



Molecular alterations in gastric cancer with special reference to the early-onset subtype

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Abstract

Currently, gastric cancer (GC) is one of the most frequently diagnosed neoplasms, with a global burden of 723000 deaths in 2012. It is the third leading cause of cancer-related death worldwide. There are numerous possible factors that stimulate the pro-carcinogenic activity of important genes. These factors include genetic susceptibility expressed in a single-nucleotide polymorphism, various acquired mutations (chromosomal instability, microsatellite instability, somatic gene mutations, epigenetic alterations) and environmental circumstances (*e.g.*, *Helicobacter pylori* infection, EBV infection, diet, and smoking). Most of the aforementioned pathways overlap, and authors agree that a clear-cut pathway for GC may not exist. Thus, the categorization of carcinogenic events is complicated. Lately, it has been claimed that research on early-onset gastric carcinoma (EOGC) and hereditary GC may contribute towards unravelling some part of the mystery of the GC molecular pattern because young patients are less exposed to environmental carcinogens and because carcinogenesis in this setting may be more dependent on genetic factors. The comparison of various aspects that differ and coexist in EOGCs and conventional GCs might enable scientists to: distinguish which features in the pathway of gastric carcinogenesis

are modifiable, discover specific GC markers and identify a specific target. This review provides a summary of the data published thus far concerning the molecular characteristics of GC and highlights the outstanding features of EOGC.

Key words: Gastric cancer; Early-onset gastric cancer; Molecular alterations; Chromosomal instability; Single-nucleotide polymorphism; Microsatellite instability; Epigenetic alterations; Loss of heterozygosity

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Core tip: There are numerous factors that may trigger gastric carcinogenesis. They include genetic susceptibility, acquired mutations and favourable environmental circumstances, which combine and multiply within the lifetime. Therefore, the incidence of gastric cancer is the highest among the elderly. Conversely, young patients are exposed to environmental carcinogens for a short period, so they are a reliable subgroup in which to study primary genetic alterations. This review provides a summary of the data published thus far concerning the molecular characteristics of gastric cancer and highlights the outstanding features of early-onset gastric cancer.

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INTRODUCTION

Currently, gastric cancer (GC) is one of the most frequently diagnosed neoplasms worldwide.

Its incidence rate in 2012 reached approximately 140000 new cases in Europe and approximately 952000 worldwide. In Europe, GC is responsible for approximately 107000 deaths annually, placing it as the fourth most common cause of cancer-related death. Globally, GC caused 723000 deaths in 2012, making it the third leading cause of cancer-related death worldwide^[1,2]. Fortunately, the global incidence of GC has been decreasing since the Second World War^[3].

The most common classification used, the Lauren classification, differentiates between intestinal and diffuse types of GCs^[4]. These two types of GCs vary not only in morphology but also in epidemiology, progression pattern, genetics and clinical picture. Recently, it has been suggested that tumour location also matters because there appears to be a difference between proximal and distal non-diffuse GCs due to their distinct gene expression levels^[5,6].

Despite the scientific tendency to consider the intestinal and diffuse GC types as separate entities, clinically, all of them are treated similarly. For the time being, slow but satisfactory effects^[7-9] have resulted in decreasing the overall incidence of GC. However, there are supporters of the theory that more individualized treatment would be more beneficial^[5].

Alternatively, GCs can be divided into early-onset gastric carcinoma (EOGC)-occurring in patients at the age of 45 years or younger^[10]-and conventional GCs, which liberally encompass the remaining group of patients. Sometimes, there are also special subgroups that are distinguished: patients with hereditary diffuse GC and patients with gastric stump cancer; however, these two types can overlap with both EOGC and conventional gastric cancer^[11] (Figure 1).

There are many possible alterations that eventually stimulate the pro-carcinogenic activity of genes. Most of these pathways overlap, and authors agree that a clear-cut pattern of mutations in GCs does not exist^[10]; thus, the categorization of carcinogenic events is highly complicated. The current scientific challenge is to recognize which alterations of GC are crucial, what are the relationships between these alterations and how to prevent their incidence.

