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EDITORIAL

Early-onset gastric cancer: Learning lessons from the young

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Abstract

There is by no means a clear-cut pattern of mutations contributing to gastric cancers, and gastric cancer research can be hampered by the diversity of factors that can induce gastric cancer, such as *Helicobacter pylori* infection, diet, ageing and other environmental factors. Tumours are unquestionably riddled with genetic changes yet we are faced with an unsolvable puzzle with respect to a temporal relationship. It is postulated that inherited genetic factors may be more important in early-onset gastric cancer (EOGC) than in gastric cancers found in older patients as they have less exposure to environmental carcinogens. EOGC, therefore, could provide a key to unravelling the genetic changes in gastric carcinogenesis. Gastric cancers occurring in young patients provide an ideal background on which to try and uncover the initiating stages of gastric carcinogenesis. This review summarizes the literature regarding EOGC and also presents evidence that these cancers have a unique molecular-genetic phenotype, distinct from conventional gastric cancer.

Key words: Gastric cancer; Early-onset gastric cancer; *Helicobacter pylori*

INTRODUCTION

Gastric cancer is the fourth most common malignancy in the world and ranks second in terms of cancer-related death[1]. It is thought that gastric cancer results from a combination of environmental factors and the accumulation of generalized and specific genetic alterations, and consequently affects mainly older patients often after a long period of atrophic gastritis. The most common cause of gastritis is infection by *Helicobacter pylori* (*H. pylori*), which is the single most common cause of gastric cancer[2,3] and has been classified by the World Health organization (WHO) as a class I carcinogen since 1994[4]. The risk of infection varies with age, geographical location and ethnicity, but overall 15%-20% of infected patients develop gastric or duodenal ulcer disease and less than 1% will develop gastric adenocarcinoma[4]. Environmental and other risk factors for gastric cancer are summarised in Table 1 and have been recently reviewed by Milne *et al*[5,6].

A pattern of gastritis has also been shown to correlate strongly with the risk of gastric adenocarcinoma. The presence of antral-predominant gastritis, the most common form, confers a higher risk of developing peptic ulcers; whereas corpus predominant gastritis and multifocal atrophic gastritis lead to a higher risk of developing gastric ulcers and subsequent gastric cancer[7,8]. The response to *H. pylori* infection and the subsequent pattern of gastritis depends on the genotype of the patient and in particular a polymorphism in IL-1β, an inflammatory mediator triggered by *H. pylori* infection, is known to be of importance[9]. Multifocal atrophic gastritis is usually accompanied by intestinal metaplasia and leads to cancer *via*

dysplasia, and thus intestinal metaplasia is considered to be a dependable morphological marker for gastric cancer risk. Unlike intestinal gastric cancer, the diffuse type typically develops following chronic inflammation without passing through the intermediate steps of atrophic gastritis or intestinal metaplasia.

Several classification systems have been proposed, but the most commonly used are those of the WHO and of Laurén who describes two main histological types, diffuse and intestinal[10]. Intestinal adenocarcinoma predominates in high-risk areas whereas the diffuse adenocarcinoma is more common in low-risk areas[11]. Although classification varies between Japan and the West, attempts have been made recently to standardize systems[12]. Early gastric cancer is a term to describe carcinomas limited to the mucosa or to both the mucosa and submucosa, regardless of nodal status. The prevalence of this lesion is higher in countries such as Japan, where a screening programme is carried out.

There is by no means a clear-cut pattern of mutations in gastric cancers, with no known multi-step pathway, and genetic research can often be hampered by the diversity of changes that are induced by *H. pylori* infection, diet, ageing and other environmental factors. Tumours are unquestionably riddled with genetic changes, as summarized in Figure 1, yet we are faced with an unsolvable puzzle with respect to a temporal relationship. In order to solve this problem, one approach is to investigate tumours that are less influenced by these environmental factors. Gastric cancers occurring in young patients, known as early-onset gastric cancers (EOGC), provide an ideal background on which to try and uncover the initiating stages in gastric carcinogenesis. In addition, hereditary cancers can often illuminate discrete mutations that can initiate the pathway of gastric carcinogenesis.

