

GENETIC SUSCEPTIBILITY IN GASTRIC CANCER

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Abstract: There are many evidences suggesting that genetic predisposition plays an important part in gastric cancer genesis. About 10% of gastric neoplasms express family aggregation, and a family history of gastric cancer increases the risk to develop it by 2-3 times. Familial aggregation of gastric cancers comprises two main categories: hereditary tumours with genetic etiology and tumours induced by family exposure to the same risk factors. Recently, familial gastric cancer syndromes have been described.

Gastric cancer affects nearly 1 million individuals every year (1), making it the third most lethal cancer worldwide (nearly 800 000 deaths per year.). This high mortality - 70–85% of the patients die within 5 years of diagnosis (2) - associated with gastric cancer is mainly a result of late diagnosis and limited therapeutic options.

Although the downward trend in the incidence of gastric cancer in recent decades can be explained by changes in lifestyle, eating habits and decrease of *Helicobacter pylori* infection, the fact that some individuals develop this neoplasia and others do not, although they are exposed to the same environment conditions, suggest that genetic predisposition plays an important part in the genesis of this disease.

Moreover, the role of genetic factors in the etiology of gastric cancer is stressed by the existence of families with gastric cancer aggregation, a higher incidence among relatives of those diagnosed with gastric cancer and in homozygous twins compared to dizygotic twins, and the relatively constant incidence in younger patients despite the sharp decline of gastric cancer worldwide.

About 10% of gastric neoplasms express family aggregation (3,4), regardless the histologic type (5); a family history of gastric cancer increases the risk to develop it by 2-3 times.(6,7) This risk persists even after adjustment for other etiological agents (dietary factors, *Helicobacter pylori*) and is higher if mother is the affected parent, if both parents are affected or if there are two or more relatives with gastric cancer.(8) Only a small proportion of gastric carcinomas (1-3%) matches the features of gastric cancer hereditary syndromes.(3,9)

A major study on gastric cancer heredity was conducted in Sweden and included 44 788 twins. If one of the brothers was diagnosed with gastric cancer, the risk of developing the same pathology was estimated at 6.6 for dizygotic twins and 10 for monozygotic twins. Inherited genes would have a 28% contribution to the risk, but the environmental factors exerted separate on twins would be the most consistent etiological component.(10)

Familial aggregation of gastric cancers comprises two main categories:

- hereditary tumours with genetic etiology;
- tumours induced by family exposure to the same risk factors.

In some cases with familial aggregation, a combination of increased genetic susceptibility and exposure to some environmental factors can lead to a higher incidence of gastric cancer among these families. There are genes with low penetrance that involve an increased individual susceptibility to gastric carcinoma, like gene which encodes interleukin-1, described by EL-Ohmar et al. (11) and confirmed by Machado et al. (12) in a number of cases of sporadic gastric cancer. Its presence increases the risk by 46% compared to general population. Another example is the gene encoding tumour necrosis factor (TNF- α); its mutations have been associated with susceptibility to the occurrence of gastric cancer. This has been demonstrated in patients with sporadic gastric cancer by identification a significantly polymorphism of this gene, correlated with the presence of *Helicobacter pylori*, subtype cagA.(13)

Furthermore, the presence of blood group A contributes to a 20% additional risk for the development of the gastric neoplasia, particularly the diffuse type.(14,15) In addition, gastric carcinoma is a well-known disease in some hereditary neoplastic syndromes, such as non-polyposis hereditary colorectal cancer, familial adenomatous polyposis, Cowden syndrome or Peutz – Jeghers syndrome.

Recently, familial gastric cancer syndromes – with consistent hereditary implication - have been described.

Guilford et al. have documented for the first time in 1998 a germline mutation of CDH1 gene (E-cadherin) in a Maori family in New Zealand.(16) Later, they demonstrated the presence of other similar mutations in two other families of the same ethnic origin. After that, other researchers have also reported germline mutations of CDH1 gene (Richards et al. in 1999, Dussaulx-Garin et al. in 2001, Humar et al. in 2002, Oliveira et al. in 2002) as a feature of a new disease: hereditary diffuse gastric cancer.(17)

It was this new syndrome of hereditary cancer the reason to organize a symposium in Vancouver (International Gastric Cancer Linkage Consortium - IGCLC) in 1999 (reissued in 2010), where a group of geneticists,

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gastroenterologists, surgeons, oncologists and molecular biologists have issued statements of consensus and guidelines for familial gastric cancer.