Recently, it has been claimed that research on EOGC and hereditary GCs may contribute towards unravelling some part of the mystery of the GC molecular pattern because younger patients are less exposed to environmental carcinogens, and their neoplasms rely more on genetic and molecular factors^[10].

The comparison of various aspects that differ and coexist in EOGCs and conventional GCs might enable scientists to distinguish which features in the pathway of the gastric carcinogenesis are modifiable, discover specific GC markers and identify a target for specifically directed treatment.

This review summarizes the data published thus far regarding the molecular characteristics of GC and highlights the outstanding features of EOGC.

EOGC

EOGC, as mentioned earlier, may pave the way for elucidating the primary alterations that initiate the gastric malignant process. The occurrence of gastric cancer in young patients could be explained in at least a few ways. Younger patients are exposed to the same environmental factors as the rest of the population; however because of some unknown reasons, they are more prone to develop gastric tumours at an earlier age. First, their molecular susceptibility to gastric carcinogenesis is to blame^[12], probably with a hereditary component^[13]. There are reports that an early diagnosis is associated with a higher GC risk for other family members^[14] and that a paternal history of GC correlates with an earlier diagnosis than in the general population^[15]. The limitations of the hypothesis

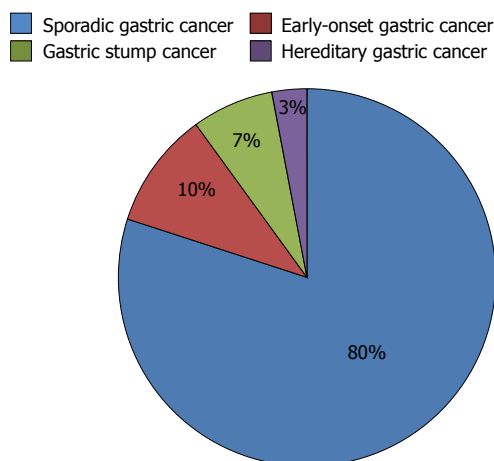


Figure 1 Types of gastric cancers.

concerning the EOGC hereditary background are environmental risk factors shared by members of one family^[16].

From another point of view, the early occurrence of GC may not be a fault of the host but of a specific tumour that is very aggressive, skips the consecutive steps of traditional neoplastic development and does not stay latent for years but, instead, progresses rapidly after the first alterations. The latter hypothesis would be supported by a poorer prognosis in younger patients^[17]. However, others have claimed that prognosis, similar to that in older patients, depends on an early diagnosis and curative resection^[18,19].

Nevertheless, Kwak *et al.*^[15] suggested that there is a third, pragmatic reason for the diagnosis of EOGC likely concerning patients with a family history of GC. These patients undergo screening earlier, or, unlike the general population (screening standards depend on the country). Consequently, their tumours are recognized at an early stage; however, under common circumstances, these tumours would be found later, at an older age, when the cancer has caused symptoms.

HEREDITARY GASTRIC CANCER

In approximately 30%-40% of cases of hereditary diffuse gastric cancer (HDGC), an E-cadherin (*CDH1*) germline mutation is detectable^[20]. *CDH1* is the gene that encodes E-cadherin, the protein that is essential in cell-cell adhesion^[21]. A high percentage (approximately 80%) of *CDH1* mutation carriers generate premature termination codons, which induce nonsense-mediated decay (NMD), resulting in impaired transcript loss. This predisposition can then be the cause of the early onset of GC in *CDH1*-mutation carriers^[22]. It has been proven that heterozygous germline mutations of *CDH1* causes an autosomal dominant condition that is associated with HDGC^[23-25]. The mutation may be caused by several mechanisms, including deletion, frameshift mutation, missense mutation and splice-site mutation. Moreover, the mutation in HDGC may affect any part

of the *CDH1* gene length^[26], including the untranslated regions^[24], which distinguish HDGC from sporadic diffuse GC where mutations are observed in exons 7-9 of the E-cadherin gene^[26].

It has been observed that the penetration of mutations is high, between 70%-80%^[27]. The remaining allele is deactivated by mutation and loss of function by various mechanisms. The most frequent method is methylation^[28-31]. However, as long as the remaining allele works properly, the gastric mucosa remains normal. Arguably, the second hit could occur simultaneously in multiple cells in cooperation with micro-environmental cofactors^[32,33], possibly explaining the multifocal growth pattern of the tumour^[34].

