Gastric Cancer: Where Are We Heading?

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Abstract

Background: Despite its decreasing incidence, gastric cancer (GC) remains one of the leading cancers in the world and an important global healthcare problem due to its overall high prevalence and high mortality rate. **Summary:** GC is a consequence of *Helicobacter pylori* infection in 90% of cases, while in 10% Epstein Barr Virus may be responsible. Moreover, some recent epidemiological data suggest an increasing incidence in some young patients groups possibly due to autoimmunity, and if this tendency is confirmed, it may change the epidemiology of GC in the future. The pathogenesis of GC is mainly related to *H. pylori* infection, but recent data indicate the possible role of other bacteria and their metabolites, like N-nitrosocompounds or acetaldehyde, interfering during the last steps of carcinogenesis. The new molecular classifications of GCs show a great heterogeneity of this neoplasia, which may in the future help to define personalized treatment strategies for the patients. Early detection and proper surveillance of high risk patients should be our major objectives. **Key Messages:** GC is still an important healthcare problem, with its several aspects which remain the major challenges for the future.

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Epidemiology

Gastric cancer (GC) represents an important global health problem since it is the fifth leading cancer in the world and the third leading cause of cancer-related death, responsible for almost 800,000 deaths every year [1]. It occurs approximately twice as frequently in men as in women, with most cases occurring after the age of 60 [1, 2]. The incidence of GC varies widely across different geographic regions, with the highest incidence observed in East Asia, some Eastern Europe and South American countries, and the lowest in North America and Africa. Globally, over 70% of GC occurs in developing countries [3].

GC was the leading cause of cancer death worldwide until the 1980s [4]. During the last 5 decades, however, a clear decline in the GC incidence was observed. This decline has been mainly attributed to the decreased prevalence of *Helicobacter pylori* infection, but also to the progress in food storage and preservation, probably by allowing the reduction of salty and smoked food consumption [5, 6]. This decline concerns mainly distal GC, usually called “non-cardia” GC, while the incidence of proximal GC or “cardia cancer,” has been steadily increasing, probably due to an increased rate of obesity and gastro-oe-

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sophageal reflux disease, which are considered the major risk factors for the latter [7].

Moreover, some recent data, based on studies performed in the United States, indicate an increase in the incidence of non-cardia GC in a group of young individuals, especially women under the age of 50 [8]. The etiology of this GC, named “for corpus-dominant, young age-dominant, female-dominant”, is not clear, but it could be related to autoimmune inflammation and changes in gastric microbiota [9]. Other studies, especially in Europe, will be necessary to confirm this trend, but if it turns out to be real, it may change the epidemiology of GC in the future, when the incidence of GC may increase, especially in women [8].

Pathophysiology

Gastric carcinogenesis is a multifactor and multi-step process, characterized by a complex interplay between the host and environmental factors. Among the latter, the most important is the chronic infection with *H. pylori*, already recognized in 1994 as a Group 1 carcinogen by the International Agency on Research on Cancer [10]. The causal association between *H. pylori* infection and non-cardia GC has been well documented first by epidemiological studies showing a positive association between the prevalence of *H. pylori* and distal GC incidence [11–13], and then by experimental studies showing the evolution to GC in *H. pylori* infected gerbils [14], and mechanistic studies showing the role of the bacterium, via its virulence factors and associated inflammation, to induce the consecutive changes in the gastric mucosa leading to the development of cancer [15–18]. In case of GC of intestinal type, these progressive steps are known as the “Correa’s cascade,” which begins with *H. pylori*-induced chronic gastritis, and may evolve into atrophic gastritis, intestinal metaplasia (IM), dysplasia and ultimately GC. It is clear that by itself the infection is not sufficient to induce GC, which develops only in a minority (<1%) of infected individuals, indicating that other factors are necessary. Among them, several dietary factors, like a high salt, red meat, and smoked food consumption, as well as a low fruit and vegetables intake, and smoking have been incriminated as risk factors [19]. It is also well known that the carcinogenic potential of different *H. pylori* strains is not the same and that some *H. pylori* strains are more prone to induce GC than others, probably by inducing more severe gastric inflammation [20, 21]. To better understand the role of *H. pylori* in GC development, an in-

ternational project called “*H. pylori* Genome Project,” started in 2016. This study, which is planned to be completed in 2020, will hopefully allow to identify the genetic and epigenetic variations among *H. pylori* isolates that may affect the risk of progression to GC [22].