According to IGCLC, there are four types of familial gastric cancer:

1. Hereditary diffuse gastric cancer (HDGC);
2. Familial diffuse gastric cancer (FDGC);
3. Familial intestinal gastric cancer (FIGC);
4. Gastric cancer in other familial cancer syndromes.

1. *Hereditary diffuse gastric cancer (HDGC)* has been defined (18) as familial cancer due to germinal mutations that meets the following criteria:

- two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosis before age of 50 or;
- three or more cases of diffuse gastric cancer in first or second degree relatives, regardless the age of onset.

Hereditary diffuse gastric cancer is a poorly differentiated adenocarcinoma, infiltrating the stomach wall and causing its thickening (plastic linitis) without forming a distinct tumour mass. The average age of onset is 38 years, with a range from 14 to 69 years. The cumulative risk of gastric cancer by the age of 80 years is estimated at 80% for both men and women, also involving a risk of 39% for breast cancer.(19)

HDGC has an autosomal dominant pattern; the affected gene is passed from one parent and the risk of transmission to each offspring is of 50%. Until recently, E-cadherin (CDH1) was the only gene associated with HDGC, whose germline mutations were identified in 40% of cases.(2) Once inherited the mutation, the risk of developing gastric cancer is 2 000 times higher than the general population.(20) So far, 104 mutations have been identified.(2)

Two years ago, a new gene involved in the HDGC etiology was documented: CTNNA1 gene, whose germline mutations were revealed within one family diagnosed with this neoplasia.(21) Mutation penetrance is incomplete, similar to CDH1 penetrance in HDGC and the reduction in expression of E-cadherin is associated with complete loss of CTNNA1 expression.

Another gene that awaits the attention of researchers is MAP3K6. Last year, the authors of a study (22) identified 5 germline mutations of this gene in patients with hereditary diffuse gastric cancer.

2. *Familial diffuse gastric cancer (FDGC)* expresses familial aggregation, but it does not meet all criteria for HDGC. Particularly, it tends to locate near cardia showing more aggressiveness than sporadic gastric cancer.(23)

Recently, some authors (24) have attributed the term of “hereditary diffuse gastric cancer” to familial diffuse gastric cancer, yet contributing unduly to the emergence of some confusion regarding this pathology.

3. *Familial intestinal gastric cancer (FIGC)* was defined according to the incidence of gastric cancer in the population. Thus, in countries with high incidence (Japan, Portugal) the diagnostic is made using criteria similar to Amsterdam criteria used for Hereditary Non-Polyposis Colorectal Cancer: (1) at least three relatives with intestinal gastric cancer and one of them is first relative with other two; (2) at least two successive generations affected; (3) one of the diagnosis has been made before 50 years. In countries with a low incidence (USA, UK), FIGC was defined as: (1) at least two first or second relatives affected by intestinal gastric cancer, one of them being diagnosed before age 50;

(2) three or more relatives with intestinal gastric cancer, regardless the age of onset.

By histology, the tumours show the features of adenocarcinoma, intestinal-type. So far, there has been no germline mutation identified in family members with FIGC.(25)

4. *Gastric cancer in other familial cancer syndromes*

4.1. *Non-polyposis hereditary colorectal cancer (HNPCC)* is a familial cancer syndrome with high penetrance comprising about 5-10% of all colorectal cancer (CRC). Microsatellite instability is the classic molecular phenotype of this morbid condition caused by mutations in the mismatch repair gene systems: MLH1, MSH2, MSH6, PMS1, PMS2 or EPCAM.(26)

There are two distinct syndromes within HNPCC: type I Lynch syndrome, comprising patients at high risk of developing CRC and type II Lynch syndrome, comprising patients with additional high risk of extra-colonic cancers (stomach, ovary, endometrium).(27) Gastric cancer is the most common malignancy associated with HNPCC (with an incidence of 13-20% in these patients); the intestinal type has a higher frequency compared to diffuse type.(28)