The loss of E-cadherin function together with overexpression of epidermal growth factor receptor (EGFR) is the most common alteration in diffuse-type GC. Mutant E-cadherin binds EGFR poorly, or the bound complex is less stable. This may enhance EGFR surface motility and facilitate its activation^[35].

Two-thirds of the families susceptible to HGC lack the *CDH1* mutation, and their predisposition remains genetically unexplained. It is likely caused by alterations in other genes. Oliviera *et al.*^[36] suggested that there may be a need to screen these families for a *TP53* mutation. Majewski *et al.*^[37] identified a mutation in the *CTNNA1* gene encoding the α -E-catenin protein, which functions in the same complex as E-cadherin. However, this alternative mutation has not reoccurred in other studies, likely because of the founder effect or other unrecognized factors, such as geographical influences^[38].

The role of *CDH1* mutation needs further investigation. It was reported that the absence of E-cadherin in a transgenic mouse model did not cause gastric malignancy. The authors suggested that the loss of E-cadherin induces possible pre-cancerous lesions in the gastric mucosa but may not be sufficient for its malignant conversion^[39]. It is possible that environmental influences modify the disease risk in susceptible individuals^[33].

Another example of HGC occurs in Lynch syndrome (hereditary nonpolyposis colon cancer, HNPCC). The essence of this disease is a mutation within mismatch repair genes (*MSH2*, *MSH6*, *PMS2* or *MLH1*), leading to an increased mutation rate in oncogenes and tumour suppressor genes and the development of a neoplasm. Frequent extracolonic locations of tumours in HNPCC are the stomach and uterus^[40]. According to some reports, HNPCC increases the lifetime risk of gastric cancer up to 7%^[41].

Other rarely occurring mutations connected with HGC are: *TP53* mutation in Li-Fraumeni syndrome^[42,43], *STK11* mutation in Peutz-Jeghers syndrome^[44,45], *APC* mutation in familial adenomatous polyposis^[46,47] and *BRCA2* mutation^[48].

SPORADIC GASTRIC CANCER

The cause of GC is multifactorial and includes: (1)

genetic susceptibility expressed in a single-nucleotide polymorphism (SNP); (2) various acquired mutations [e.g. chromosomal instability (CIN), microsatellite instability (MSI), somatic gene mutations, epigenetic alterations] that are heterogeneous intra- and interpatient^[38]; and (3) favourable environmental circumstances [e.g., diet, *Helicobacter pylori* (*H. pylori*) infection, EBV infection, and smoking]^[49,50].

Nishimura^[51] assessed the number of genomic alterations that can start malignant gastric processes to be 4.18, based on the frequencies of the major genome alterations, which represent the expected value of the occurrence.

Genetic susceptibility

Single-nucleotide polymorphism: One in 100-300 nucleotides in the human genome varies. These widely known polymorphisms, known as SNPs, are responsible for 90% of genetic variability^[52]. Genetic resemblance suggests ethnic kinship. Some variations, together with environmental triggers, make the carrier more prone to develop a range of diseases, including GC. Moreover, the coexistence of some SNPs even accumulates the risk of GC^[50,53]. This is a reasonable explanation of the high incidence of GC in the Japanese population, which, unlike the European population, has a low incidence of *H. pylori* colonization. However, > 60% of the Japanese population carry at least one high-risk GC-associated SNP^[54].

The candidate SNPs in GC concern genes involved in: (1) the inflammatory response [interleukin (IL)-1^[55-60], IL-17^[61-64], tumor necrosis factor (TNF) α ^[65,66], toll-like receptors (TLRs)^[67,68]]; (2) protection against invading pathogens (MUC1)^[69,70]; (3) cell-to-cell adhesion (*CDH1*)^[71-73]; (4) the repair of DNA damage related to *H. pylori* (*XPA*, *XPC*, *ERCC2*)^[32,74-76]; (5) the metabolism of foliate (methylene tetrahydrofolate reductase)^[77,78]; (6) the metabolism of polycyclic aromatic hydrocarbons (*GSTT1*, *SULT1A1*, *NAT2*, *EPHX1*)^[79,80]; (7) the metabolism of oestrogen and androgen^[81]; (8) the metabolism of xenobiotics (Cyp2e1)^[82]; and (9) other functions that are not fully understood, for example *PSCA*^[83].

