Advances in gastric cancer prevention

Antonio Giordano, Letizia Cito

Antonio Giordano, Letizia Cito, INT-CROM, “Pascale Foundation” National Cancer Institute-Cancer Research Center, 83013 Mercogliano, Italy
Antonio Giordano, Human Pathology and Oncology Department, University of Siena, 53100 Siena, Italy

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Correspondence to: Letizia Cito, PhD, INT-CROM, “Pascale Foundation” National Cancer Institute-Cancer Research Center, 83013 Mercogliano, Italy. letizia.cito@cro-m.eu
Telephone: +39-825-1911736 Fax: +39-825-1911705
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Abstract

Gastric cancer is a multifactorial neoplastic pathology numbering among its causes both environmental and genetic predisposing factors. It is mainly diffused in South America and South-East Asia, where it shows the highest morbidity percentages and it is relatively scarcely diffused in Western countries and North America. Although molecular mechanisms leading to gastric cancer development are only partially known, three main causes are well characterized: Helicobacter pylori (H. pylori) infection, diet rich in salted and/or smoked food and red meat, and epithelial cadherin (E-cadherin) mutations. Unhealthy diet and H. pylori infection are able to induce in stomach cancer cells genotypic and phenotypic transformation, but their effects may be crossed by a diet rich in vegetables and fresh fruits. Various authors have recently focused their attention on the importance of a well balanced diet, suggesting a necessary dietary education starting from childhood. A constant surveillance will be necessary in people carrying E-cadherin mutations, since they are highly prone in developing gastric cancer, also within the inner stomach layers. Above all in the United States, several carriers decided to undergo a gastrectomy, preferring changing their lifestyle than living with the awareness of the development of a possible gastric cancer. This kind of choice is strictly personal, hence a decision cannot be suggested within the clinical management. Here we summarize the key points of gastric cancer prevention analyzing possible strategies referred to the different predisposing factors. We will discuss about the effects of diet, H. pylori infection and E-cadherin mutations and how each of them can be handled.

INTRODUCTION

Gastric carcinoma is one of the most frequent cancers and it can be considered one of the major contributors to mortality worldwide. Environmental and genetic causes may be involved and a pivotal role in reducing the incidence of gastric carcinoma may be addressed to prevention. Diet rich in salted and smoked food, so as Helicobacter pylori (H. pylori) infection, are the best known environmental causes, whereas epithelial cadherin (E-cadherin) and runt-related transcription factor 3 (RUNX3) loss of expression are often genetic trademarks of gastric cancer. Hence, prevention might be considered from different viewpoints. A general improvement of lifestyle, including a diet rich in vegetables and a reduced intake of red meat and of alcohol may be helpful in preventing gastric cancer, yet more specific strategy have
to be adopted according to different people environmental and genetic background. In some cases, such as in families carrying E-cadherin mutations, prevention may be focused above all on well scheduled endoscopies and, sometimes, preventive gastrectomy may be the most suitable choice.\textsuperscript{[13,14]}

H. pylori infection and unhealthy diet cause epigenetic and genetic modification, respectively, in stomach cells. In fact, higher methylation levels were found both in some marker CpG islands\textsuperscript{[15]} and in promoter regions of microRNA genes\textsuperscript{[16,77]} in patients suffering from H. pylori infection. On the other hand, high N-nitroso compounds were found in case of diet rich in red meat, whereas polycyclic aromatic hydrocarbons and heterocyclic amines are typical of high intake of smoked and roasted food. All these compounds are highly mutagenic, hence their introduction through nutrition represents an important predisposing factor to stomach cells carcinogenic transformation. Mechanisms by which high consumption of salted food contribute to gastric cancer development have been not completely clarified so far, yet a synergic action with H. pylori and N-nitroso compounds\textsuperscript{[18-20]} and an increase in inflammatory response of gastric epithelium were found\textsuperscript{[21]}

Prevention of gastric cancer has to be performed acting on two different directions: removing and contrasting possible causes. Considering diet habits, a powerful strategy is represented by replacing processed with fresh food, taking care of introducing high intake of vegetables. Adopting a healthy diet is an effective approach to prevent stomach tumors in people suffering or not, from H. pylori infection. Yet, in this last case a suitable eradication therapy has to be established and a well scheduled follow-up has to performed. Here we will discuss in detail all these different sides, together with the prevention strategy of gastric cancer caused by E-cadherin mutations.