Table 1 Environmental and other risk factors for conventional gastric cancer

Increased risk of gastric cancer	Decreased risk of gastric cancer
CHD1, TP53, BRCA2 germline mutation	Fruit and vegetables
Hereditary non-polyposis colorectal cancer	Ascorbic acid
Helicobacter pylori infection	Carotenoids
Ebstein barr virus infection	Folates
Cigarette smoking	Tocopherols
Smoked or cured meat and fish	Cereal fibres
Pickled vegetables	Numerous polymorphisms
Chilli peppers	(as mentioned under
Alcohol	increased risk)
Exposure to nitrosamines + inorganic dust	
Obesity	
Pharmacological gastric acid suppression	
IL-1β-31 polymorphism	
1195 COX-2 polymorphism	
Other polymorphisms: MTHFR, PSCA, XPA, XPC, ERCC2, GSTT1, SULT1A1, NAT2, EPHX1, Toll-like receptor 4	

EARLY ONSET GASTRIC CANCER

Gastric cancer is rare below the age of 30 thereafter it increases rapidly and steadily to reach the highest rates in the oldest age groups, both in males and females. The intestinal type rises faster with age than the diffuse type and is more frequent in males than in females. EOGC is defined as gastric cancer presenting at the age of 45 or younger. Approximately 10% of gastric cancer patients fall into the EOGC category[13], although rates vary between 2.7%[14] and 15%[15] depending on the population studied. Young patients more frequently develop diffuse lesions, which often arise on the background of histologically "normal" gastric mucosa. It is postulated that genetic factors may be more important in EOGC than in older patients as younger patients have less exposure to environmental carcinogens[5,16], thus these cancers could provide a key to unravelling the genetic changes in gastric carcinogenesis. *H. pylori* may still play a role in the development of gastric cancer in young patients[17-19], and there is, in fact, no difference in the distribution of gastric cancer predisposing *IL1β* polymorphisms between young and old patients[20]. However, the role of *H. pylori* is likely to involve a much smaller percentage of patients than in the older age group. Epstein-Barr virus (EBV), which is observed in 7%-20% of gastric cancers, has been implicated in gastric carcinogenesis and occurs slightly more frequently in diffuse-type gastric cancers[21-23]. However, the levels of EBV infection appear to be much lower (or absent) in EOGC[24].

The clinicopathological features of gastric carcinoma are said to differ between young and elderly patients[25] and it has been claimed that young patients have a poorer prognosis[26]. Others report that tumour staging and prognosis for young patients is similar to older patients and depends on whether the patients undergo a curative resection[13,15,27]. Young patients with gastric cancer in the United States are more likely to be black, Asian or Hispanic[28]. Relative to older patients, young patients have a female preponderance, a more frequent occurrence of diffuse cancer and less intestinal metaplasia[13,28,29]. This predominance of females is considered by some to be due to hormonal factors[30,31]. Cancers in young patients are more often multifocal than in older patients[32] as is also seen in HDGC[33].

Approximately 10% of young gastric cancer patients have a positive family history[13], some of which are accounted for by inherited gastric cancer predisposition syndromes. Although the underlying genetic events are not always known, it can involve *CDH1* germline mutations[34-36], encoding an aberrant form of E-cadherin, resulting in hereditary diffuse gastric cancer (HDGC), as recently reviewed by Carneiro *et al*[36]. In fact, some suggest that when looking at *hMLH1* and *CDH1* germline mutations, 2%-3% of EOCG cases in North Americans may be due to high-risk genetic mutations[37,38]. The 90% without a family history emphasizes that the occurrence of gastric cancer in young patients remains largely unexplained, and is probably caused by a predisposing genotype that has facilitated cancer development due various environmental triggers[6].