It has been reported that *IL-1 β -31**C, *IL-1 β -511**T and *IL-1RN**2/*2 are variations of the *IL-1* gene cluster that have the greatest importance in GC susceptibility in various ethnic populations^[55,56], particularly among the Caucasian population^[57-60]. However, there are also studies that undermine the role of these variations in GC development^[84-86] and pertain to Irish^[87], Swedish^[88], German^[89] and Japanese populations^[90]. On the other hand, Sitarz *et al*^[91] showed that the *IL-1 β -31**C allele promoter polymorphism is significantly associated with gastric stump cancer, whereas it does not influence the occurrence of any type of sporadic GC. The authors emphasize that the differences between the studies may be due to many factors, such as heterogeneous patient groups, different populations, sample sizes,

different clinical characteristics, controls drawn from high-risk areas for chronic gastritis, confounding factors from other environmental cofactors, interactions with other genes regulating inflammatory responses and others^[87]. Therefore, the issue needs further investigation and a wider comparable analysis.

The *IL-17* 187G>A polymorphism is associated with a higher risk of developing GC based on *H. pylori* colonization^[61-64].

Gorouhi *et al*^[65] reported that the *TNF α -308AA* genotype was associated with a statistically significant increased risk of GC, whereas *TNF α -857TT* raised attention and required more studies. These results were supported by the parallel meta-analysis of Zhang *et al*^[66] and seemed to concern the Caucasian population in particular.

TLR polymorphisms are linked to gastrointestinal malignancies^[67]. *TLR4* may increase the risk of non-cardia cancer^[68].

Mucins are a family of proteins that maintain the integrity of the mucus layer and protect it from environmental invaders. Due to their vast role in regulating cell homeostasis and their role in several cancers, they have been categorized as oncoproteins^[92-95]. The *rs4072037*(G>A) polymorphism plays a role in increasing the risk of gastric malignancy. The G allele version seems to be protective, it causes MUC1 under-expression^[70], resulting in better conditions for *H. pylori* to invade and cause extensive inflammation. However, it seems that alterations of MUC regions do not cause clinical progression in patients with a premalignant phenotype^[96].

Autosomal-dominant mutations of *CDH1* are the cause of HDGC. However, it seems that the *CDH1* polymorphism is also significant in sporadic GC. It has been reported that the promoter polymorphism at position -160 C/A of *CDH1* importantly increases the risk of GC in Europeans, whereas Asians seem to be tolerant to this polymorphism^[71]. Jenab *et al*^[72] showed that three *CDH1* polymorphisms within the *CDH1-160C/A* haplotype block the increased risk of GC in smokers but not in never-smokers.

Other SNPs concern those of methylenetetrahydrofolate reductase, which has demonstrated 281 polymorphic variants. *MTHFR* 677C>T and *MTHFR* 1298A>C were shown to be associated with GCs in East Asians^[77,78]. Another SNP, *CYP2E1**2 (C2), was reported to enhance the GC risk in the Asian population^[82].

Similarly, a polymorphism in exon 1 of *PSCA* was shown to increase the risk of diffuse GC and to distinguish it from the intestinal subtype^[83,97-101]. It is likely that *PSCA* protein regulates gastric epithelial cell proliferation; therefore, the down-regulation of *PSCA* may lead to pathological cell division. The SNPs concern the alleles *rs2976392* and *rs2294008*^[83]. However, other studies have reported conflicting data, hindering the interpretation. The issue remains open to further research.

Various acquired mutations

Chromosomal instability: The term chromosomal instability comprises altered DNA copy number (aneuploidy) and various changes in chromosome regions, such as translocation, amplification, deletion or the loss of one allele in a pair [loss of heterozygosity (LOH)]^[102,103]. Altogether, CIN results in the loss or gain of function of some genes, including oncogenes and tumour suppressor genes.