\section*{PREVENTION OF GASTRIC CANCER IN PEOPLE SUFFERING FROM H. PYLORI INFECTION}

H. pylori is a gram-negative bacterium colonizing stomach which may cause gastritis in infected patients. It is able to survive in gastric acidic environment because of its capability of synthesizing urease, an enzyme which can neutralize the stomach acidic pH\textsuperscript{[22]}. Various papers focused their attention on the pivotal role exerted by cytotoxic associated genes in the pathogenicity island (Cag PAI), vacuolating toxin A and IceA (induced by contact with epithelium A), whose positivity characterizes different H. pylori strains, in clinical response of patients\textsuperscript{[23-28]}. More specifically, their data show that in genesis of gastric cancer a key role may be exerted by Cag PAI\textsuperscript{[29-28]}, a group of about 30 genes encoded by a 40 kilobases region. Among the thirty related proteins, some of them are involved in the constitution of type IV secretion system (T4SS) a “molecular syringe”,\textsuperscript{[22,26]} helping CagA (a protein belonging to the Cag PAI group) to enter into gastric cells cytosol. CagA has been considered the most important virulence factor involved in gastric cancer development mediated by H. pylori\textsuperscript{[30-32]}, although in a recent paper Rizzato et al\textsuperscript{[33]} highlighted other important genes, such as CagE and CagL, whose polymorphisms may affect patients clinical outcome. H. pylori seems to exert a role in mechanisms leading to gastric cancer by inducing methylation in different genes\textsuperscript{[33]}, interfering with apoptotic pathways\textsuperscript{[34]} and by causing inflammatory events leading to gastritis, then to atrophic gastritis and possibly to gastric cancer\textsuperscript{[35-39]}. The infection is generally treated by triple therapy, based on proton pump inhibitor-clarithromycin-amoxicillin or metronidazole treatment\textsuperscript{[40]}, yet this strategy recently produced disappointing results\textsuperscript{[41,42]}. A possible explanation was referred to an increase of H. pylori strains showing clarithromycin resistance\textsuperscript{[43-45]}, which challenged different studies focused on different therapeutic protocols. These are based on drugs administrations deferred over time, the so called sequential 10-d therapy\textsuperscript{[46-49]}, on the concomitant four drugs administration\textsuperscript{[60]}, or on both\textsuperscript{[61]}

In spite of the increased successes and improvements of therapies to eradicate H. pylori, controversial data\textsuperscript{[62-65,53]} are referred to similar successful decrease of gastric cancer due to eradication itself. Most of papers discussing this paradox show by consent that a key role may be referred to the step of the gastric disease development in which eradication therapy is performed. So, an early eradication therapy, during young age, is more effective in preventing gastric cancer, rather than a therapy performed in elder age, when phenotypic and genotypic transformations induced by H. pylori are more serious\textsuperscript{[66-71]}. Then, prevention of gastric cancer in people affected by H. pylori may be performed starting by an early diagnosis followed by an early eradication therapy.

Recent papers describe new forms of gastric cancer developing after H. pylori eradication therapy. Yamamoto et al\textsuperscript{[72]} focused their attention on phenotypic and genotypic differences gastric cancers arising in patients undergone to the therapy and patients not undergone, but suffering from the infection. Matsuo et al\textsuperscript{[73]}, instead, studied patients undergone to eradication therapy, patients not undergone and patients negative for H. pylori infection. Results gained by the two groups showed discrepancy about histotype of gastric cancers arisen in patients treated to eradicate H. pylori, since Yamamoto et al\textsuperscript{[72]} found prevalence of diffuse histotype, while Matsuo et al\textsuperscript{[73]} found prevalence of intestinal histotype. These differences suggest the need of considering a higher number of patients, but these studies highlight the possibility of developing gastric carcinoma also after eradication therapy.