Apart from *H. pylori*, other bacteria may be involved in the last steps of GC development. It has been recently shown that gastric microbiota composition in patients with GC is modified, and in particular is characterized by a reduced microbial diversity and enrichment in other bacterial genera, mainly oral and intestinal commensals [23–25]. Interestingly, the microbiota of patients with GC showed increased activity of nitrate and nitrite reductases; this observation being consistent with the hypothesis that during gastric carcinogenesis, the changes in the stomach mucosa that lead to a decreased acid secretion, allow the growth of bacteria that are able to reduce nitrates to nitrites, precursors of carcinogenic N-nitroso compounds [16, 26]. Similarly, hypochlorhydric stomach secondary to atrophic gastritis, may be colonised by some bacteria and yeasts which produce high quantity of alcohol dehydrogenase and thus have the capacity to produce locally acetaldehyde, from ethanol or from glucose [27]. Acetaldehyde is a highly toxic and carcinogenic compound, also classified as class I carcinogen, which may directly contribute to the epithelial damage and GC development [28].

Furthermore, the causal association between the infection with Epstein Barr virus (EBV) and GC has been well documented, and it is now considered that about 10% of cases of GC are due to this viral infection [29]. EBV is known for its oncogenic properties related to its interference with cell cycle, and has been causally associated with several other cancers.

GC as an Heterogenous Disease

An important aspect of GC is its heterogeneity. Different types of GC may be distinguished, according to their location (distal or non-cardia GC and proximal or cardia GC) or according to their histological type (intestinal and diffuse type according to Lauren’s classification) [30–32]. These different types of GC have different epidemiology and physiopathology, the Correa’s cascade of gastric carcinogenesis being implicated in the intestinal type non-cardia GC, the chronic oesophageal-reflux disease in cardia cancer, and the genetic factors essentially in diffuse type of GC. In addition to histological analysis, the immunohistochemical evaluation of human epidermal growth factor receptor 2 (HER2) expression and replication error

(RER) phenotype of the tumor is now routinely performed since these markers may have therapeutic consequences, that is, indication of anti-HER2 drugs in HER2-positive tumors, and potential interest of immunotherapy in RER+ (microsatellite instable [MSI]) tumors.

More recently, molecular classifications of GC, based on gene expression profile analysis, have been proposed. According to the first classification, published in 2014 by The Cancer Genome Atlas network, 4 types of gastric tumors can be distinguished: (1) positive for EBV, (2) MSI, (3) genomically stable, and (4) chromosomally unstable [33]. Each of these 4 types has a different molecular signature, suggesting the upregulation of different molecular pathways in the tumors cells. All this information brings more insight into the pathogenesis of these different types of tumors, but also indicates a potential susceptibility of these tumors to anti-tumor agents (like for instance, potential susceptibility of MSI and EBV-positive tumors to immunotherapy, etc.) [34, 35]. Other genetic classifications have been published since then [36], but altogether, the prognosis and predictive value of all these classifications still remains to be proven.

Diagnosis and prevention

Another important issue is early endoscopic diagnosis and prevention of GC. Early GC is limited to the mucosa or submucosa, regardless of nodal status, and has an excellent prognosis with a 5-year survival rate over 90% [37]. Endoscopic resection of these early lesions, fulfilling the established eligibility criteria for endoscopic treatment, preferably performed by endoscopic submucosal dissection, is a treatment of choice which gives excellent long-term results [38–43]. However, this implies our capacity to detect and correctly diagnose the early gastric lesions. This diagnosis relies on careful endoscopic evaluation of the gastric mucosa and histological analysis of the biopsy specimens. The tremendous progress in the quality of endoscopic devices has allowed a marked improvement of our capacity to detect early neoplastic lesions. The introduction of new endoscopic techniques of so called “virtual chromoendoscopy,” like narrow band imaging, blue laser imaging, or linked color imaging, facilitates considerably the detection of early GC, allowing to increase the diagnostic yield as compared to the standard white light endoscopy [44–46]. The future direction should be a better dissemination of these techniques to make them widely available, and to organize an appropriate training of endoscopists to allow them to benefit from these techniques.