CIN is an inherent part of carcinogenesis that occurs at each stage of the oncologic diseases^[103]. It is not permanent, differs within geographical regions^[104] and increases with disease progression^[102,105]. Therefore, recognizing frequent CIN patterns in GC can result in improving early diagnosis, staging and treatment.

It was reported that intestinal GC correlates with the gain of copy number at 8q, 17q and 20q^[105-109] and with amplification and overexpression of EGF and c-ErbB2, which are the molecules involved in self-sufficient growth^[110,111]. Diffuse GC is characterized by a gain of copy number at 12q and 13q^[105-109] and with amplification of FGFR^[112,113]. Both subtypes display overexpression of HGF and c-myc^[112,114,115] and amplification of the HER2 gene (*ERBB2*). The latter feature is of particular clinical interest because HER2 can be therapeutically blocked by monoclonal antibodies^[116,117]. GC patients treated with a humanized antibody against HER2 (trastuzumab) benefit with a 2.5-mo longer survival than the group treated with standard chemotherapy^[118]. However, thereafter, the disease progresses, and resistance develops, raising doubt about the usefulness of this agent^[50].

Other changes that promote uncontrolled cell growth are inversions causing the generation of the *SLC1A2-CD44* fusion protein^[119] and the *ROS1* gene rearrangement. However, the latter alteration rarely occurs in GCs (< 1%) and differentiates the subgroup of patients who hypothetically may be treated with kinase inhibitors^[119,120].

LOH is a common event in GC. The frequently occurring LOH in the genes *APC*, *TP53* and *NME1* play a possible role in evaluation of a patient's clinical status^[121,122]. Gains at chromosomes 17q, 19q and 20q are distinctive for GCs in young patients^[10,123].

Microsatellite instability: MSI is defined as the presence of small deletions or expansions in a tumour's DNA within short tandem repeats (microsatellite regions) and do not match normal DNA.

MSI is not only present in HNPCC but occurs in up to every second sporadic GC^[50,124]. In GCs, MSI is mostly caused by the epigenetic alterations in the mismatch repair genes (MMRs)^[125,126]. Consequently, the impaired mismatch repair system fails to fulfil its task, resulting in multiple mutations within cell growth-regulating genes (*TGF-βRII*, *IGFIIR*, *RIZ*, *TCF4*, *DP2*), apoptosis genes (*BAX*, *BCL10*, *FAS*, *CASPASE5*, *APAF1*) and DNA repair genes (*hMSH6*, *hMSH3*,

MED1, *RAD50*, *BLM*, *ATR*, *MRE11*)^[125,127-130]. However, the inactivation of mismatch repair genes, by itself, is thought to be insufficient to induce carcinogenesis but might be a coexistent factor^[126].

The high incidence of microsatellite instability in GCs (MSI-H GC) is more likely to occur at an antral location, in the intestinal type, in the expanding type, and with *H. pylori* seropositivity, and correlates with a lower prevalence of lymph-node metastases^[131-133]. Moreover, MSI correlates with a lower incidence of *TP53* mutations^[133] and is characterized by a better survival rate than with tumours with low levels of MSI^[134,135]. It is possible that high levels of MSI indirectly cause nonspecific immunological reactions in the hosts, resulting in tumour cell elimination^[136].

MSI seems to be a promising tool to identify patients with genetic instability and patients with precancerous lesions because it occurs in both gastric adenoma and intestinal metaplasia^[126].

Epigenetic alterations: Epigenetic alterations are responsible for the diversity in the expression of a gene and are not caused by changes in DNA sequences but by modifications outside DNA, such as DNA CpG island hypermethylation [CpG island methylator phenotype, (CIMP)], hypomethylation, histone modification, chromatin remodelling or miRNA changes. The literature dedicated to GC highlights the role of CpG island methylation and miRNA.