H. pylori is a powerful carcinogen, belonging to group 1, according to the International Agency for Research on Cancer\textsuperscript{[74]}, since it is able to induce genetic changes, such as hypermethylation events\textsuperscript{[34,61]}, contributing to cell transformation\textsuperscript{[62]}. Hence, a support strategy in preven-
tion $H.\text{ pylori}$ carcinogenic potential may be focused in reducing its infective potential. A significant contribution may derive from food. Broccoli sulforaphane exerts protective effects in case of $H.\text{ pylori}$ infection, since it can induce phase 2 detoxication enzymes, such as glutathione-S-transferase (GST), and may act as a bactericide in gastric rodents tissue[63]. These data may be referred to humans too, as it was shown that $H.\text{ pylori}$ eradication induces restored GST levels and considering that GST decreased levels are an hallmark gastric cancer, also led by $H.\text{ pylori}$ infection[64]. Moreover, C57BL/6 female mice infected with $H.\text{ pylori}$ Sydney strain 1, and whose diet was maintained in a high salt intake, when fed with broccoli rich in sulforaphane showed reduced stomach bacterial colonization, a reduced level of tumour necrosis factor-alpha and interleukin-1 beta[65]. In humans consuming 70g/d of broccoli rich in sulforaphane, a reduced level of urease (biomarker of $H.\text{ pylori}$ inflammation) in breath test and of serum pepsinogen I and II (both inflammation biomarkers)[66] was found. Then, it can be deduced that the highest sulforaphane intake, the lowest $H.\text{ pylori}$ inflammation levels.

Considering the plethora of publications focused on $H.\text{ pylori}$ carcinogenic potential it can be gathered that its mutagenic effects must be stopped as more promptly, as possible. This goal may be achieved with an early diagnosis, an early eradication and a healthy diet rich in cruciferous crops.

Since most of $H.\text{ pylori}$ infections are asymptomatic[67], screening programs may be useful, especially among children, so as to reduce the possibility of accumulating mutations from childhood. It has to be stated that $H.\text{ pylori}$ infection in children is above all diffuse in developing countries, because of poor socioeconomic status, as showed from various authors[68-70]. Moreover it is also responsible of worsening their malnutrition, since $H.\text{ pylori}$ reduces the absorption of various micronutrients[70,72], and then of contributing to their growth failure[72-74]. Hence, an effective strategy of early diagnosis and treatment would be desirable, so as to combining short-term and long term advantages, against malnutrition/growth failure and possible gastric cancer, respectively. Yet, extensive population screening programs would represent a welfare spending disproportionately high with respect to actual advantages, so as to encourage focused screening just on really high risk groups such as Japanese[75]. Obviously, this restriction of screening programs would be more targeted to prevention of gastric cancer than of malnutrition, which may be caused by $H.\text{ pylori}$. Various non invasive tests helping $H.\text{ pylori}$ diagnosis in children are available, such as [13C] urea breath test and stool antigen test[69] and different periods of administration of triple therapy showed a good efficacy in treating the infection[68,70]. Notwithstanding, close attention should be paid to the use of multiple antibacterial therapies during childhood, because of the possibility of $H.\text{ pylori}$ clarithromyce resistant strains development[68,76]. Hence, a good strategy to have a balance between the possibility of preventing and fighting against $H.\text{ pylori}$ and the necessity to bypass antibiotics resistance of some strains, may be represented by an healthy diet rich in cruciferous crops. Their intake starting from childhood may contrast possible infections, contributing to decrease infective potential of $H.\text{ pylori}$. Then, good healthy habits acquired in young age may be helpful from beginning of their gaining and lifelong. A regular intake of cruciferous crops could help to impair both immediate and long term effects of $H.\text{ pylori}$ infection, reducing the consequent malnutrition and the possible accumulation of DNA modifications. Diet rich in cruciferous and, more generally, in vegetables, is a pivotal element of a healthy lifestyle (as it will be discussed in the next paragraph), hence it can be adopted from the early childhood, without a particular starting age.