Gastric precancerous lesions, that is, atrophic gastritis and IM, are associated with an increased risk of GC [47] and their surveillance appears as a logical strategy to prevent advanced GC. Indeed, several international guidelines on the management of these lesions have been recently published [48–51]. Most of these guidelines, except for AGA guidelines, recommend systematic surveillance of severe and extensive, pangastric, atrophy or IM, as evaluated by the operative link on gastritis assessment or operative link on gastric IM) scores, but the indication of surveillance of antrum-limited lesions appears less clear, depending on patient’s characteristics and specific characteristics of the lesions (like the type of IM, complete or incomplete, etc.) [49, 52, 53]. Clearly, in addition to the histology, other criteria would be necessary to better define the population of patients with atrophic gastritis or IM the most susceptible to benefit from systematic surveillance. In this respect, several blood markers have been proposed to detect patients at risk of GC, alone or in combination with histology. The strongest evidence has been accumulated for a low serum pepsinogen I level and low pepsinogen I to pepsinogen II ratio, as reliable markers for gastric atrophy [54], and this marker is the only non-invasive marker integrated in the current guidelines. Low pepsinogen I level has shown in different studies a variable but overall good sensitivity of about 70%, and specificity close to 90%, for the detection of gastric atrophy [55]. Other blood markers have also been studied, like trefoil factors, serum ghrelin, a panel of microRNAs, DNA methylation and tumor-associated antigens [56–65], but none of them can be proposed today in clinical practice. Very recently, it has been suggested that analysis of serum protein profile using multiplex proximity extension assay may allow the possibility to identify serum protein biomarkers of GC [66], but this approach still needs to be validated.

Screening for GC

Another important question is whether there is room for a population-based screening for GC, as it is performed for colon cancer. While it is justified and already adopted in several Asian countries where the GC incidence is high, it is much more debatable in Europe where in most of the countries the GC incidence is low. However, population-based screening could be considered in Europe, especially in the countries with a moderate GC incidence rate, like some Baltic States in Northern Europe, where a potential efficacy of such a screening, based on a

systematic *H. pylori* eradication in all infected individuals, is now being tested in the GISTAR study in Latvia [67]. There is also a project of involving European authorities to discuss the benefit of a general screening for GC, adapted to each European country (depending on specific GC incidence, economic context, etc.). A potential negative impact of such a screening, like an increase in bacterial resistance to antibiotics and negative impact on human microbiota, should also be considered.

Treatment of Advanced GC

Treatment of advanced GC is a real challenge and unfortunately, insufficient progress has been made during the last 2 decades in terms of complete cure rate of GC [40, 68]. Although we are quite successful in prolonging survival of the patients by using multimodal treatments combining surgery with systemic multi-line chemotherapy, we still cannot save the life of >70% of patients [69]. This underlines the necessity, on one hand, to reinforce all the means allowing the diagnosis of GC at early and curable stage, and on the other hand, to put more efforts into the development of new and more efficient drugs for advanced GC. The cornerstone treatment of metastatic GC is still cytotoxic chemotherapy, since most of the targeted therapies, effective in other digestive cancers like colorectal cancer (bevacizumab, cetuximab), appear ineffective in GC. Positive results have been obtained only for anti-HER2 agent, trastuzumab, in HER2 positive GC, which may be used as first-line treatment, and for an anti-angiogenic agent, ramucirumab, which may be used in the second line of treatment, and for which no predictive factors of response have been identified [70–72]. The recent interest in the potential efficacy of immune check points inhibitors brought some hope, with some positive phase II and III studies [73, 74], but not confirmed by

other studies [75, 76]. The future challenge will be to use all the available histological and molecular markers to identify the patients susceptible to benefit from specific treatments.

In conclusion, in the field of GC, we should be heading in the direction of better detection of early cancers, more appropriate surveillance of gastric precancerous lesions, more precise identification of patients susceptible to benefit from specific treatments, and better understanding of gastric carcinogenesis in order to identify new therapeutic targets for advanced GC.

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Author Contributions

P.P. prepared the first draft of the manuscript. T.M.-B. designed the structure and wrote the final version of the manuscript. P.P. and N.C. were responsible for literature research.

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