In GCs, CpG island methylation involves primarily the promoters of the *CDH1*, *CDKN2A*, *CDKN2B* and *hMLH1* genes and results in the down-expression of their products (E-cadherin, p16, p15, MLH1)^[137,138]. CpG island methylation seems to frequently occur in GC cells, regardless of their stem cell origin and independent of one another. Possibly, CpG island methylation carries the carcinogenic process a step further. This hypothesis would be consistent with the observation that promoter hypermethylation is accelerated with histopathological progression of malignancy, from chronic gastritis, intestinal metaplasia and adenoma to carcinoma^[138-140].

miRNAs are short stable RNA segments that, despite noncoding characteristics, play a vast role in the regulation of gene expression. They attain this goal by binding to DNA or by inhibiting or degrading mRNA that is ready for translation. Altogether, they regulate approximately 60% of the coding genes; therefore, their role in GC seems to be significant^[141].

miRNAs can act as oncogenes (oncomiRNAs), tumour suppressors (tsmiRNAs) or cellular pathway modulators, such as metastasis regulators (metastamiRNAs). Research over the last decade has identified numerous miRNAs that have varied roles in GC development.

Questions for the future include the following: are miRNA alterations necessary for tumour progression, can they be used as diagnostic and/or prognostic markers^[141-145], can they be targeted pharmacologically^[146]

and can they influence the individual response to chemotherapy^{[147-149]?}

Somatic gene mutations: In recent research^[150], which is a part of The Cancer Genome Atlas Project, the authors suggested that both the rate of somatic mutations and their singularity should not be disregarded in the GC classification. In fact, they provided a roadmap for patient stratification and trials of targeted therapies. The authors of the study identified many mutations that are repeated in each subtype of GC but with different frequencies. Examples of the most common mutations occur in the genes *TP53*, *CDH1*, *SMAD4*, *PIK3CA*, *RHOA*, *ARID1A*, *KRAS*, *MUC3*, *APC*, *ERBB1*, *PTEN*, *HLAB*, and *B2M*.

Some of these alterations were investigated separately in earlier studies. Zang *et al.*^[151] reported that somatic inactivation of *FAT4* and *ARID1A* may be the key to malignant events in GCs. Wang *et al.*^[152] suggested that *ARID1A* seems to be a good prognostic indicator because its alterations were clinically associated with better prognosis in a stage-independent manner. Other studies^[153] proved that *RHOA* mutations occur specifically in diffuse GCs, so they are a potential therapeutic target for this poor-prognosis subtype of GC.

Favourable environmental circumstances

EBV is an infectious agent that occurs in epithelial cells of 9% of GCs^[154]. However, the distribution of EBV-positive GCs varies globally^[3]. EBV-positive tumours are associated with an extreme CIMP^[150,155], and differ from the MSI subtype^[156]. In Bass *et al.*^[150], all EBV-positive tumours lacked *MLH1* alterations, characteristic of MSI^[157]; however, they displayed promoter hypermethylation within the *CDKN2A* (p16^{INK4A}) region, and most of them had mutations in diverse locations within the *PIK3C1* gene, confirming previous reports^[158,159]. This particular feature separates EBV-positive tumours from other GCs that display *PIK3C1* mutations in 3%-42% but are localized in the kinase domain, exon 20^[150].

Gastritis is the single most common cause of GC, and *H. pylori*, a class I carcinogen according to WHO classification^[160], is the most common cause of gastritis^[161,162]. Therefore, *H. pylori* plays a role in the environmental trigger that creates a favourable background for GC through several mechanisms. One of them is depleting the mucosa's antioxidant competences^[163], as shown in mouse models^[164]. *H. pylori* was also reported to initiate the down-regulation of sonic hedgehog (Shh) expression, paving the way for early premalignant changes^[165]. Shh is a protein that plays a role in cellular differentiation in gastric mucosa. Under expression of Shh promotes an intestinal phenotype by the upregulation of *Cdx2*, *MUC2* and *villin*, which are intestine-related

genes^[32,166]. It seems that the levels of Shh expression fluctuate during the beginning of metaplasia to advanced cancer, and it is associated with tumour stage^[167].

Moreover, *H. pylori* can promote intestinal transformation by the interaction of CagA (bacterial virulence factor) with E-cadherin^[168]. It was also reported that decreased levels of E-cadherin may occur in relation to *H. pylori* infection^[169].

According to the currently accepted hypothesis, GC develops from cancer stem cells (CSCs)^[32]. However, under chronic inflammation, this role might be carried out by bone marrow-derived cells (BMDCs)^[170-172].

Chronic inflammation alters the secretion of gastrin in gastric mucosa. Hypergastrinaemia and hypo-gastrinaemia are both suspected of being involved in the development of GC^[168,173,174].

