highlighted possible methodological problems

which may affect the generalisation of the results; however, the authors concluded that *H. pylori* eradication as a preventive therapy of metachronous lesion can be cost effective <sup>74</sup>. On the contrary, prospective randomised trials have shown no significant reduction of metachronous lesions following *H. pylori* eradication <sup>75</sup>.

Indeed, several authors support the hypothesis of the existence of the so-called “point of no return”, defined as mucosal alterations beyond which the effectiveness of *H. pylori* eradication is lost or reduced. Evidence supporting this thesis came from randomised trials and meta-analysis showing no significant reduction of gastric lesions in high-risk patient and in presence of preneoplastic conditions <sup>44</sup>.

The risk of developing gastric cancer remains following *H. pylori* eradication and endoscopic surveillance is recommended by the ESGE guidelines suggesting a follow-up endoscopy after 3-6 months and then annually <sup>71</sup>, and by the Japanese guidelines that suggest follow-up with annual or biannual endoscopy associated with abdominal ultrasonography or CT-scan for tumours with expanded indication for resection <sup>70</sup>.

Besides endoscopic follow-up, several drugs have been evaluated in the chemoprevention of metachronous lesions. A retrospective study has shown that Rebamipide is associated with a significant reduction of risk of gastric cancer in patients who underwent endoscopic submucosal dissection for early gastric cancer reporting a hazard ratio of 0.858 (95%CI 0.739-0.995) <sup>76</sup>. Moreover, a study on Colecoxib, a Cox-2 inhibitor, has shown a significant effect on regression of advanced gastric lesions <sup>77</sup>. In order to test the hypothesis that aspirin can reduce the incidence of metachronous gastric cancer following endoscopic resection of early gastric cancer, a multi-centre randomised trial is currently ongoing <sup>78</sup>. Despite these encouraging results, the evidence for chemoprevention of metachronous lesions is limited and endoscopic follow-up is currently the primary tool for the prevention of metachronous lesions after endoscopic resection of early gastric cancers.

Finally, in recent years, increasing evidence has focused on the role of evaluating the genomic damage level in the gastric mucosa to assess the risk of cancer. Indeed, methylation levels accumulated in tissues have been correlated with GC risk,<sup>79</sup> and *H. pylori* infection is associated with high methylation levels in the gastric mucosa.<sup>80</sup> Therefore, the assessment of the degree of an epigenetic field defect using methylation levels appears to be a promising biomarker of cancer risk, also applicable for patients after endoscopic resection to assess the risk of developing metachronous gastric cancers.<sup>81</sup>

## **Conclusions**

The increasing knowledge and correction of potential risk factors, and the promotion of protective factors explains, at least in part, the declining incidence of GC. Among all, eradication of *H. pylori* is considered the best strategy to reduce the risk of developing GC; nevertheless, in subjects carrying other risk factors GC can still occur despite *H. pylori* eradication. Serology can be used to screen for high risk subjects to whom offer endoscopy, while endoscopic screening appears to be effective in regions with considerably increased risk of GC. Recent evidence supports the usefulness of histomorphological staging systems, such as the OLGA/OLGIM systems, and of dye or virtual chromoendoscopy (NBI), for identifying precancerous conditions and lesions during endoscopic screening. Finally, since the evidence for chemoprevention of metachronous lesions is still limited, endoscopic follow-up is recommended also after endoscopic resection of gastric cancer.

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## Figures

**Figure 1:** Protective and risk factors for gastric cancer. Left from the top: aspirin and NSAID, citrus fruit, vegetables and fruit, vitamin group ACE, physical activity; Right from the top: smoking, high intake of salt, red meat, processed and smoked meat, Helicobacter pylori.

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