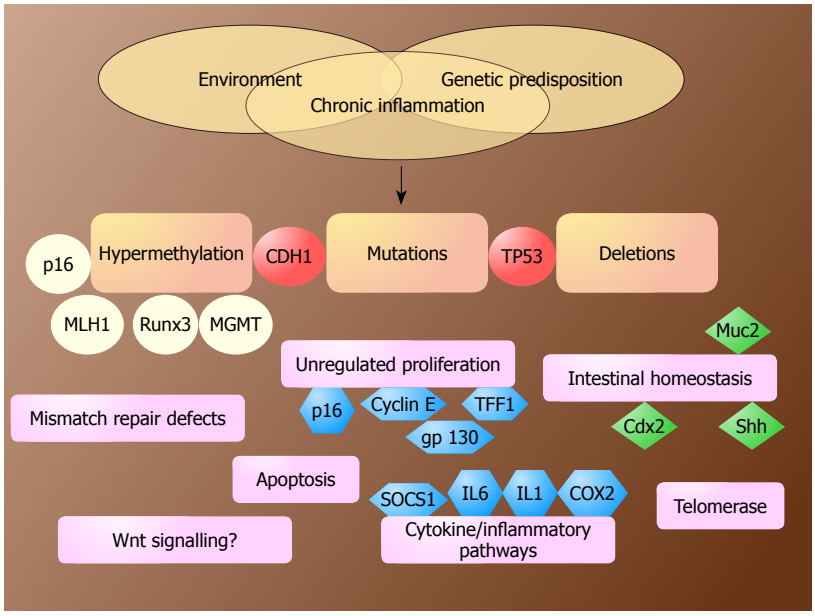

Figure 1 This figure summarizes the molecular genetic changes in conventional gastric cancer and emphasizes the lack of a multi-step pathway in gastric cancer, despite extensive research in the field. It highlights the need for a new approach to understanding gastric cancer, such as examining early-onset gastric cancers and hereditary gastric cancers, where we can learn from the young.

It has been discovered that EOGCs have a different clinicopathological profile than conventional gastric carcinomas. This suggests that they represent a separate entity within gastric carcinogenesis and indeed evidence at a molecular genetic level supports this. The majority of gastric adenocarcinomas, like many other solid tumours, show defects in the maintenance of genome stability, resulting in DNA copy number alteration that can be analysed by (microarray-based) comparative genomic hybridization (array CGH). Hierarchical cluster analysis of array CGH data on 46 gastric cancer patients (including 12 young patients) revealed clusters with genomic profiles that correlated significantly with age[39]. Gains at chromosomes 17q, 19q and 20q have been found in EOGC with comparative genomic hybridization[40] and LOH findings have also shown that losses are infrequent in EOGC[24].

The presence of microsatellite instability (MSI), which usually occurs at a frequency of 15%-20% in older gastric carcinomas, also varies dramatically between gastric cancer in young and old patients, with MSI consistently absent in EOGC[24,29,41,42]. These results have been found despite the analysis of distal tumours (where MSI is usually more common) and inclusion of mixed and intestinal type tumours (diffuse tumours generally have less MSI)[43]. However, it may be that geographical factors play a role[44]. A lack of MSI excludes the mutator phenotype as an important predisposing factor in the development of EOGC. This contrasts with the situation in colorectal cancer where 58% of patients without HNPCC aged under 35 years showed evidence of MSI[45]. EOGC also contrasts with colorectal cancer with respect to the tumor suppressor gene *APC*, which causes familial adenomatosis polyposis syndrome. The role of *APC* in EOGC is limited and nuclear expression of β-catenin has not been found to differ between EOGC and conventional gastric cancers[46,47].

Molecular expression profiles of EOGC and conventional gastric cancers have been found to differ and EOGC has a COX-2 Low, TFF-1 expressing phenotype[46]. In light of studies showing the reduced risk of gastric cancer in non-steroidal anti-inflammatory drug users[48,49], these results may have clinical implications, as they suggest that this reduced risk may apply only to gastric cancer in older patients, as COX-2 does not appear to play an important role in EOGC. It also implies that genetic changes typical for conventional tumors more readily induce COX-2 expression than those associated with EOGC. Interestingly, this COX-2 low phenotype cannot be explained by the increased presence of the *COX2* -765 G>C polymorphism in EOGC[50]. A higher incidence of aberrant E-cadherin expression in EOGC regardless of histological type[29] has also been reported, although a more recent report that compared EOGC with conventional cancers showed that aberrant expression of E-cadherin correlated significantly with the diffuse type[46].

Deregulation of the cell cycle is known to be a critical event in the onset of tumourigenesis, and thus the finding of low molecular weight isoforms of cyclin E in EOGC, which are reported to be constitutively active in breast cancer[51], are of great interest. The expression of these isoforms differs between EOGC and conventional cancers, being present in 35% of EOGCs, compared to in 8% of conventional gastric cancers and 4% of stump cancers[52]. In addition, these low molecular weight isoforms in EOGC diverge from the classical role of cyclin E as oncogenes and were found to be an independent positive prognostic indicator in EOGC[52] adding to reports where the role of cyclin E conflicted with previous dogma[53,54]. This complexity of molecular wiring in carcinogenesis has also been emphasized in recent literature, with the conclusion that cancer can no longer be viewed purely in terms of a network of oncogenes and tumour suppressor genes[55,56].