A proper inflammatory response is highly dependent on the condition of the immune system, which is also involved in GC. For example, it was reported that the *CTLA-4* polymorphism attenuates the T-cell response and increases the risk of gastric cardia cancer^[175]. The accumulation of regulatory T cells (Tregs), which are associated with CCL17 and CCL22 chemokines^[176], reflects the clinical status because it correlates with regional lymph node metastasis and patient survival^[177].

The role of elevated eosinophil levels remains uncertain. In low-risk areas, eosinophils are recruited by Th2 lymphocytes and act to prevent GC; however, in high-risk areas, they are attracted by Th1 lymphocytes and favour the spread of the lesions^[178].

COX-2 overexpression is known to be an important mechanism in GC development. It occurs commonly, but remains uncertain why. Suggested mediators include the C/EBP- β transcription factor^[115,179,180] and Wnt/ β -catenin signalling pathway^[181]. *COX-2* overexpression particularly concerns adenocarcinomas^[182], appears at early stage of carcinogenesis and is detected even in precursor lesions^[115,183,184]. Silencing *COX-2* by promoter hypermethylation or FOXP3^[185] seems to protect against GC progression because it is correlated with longer remission and improved survival^[186]. Therefore, *COX-2* could be used as a prognostic indicator^[187,188].

The *COX-2* genotype also matters because the *1195AA COX-2* genotype was reported to increase the risk of GC more than twice, and, with coexistent *H. pylori* infection or smoking, even enhances malignant progression^[189].

Non-steroidal anti-inflammatory drugs may disrupt the pathway of carcinogenesis dependent on *COX-2* related processes. Their long-term use turns out to show a reduced risk of GC^[190-192]. This group of drugs might be used in lymph node metastasis prophylaxis^[193]. However, Sitarz *et al.*^[194] found that a reduction of *COX-2* using nonsteroidal anti-inflammatory drugs in GC chemoprevention may be relevant only for older patients.

Table 1 Sporadic gastric cancer factors

Factors ¹	Sporadic gastric cancer	Ref.	
SNP	<i>IL-1, IL-17, TNFα, TLRs</i> (inflammatory response)	[55-68]	
	<i>MUC1</i> (protection against invaders)	[69,70]	
	<i>CDH1</i> (cell-to-cell adhesion)	[71-73]	
	<i>XPA, XPC, ERCC2</i> (repair of DNA damage related to <i>H. pylori</i> infection)	[32,74-76]	
	<i>MTHFR</i> (metabolism of foliate)	[77,78]	
	<i>GSTT1, SULT1A1, NAT2, EPHX1</i> (metabolism of polycyclic aromatic hydrocarbons)	[79,80]	
	<i>Cyp2e1</i> (metabolism of xenobiotics)	[82]	
	<i>PSCA</i>	[83]	
	CIN	gain of copy number at 8q, 17q, 12q, 13q and 20q	[105-109]
		amplification of EGF and c-ErbB2	[110,111]
amplification of FGFR		[112,113]	
amplification of <i>ERBB2</i>		[116,117]	
overexpression of HGF and c-myc		[112,114,115]	
<i>SLC1A2-CD44</i> fusion		[119]	
LOH	<i>ROS1</i> rearrangement	[120]	
	<i>APC, TP53, NME1</i>	[121,122]	
MSI	<i>TGFβRII, IGF1R, RIZ, TCF4, DP2</i> (cell growth-regulating genes)	[125,127-136]	
	<i>BAX, BCL10, FAS, CASPASE5, APAF1</i> (apoptosis genes)		
Somatic gene mutations	<i>hMSH6, hMSH3, MED1, RAD50, BLM, ATR, MRE11</i> (DNA repair genes)		
	<i>TP53, CDH1, SMAD4, PIK3CA, RHOA, ARID1A, KRAS, MUC3, APC, ERBB1, PTEN, HLAB, B2M, FAT4</i>	[150-153]	
Epigenetic alterations	CpG island methylation of the promoters of <i>CDH1, CDKN2A, CDKN2B</i> and <i>hMLH1</i>	[137,138]	
	miRNA variations	[141]	
Environment	Diet	[200]	
	<i>H. pylori</i> infection	[163,165,168]	
	EBV infection	[150,154-156]	
	Hyper/hypogastrinaemia	[168,173,174]	
Others	Smoking	[200]	
	<i>COX-2</i> overexpression	[182-189]	

¹All of the above factors may overlap. The division is the simple generalization done to outline the problem. SNP: Single-nucleotide polymorphism; CIN: Chromosomal instability; LOH: Loss of heterozygosity; MSI: Microsatellite instability; *H. pylori*: *Helicobacter pylori*.