A special topic is represented by the influence of $H.\text{ pylori}$ infection on aetogenesis of Barrett’s esophagus, a pathology consisting in the substitution of the normal squamous epithelium of the distal esophagus with columnar epithelium[75]. This condition predisposes to esophageal adenocarcinoma, since the characterizing columnar epithelium looks like a partial intestinal metaplasia, defined specialized intestinal metaplasia[76]. Gastroesophageal reflux is a well known cause of Barrett’s esophagus, since an excess of acidic fluid accumulating in cardia after meals, can induce modifications of the squamous mucosa lining[80]. Therapy of this condition is based on the use of proton pump inhibitors, so as to control gastric fluid pH. The capability of $H.\text{ pylori}$ in neutralizing acidic pH of gastric environment[69] has been considered a possible explanation of the documented inverse correlation between $H.\text{ pylori}$ infection and Barrett’s esophagus[80]. Yet, in a more recent paper, some authors showed that this correlation is tightly related to parameters used to perform the comparison. More specifically, if control samples are represented by endoscopic reports, $H.\text{ pylori}$ infection and Barrett’s esophagus are inversely correlated, while if control samples are based on blood donors a clear association cannot be found[82]. Since both the papers cited represent a meta-analysis, their results can be considered an effective overview on scientific literature focused on the topic under consideration. A concise conclusion cannot be gained, since further investigations should be performed and a clear mechanism explaining the relationship between $H.\text{ pylori}$ and Barrett’s esophagus is not known[79].

### PREVENTION OF GASTRIC CANCER

#### INDUCED BY DIET

Stomach is one of the first organ contacting food, after oral mucosa and esophagus, performing the second step of chemical and mechanical digestion. The link between food and gastric cancer development has been largely studied. Various authors reported that reliable causes of stomach neoplasms are high intake of red meat[83-85], salted[82,86-87] and smoked food[88-90]. These diet habits are
source of compounds with high carcinogenic potential such as N-nitroso compounds, polycyclic aromatic hydrocarbons and heterocyclic amines. In countries with high incidence of gastric cancer, placed in South-East Asia, Maldives and South West America typical dishes include fish and vegetables consumption, both fresh and salted, fermented and pickled. In 1990, Tsugane et al published their results highlighting that Japan populations living in Hawaii showed a lower incidence rate of gastric cancer, if compared to Japanese resident in Sao Paulo, Brazil. Brazilian diet habits include food with high N-nitrosation potential such as grilled red meat and fish, crustaceans and fried vegetables seasoned with large amount of salt. Other studies focused on the link between gastric cancer and salt intake analyzed salt excretion in 24 h-urine samples of subjects up to 75 years of age and it was found an almost linear correlation between the cumulative mortality rate for gastric cancer in five different area of Japan. Moreover, Okinawa, the Japanese prefecture with the lowest mortality rate for gastric cancer, has diet habits including the lowest salt intake of the whole Japan. Hence, the association between stomach tumours and salted food was confirmed by different ecological and epidemiological studies, but details of biological mechanisms involved have not been well clarified. An important role seems to be exerted if contemporaneous H. pylori infection occurs. In 2007, Loh et al published an interesting paper in which they showed that high dietary salt intake may enhance CagA capability of moving toward gastric epithelium, potentiating H. pylori infection and, hence, transforming power. Previous experiments on H. pylori infected Mongolian gerbils showed that high levels of salt intake caused hypergastrinemia. Others found that an increased gastrin secretion may contribute to epithelial cell growth with concurrent H. pylori infection. Finally it was found that salt can determine alterations in gastric mucus viscosity, allowing N-nitroso compounds to better perform their mutation effects. Hence, an effective prevention against gastric cancer development may be represented by low intake of salted food, avoiding to introduce a compound not mutagenic per se, but whose interaction with other predisposing factors may contribute significantly to the neoplastic pathology.