Mutations of hMSH2 and hMLH1 genes are seen in more than half of cases. Abnormalities of these two genes are associated with complete inactivation of the MMR system (“mismatch repair”), while other mutations affecting hPMS1 and PMS2 genes show incomplete inactivation.(29) The risk of gastric cancer is 4-8% in patients with germline mutations in MLH1 gene and 9% in case of MSH2 alterations. Endoscopic surveillance is necessary in patients with Lynch syndrome and mutations in MMR gene system.(30)

4.2. *Familial Adenomatous Polyposis (FAP)* is an inherited condition due to a germline mutation of the APC (Adenomatous Polyposis Coli) gene. FAP is characterized by early onset of hundreds to thousands of adenomatous polyps throughout the colon. If left untreated, all patients with this syndrome will develop colon cancer by the age of 35-40. In addition, an increased risk exists for the development of other malignancies. About 8% of patients have an attenuated form of the disease characterized by the presence of a small number of polyps and late development of neoplasia.(31)

Polyps are also developed in the upper gastrointestinal tract. Fundic gland polyps are the most common gastric polyps in FAP (identified in 88% of patients) and they may turn into malignancy.(5) Despite the obvious genetic substrate, fears regarding a higher risk of cancer developing compared with sporadic polyps seem to be unjustified.(32)

Prophylactic colectomy in these patients is mandatory because of the 100% risk of neoplasia development. In patients who underwent this procedure, the main cause of death is represented by upper gastrointestinal cancers, thus these subjects require prophylactic endoscopic surveillance.(33)

4.3. *Peutz-Jeghers syndrome (PJS)* is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in association with a distinct pattern of skin and mucosal macular melanin deposition. Patients with Peutz-Jeghers syndrome have a higher risk of developing cancer, particularly gastrointestinal and breast cancer, compared with the general population, especially in younger ages.(34)

The cumulative risk of gastric cancer is of 29% up to age of 65 years old.(35) Some cases of gastric cancer

within PJS have been described in the literature associated with germline inactivation of STK11/LKB1 gene, which normally acts as a suppressor gene.(3)

4.4. *Cowden Syndrome* is an autosomal dominant abnormality with high penetrance, also known as multiple hamartomatous syndrome. It is associated with different types of cancers (stomach, breast, thyroid, mucous membranes).(36) This disease is due to a PTEN gene mutation in 10q23 locus, but it has been demonstrated (7) that not all gastrointestinal hamartomas express loss of heterozygosity at this specific location.

4.5. *Li-Fraumeni Syndrome* is a syndrome of familial cancers comprising various sarcomas, cancers of the breast and other carcinomas, including gastric cancer, characterized by childhood onset and, frequently, metachronous developing.(37) It was first mentioned in medical literature in 1969 when, reviewing medical records and death certificates of 648 patients with childhood onset rhabdomyosarcoma, Li and Fraumeni noticed the presence of various types of cancer in brothers and cousins of 4 patients. Over 70% of families with this syndrome show mutations in p53 gene.(38)

Another heterozygous germline mutation identified by Bell et al. in CHK2 gene is also associated with Li-Fraumeni syndrome, but it does not appear to be responsible for the occurrence of gastric cancer in these families.(39)

4.6. *Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)* is characterised by the autosomal dominant transmission of fundic gland polyposis (including dysplastic lesions or intestinal-type gastric adenocarcinoma, or both) of the stomach with no evidence of colorectal or duodenal polyposis or other known hereditary gastrointestinal cancer syndromes. Its penetrance is incomplete and the genetic cause has yet to be identified. Macroscopic features of GAPPS include florid gastric polyposis, mainly with gastric polyps with diameters of less than 10 mm. More than 100 polyps carpet the gastric body and fundus, with relative sparing along the lesser curve of the stomach. The earliest case reported so far occurred in someone aged 33 years in one of the families studied.(40)

In conclusion, we may say that the best scientific evidence on genetic factors associated with gastric cancer risk will be obtained from large cohort studies that take into account simultaneously different factors involved in gastric carcinogenesis: genetic factors, *Helicobacter pylori* and environmental exposure. Success in identification of environmental factors that can modify genetic inheritance will depend on studying the direct interaction between genes and environment.

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