EARLY-ONSET GASTRIC CARCINOMA'S DISTINCTIVE FEATURES

To consider EOGC as an independent oncologic problem, scientists must precisely differentiate it from sporadic GC. In 2007, Milne *et al.*^[10] summarized the distinctive features of EOGCs, compared with conventional GCs, as including female predominance, common multifocal growth and a diffuse phenotype without intestinal metaplasia. The molecular profile included the lack of MSI, infrequent loss of heterozygosity, infrequent loss of TFF1 expression, no loss of RUNX3, gains at chromosomes 17q, 19q and 20q and more frequent expression of low-molecular-weight isoforms of cyclin E.

Newer characteristics of EOGCs have been identified in recent reports. Clinical studies include the observation of Karim^[195] that male predominance occurs among EOGC patients but decreases with age. Takatsu *et al.*^[196] reported a tendency to present lymph node metastases, a finding that was indirectly supported by studies of *CDH1* variants^[197]. Molecular alterations also include a new marker that is a genetic variant of *rs10052016* at 5p15^[198]. Moreover, Bacani *et al.*^[124] showed that MSI, in at least one marker, was found in 30% of EOGCs. They assessed that approximately

1% of EOGC is caused by germline MMR mutations. Carvalho *et al.*^[199] excluded *RUNX3* as having a tumour suppressor function in EOGC, but other authors were less convinced that this is the case^[10]. Sugimoto *et al.*^[200] was the first to describe that a de novo large genomic deletion of *CDH1* was associated with EOGC.

CONCLUSION

GC is a heterogenic and complex problem (Tables 1-3). The number of factors that influence its beginning and course is already overwhelming, and, in the light of modern technological possibilities, that number could increase exponentially. Moreover, various molecular alterations seem to overlap^[126,201,202], additionally complicating the problem. However, it seems to be reasonable to consider that there are some early triggers that impair genome stability and predispose to a further avalanche of carcinogenic events^[137].

In our research, we focused on the early steps of GC development. Therefore, we favour the classification of GC that differentiates EOGC. Patients with this type of tumour are automatically deprived of many risk factors and molecular changes that appear with the passage of a patient's and tumour's life. Therefore, young patients present a relatively pure model of

Table 2 Early-onset gastric cancer features

Factors	Early-onset gastric cancer	Ref.
SNP	<i>rs10052016</i> at 5p15	[198]
CIN	Gain of copy number at 17q, 19q, and 20q No loss of RUNX3 Infrequent loss of TFF1 expression More frequent expression of low-molecular-weight isoforms of cyclin E	[10]
LOH	Infrequent LOH	[10]
MSI	Lack of MSI <i>vs</i> 30% incidence	[10] [124]
Others	Low COX-2 expression Male predominance Tendency to metastases	[10] [195] [196]

SNP: Single-nucleotide polymorphism; CIN: Chromosomal instability; LOH: Loss of heterozygosity; MSI: Microsatellite instability.

Table 3 Hereditary gastric cancer factors

Factors	Hereditary gastric cancer	Ref.
Germline mutations	<i>CDH1</i> <i>TP53</i> (Li-Fraumeni syndrome) <i>CTNNA1</i> <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>MLH1</i> (Lynch syndrome) <i>APC</i> (Familial adenomatous polyposis) <i>STK11</i> (Peutz-Jeghers syndrome) <i>BRCA2</i>	[23-34] [36,42,43] [37] [40,41] [46,47] [44,45] [48]

gastric carcinogenesis.

From the review of the latest literature, we conclude that defining characteristic factors of early-onset GC is in progress, and the issue needs further clarification.

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