High alcohol consumption and cigarette smoking may also be considered risk factors related to stomach tumours, although some contrasting data were published. It can be inferred that since alcohol is able to induce chronic gastritis, and cigarette smoking contribute to absorb mutagenic compounds, both of them might be removed in a generally healthy lifestyle. Yet, it has to be specified that just high intake of alcohol showed a direct correlation with increased risk of gastric cancer, while it was not found in case of low, or moderate intake. Preventive effects of a healthy lifestyle, with moderate physical activity, reduced intake of alcohol, fats, red meat and salted food are well established. But strategy of prevention has to include consumption of fresh fruits and vegetables, which seem to exert a protective role on gastric cancer development. Different authors focused their attention on tomatoes, broccoli, citrus fruit and pomegranate because of their antioxidant, cytostatic and anti-inflammatory properties.

Tomatoes intake decreases micronucleated polychromatic erythrocytes and lipid peroxidation, and enhances antioxidant status in Swiss mice treated by N-methyl-N’-nitro-N-nitrosoguainidine (MNNG). micronucleated polychromic erythrocytes are a direct index of chromosomal damage, whereas final product of lipids peroxidation may be mutagenic and carcinogenic. Hence, tomatoes intake showed a contrasting effect on some of the most carcinogenic compounds, namely MNNG. Besides, combination of lycopene, a carotenoid abundant in tomatoes, and S-allylcysteine, an organosulphur which can be found in garlic, is able to modulate the apoptosis pathway Bel2-Bax-Bim, so as to reduce carcinogenic potential of MNNG and sodium chloride in stomach of Wistar rats. Then it can be gathered that diet habits including tomatoes may help in prevention of gastric cancer development, because they can both decrease the overall levels of carcinogens and stimulate apoptotic pathways in gastric cancer cells.

Citrus fruits seem to perform a high level prevention because of their capability of inhibiting gastric endogenous N-nitrosation and epidemiological studies corroborate this hypothesis. The mechanism through which they exert this inhibition is still investigated, but it was supposed that they can be effective in blocking both acid-catalysed nitrosation (ACN), typical of high risk areas, and by biologically catalysed nitrosation (BCN). ACN occurs when intragastric environment has an acidic pH, whereas BCN occurs in nearly neutral pH, so N-nitrosation phenomenon shows independence from stomach pH, but a close relationship to quality of food intake. Yet, the preventive role of citrus fruits is not only limited to reduce this phenomenon, but also to induce G2/M cell cycle arrest in AGS gastric cancer cell line, to suppress CD74, an adhesion molecule of urease H. pylori, and to disrupt the related ERK1/2 activation pathway in NCI-N87 gastric cancer cell line. Induction of apoptosis through caspase-3 activation was found too.

It is noteworthy to mention a paper published in 2004 describing an epidemiological investigation on Japanese males in which it was shown that chronic atrophic gastritis, often first step of gastric neoplastic transformation, was more frequent in men consuming broccoli once or more weekly, if compared to those who ate broccoli less frequently. The same authors considered surprising the data obtained. They supposed that a more accurate diagnostic method for chronic atrophic gastritis, than serological determination of pepsinogen I and II they used, and that a more accurate evaluation of amount of broccoli eaten would have to be performed, since they took account just of times/weekly consumed, rather than precise amount. Moreover a study published in 2008
did not show a significant protective role from fruit and vegetable intake on gastric cancer development\(^{117}\). Yet, this study was performed in United States, where a generally well nourished population live. This comment was recently done also by Key in a recently published review\(^{118}\), in which the author discussed the effective protective role of fresh fruit and vegetables on cancer development. He focused his attention on the importance of having at least a moderate intake of fresh fruits and vegetables, but also to pay attention to avoid overweight, high salted food and high alcohol consumption.

Contrasting papers on the usefulness of fresh fruits and vegetables in preventing gastric cancer, has not to be considered an advice of ignore consumption of this kind of food. Rather, experimental evidences suggesting that different compounds in fruits and vegetables may activate apoptotic and cytostatic pathways and inhibiting \textit{H. pylori} adhesion, would have to encourage to change unhealthy lifestyle toward healthier habits.