Further evidence that EOGCs display molecular characteristics different from conventional carcinomas comes from a study where amplification at 11p12-13 was found in gastric cancer using representational difference analysis and was confirmed by Southern blot analysis. It

Table 2 Clinico-pathological and molecular-genetic differences between early-onset and conventional gastric cancers

Conventional gastric cancer	Early-onset gastric cancer	Ref.
Equally common in male and females	More common in females	[13,28,30,31]
Intestinal type cancer more common	Diffuse type cancer more common	[13,28]
Usually unifocal	Often multifocal	[32,33]
Often preceded by intestinal metaplasia	No intestinal metaplasia	[13,28]
Microsatellite Instability in 15%-20%	Lack of MSI	[24,29,41-43]
Commonly find loss of heterozygosity	Infrequent loss of heterozygosity	[24]
COX2 overexpression in 66%	COX2 overexpression in 10%	[46]
Loss of TFF1 expression in 73%	Loss of TFF1 expression in 39%	[46]
Loss of RUNX3 gene	No loss of RUNX3	[58-61]
Widespread gains throughout genome	Gains at chromosomes 17q, 19q and 20q	[40]
Distinct gene clusters on hierarchical analysis	Distinct gene clusters on hierarchical analysis	[39]
Infrequent LMW isoforms of cyclin E	Frequent LMW isoforms of cyclin E	[52]
CD44v6 expression	CD44v6 more commonly expressed	[57]
Usually no family history	10% with a family history	[13]

was found that overexpression of the isoform CD44v6 correlated with this amplification in diffuse type cancer and that this overexpression occurred more commonly in EOGC regardless of histological type[57].

The gene *RUNX3* has been a subject of great debate in gastric cancer studies in recent years, following a study where loss of the gene was shown to be associated with stimulated proliferation and suppressed apoptosis of gastric epithelial cells[58]. Conflicting evidence has, however, also been present, as the expression of RUNX3 in the gastric mucosa of mice differed significantly between strains analysed[59]. Furthermore, the gastric hyperplasia observed in the *Runx3*$^{-/-}$ mice used in Li's study was not observed in the mouse strain studied by Levanon *et al*[60]. Recent literature regarding *RUNX3* has excluded it as having a tumour suppressor function in EOGC[61], although as some of the cell lines used in this study were from conventional gastric cancers, the implications may be more far-reaching and call the importance of *RUNX3* in all gastric cancers into question.

Classic genetics alone cannot explain sporadic EOGC and cancer development in patients with a weak family history. The concept of epigenetics offers a partial explanation and may have important clinical implications for these types of cancer. The best-known epigenetic marker is DNA methylation, which occurs in CpG sites (islands), has critical roles in the control of gene activity, and is influenced by the modifications in histone structure that are commonly disrupted in cancer cells. Gene promoter methylation, a phenomenon that increases with age and may account for the increase in cancer in older age groups, has also been found to occur in EOGC[47]. However, comparison with the conventional group has not yet been carried out.

As supported by the literature, summarised in Table 2, EOGCs differ from conventional gastric cancers, not only at a clinicopathological level, but also at a molecular genetic level. If this is indeed due to the fact that the environment plays a smaller role in triggering the carcinogenic pathway, the investigation of this group of cancers may reveal genetic changes that assist in the task of putting forward a multistep pathway for gastric cancer.

FUTURE PROSPECTIVES

Gastric carcinoma continues to be a cause of premature death, despite progress in detection and treatment and despite advances in our understanding of the molecular basis of cancer. The need to develop efficient and effective cancer-specific drugs is coupled with the importance of accurate prediction of disease outcome for various patient groups, some of whom, due to the biology of their disease, will do better than others and may warrant a different treatment protocol. However, the multi-step pathway of carcinogenesis that occurs in some epithelial cancers and that has allowed accurate clinical and pathologic characterization is not yet elucidated in gastric cancer. Gastric cancers often occur without any consistent mutational abnormality and with considerable variation in pathogenesis ranging from a stepwise progression of changes to tumours arising in the absence of a precursor lesion. As has been highlighted in this article, there is growing evidence to support the hypothesis that young patients develop carcinomas with a different molecular genetic profile from that of sporadic carcinomas occurring at a later age. Further study of hereditary gastric cancers and EOGC as unique subsets of gastric cancer may aid us in the search for a gastric cancer pathway.

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