**PREVENTION OF GASTRIC CANCER IN FAMILIES CARRYING \textbf{E-CADHERIN MUTATIONS}**

\textit{E-cadherin}, also known as Cadherin type 1 (\textit{CDH1}), is a cell-adhesion glycoprotein characterized for the first time in human cell lines by Shimoyama \textit{et al}\(^{119}\). Its role in gastric cancer development was firstly defined by Guilford \textit{et al}\(^8\), who identified a G→T nucleotide substitution in the donor splice consensus sequence of exon 7 in a Maori kindred. This mutation produced a truncated protein whose final result was a reduced \textit{E-cadherin} production. The family examined showed an early onset of gastric cancer characterized by diffuse histotype, as the other two families described who carried a frameshift mutation in exon 15 and a premature stop codon in exon 13, respectively. Successively, other authors identified other \textit{E-cadherin} mutations in various worldwide families\(^{120-123}\). All these germline mutations are dominantly inherited, originating the so called Hereditary Diffuse Gastric Cancer (HDGC), a dominantly familial cancer syndrome. Updated criteria established by the International Gastric Cancer Linkage Consortium define that the syndrome of HDGC must be characterized by histological confirmation of diffuse gastric criteria only for one family member, inclusion of individuals with diffuse gastric cancer before the age of 40 years without a family history and inclusion of individuals and families with diagnoses of both diffuse gastric cancer (including one before the age of 50 years) and lobular breast cancer\(^{124}\). People belonging to families showing also just one of these features should undergo to genetic test to investigate on possible \textit{CDH1} mutations. Although among familial gastric cases only 1%-3% are carriers of mutations in \textit{CDH1}, positive results should be followed by well scheduled endoscopic surveillance so as to monitor the very first neoplastic lesions. Yet, the efficacy of this strategy may be invalidated in cases of small, or intramucosal, foci\(^{125-127}\). In scientific literature total gastrectomy is often performed as a prophylactic strategy and, as much often, it represents a therapeutic strategy\(^{124-126}\), just because of frequent small foci undetectable by endoscopical techniques.

The knowledge of the effects exerted by inherited \textit{CDH1} mutations, raises different ethical questions. Descendants of carrier families have often to choose if undergoing to preventive gastrectomy, or not. Some of them preferred right this option, while other did not. In both cases physicians have to show possible advantages and disadvantages deriving from each choice. The adoption of a healthy diet, in these cases, although advisable, is not sufficient to exert an active and effective prevention of gastric cancer, since \textit{CDH1} loss of expression and/or function represent an important step towards carcinogenesis. Hence, people belonging to carrier families would have to join a constant endoscopic surveillance with a medical support, to plan the most suitable prevention strategy.

**CONCLUSION**

Up to date gastric cancer is one of the most lethal tumour, especially in South America and South-East Asia, where it shows the highest frequency and morbility. Rare cases of HDGC are caused by \textit{CDH1} mutations and their prevention is above all based on continuous surveillance, generally following an actual mutational diagnosis. Non hereditary gastric cancer number among their predisposing factors both \textit{H. pylori} infection, and unhealthy diet including high intake of salted and smoked food, red meat and alcohol and a reduced intake of vegetables and fresh fruit. Various studies have shown molecular bases related to preventive effects exerted by a healthy diet. More specifically it has been found that cruciferous crops helps to inhibit \textit{H. pylori} infection and then its mutational power. On the other hand, tomatoes, garlic and citrus fruits are able to reduce N-nitrosation and to induce apoptosis and cell cycle arrest in G2/M phase, respectively. Hence, high consumption of vegetables helps to prevent and to block phenomena triggered both by salted and smoked food and red meat, and by \textit{H. pylori} infection.

Future perspectives related to gastric cancer prevention are, above all, focused on improving strategy against \textit{H. pylori} and discovering molecular mechanisms on which healthy diet may exert a function. Very recent papers highlight the possibility of alternative target to manage the bacterial infection\(^{128}\) and to the different parameters to determine a really nutrient and balanced diet\(^{129}\). Again recently, a review written by Nagini\(^{130}\) show an effective summary of all these last keypoints, giving useful hints for further research directions.

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