Comparative investigation of early-onset gastric cancer (Review)

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Abstract. Early-onset gastric cancer (EOGC) is a serious social burden. For patients with EOGC, typically considered as those aged <45 years, the underlying cause of the disease remains unclear. In addition, several misunderstandings of EOGC remain in clinical practice. Upon diagnosis, numerous patients with EOGC are already at an advanced stage (stage IV) of the disease and are unable to benefit from treatment. Moreover, several conclusions and data obtained from different EOGC studies appear to be to contradictory. The literature indicates that the incidence of EOGC is gradually rising, and that EOGC differs from traditional and familial gastric cancer in terms of clinicopathological characteristics. Patients with EOGC typically exhibit low survival rates, poor prognosis, rapid disease progression, a low degree of differentiation (signet-ring cell tumors are common) and rapid lymph node and distant metastasis, among other characteristics. The molecular genetic mechanisms of EOGC are also significantly different from those of traditional gastric cancer. An improved definition of EOCG may provide a reference for clinical diagnosis and treatment, and clear guidelines may serve as a basis for more accurate diagnosis and the development of effective treatment strategies.

Contents

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Abbreviations: GC, gastric cancer; EOGC, early-onset GC; LOGC, late-onset GC; SEER, Surveillance, Epidemiology and End Results; BRFSS, Behavioral Risk Factor Surveillance Survey; DGC, diffusion-type GC; IGC, intestinal-type GC

Key words: early-onset gastric cancer, clinicopathological characteristics, hereditary gastric cancer, genes, mutation, traditional gastric cancer

1. Introduction

Based on the GLOBOCAN 2018 report published by the International Agency for Research on Cancer (1), the incidence and mortality rates of cancer in Western countries have significantly decreased over the past few decades, indicating that efforts to prevent and control cancer are slowly making progress. However, although the incidence of cancer in China has been relatively stable in recent years, it remains an issue of concern due to the relatively poor prognosis (1). China is the most densely populated country worldwide, with an estimated population of nearly 1.42 billion, with 4.51 million cancer cases and 3.04 million cancer mortalities expected by the end of 2020. Gastric cancer (GC) is the fifth most common type of cancer worldwide and the third leading cause of cancer-associated mortality. Although the incidence of GC has decreased over the past few decades in China, half of all worldwide cases of gastrointestinal tumors, including GC, liver cancer and esophageal cancer, in 2018 occurred in China, and the 5-year overall survival rate was <35% in China between 2013-2015 (1,2). This suggests that the management of these gastrointestinal tumors in China needs to improve significantly.

Traditional GC is most common among the middle-aged and elderly individuals, and the incidence of GC is highest in those aged 50-70 years (3). However, GC is also increasingly being diagnosed in younger patients. To date, there is no clear conceptual description of early-onset GC (EOGC), and its clinicopathological characteristics and etiology remain undefined. Health practitioners have hypothesized that EOGC is hereditary and is associated with genetic factors. The aim of the present review was to summarize the concept of EOGC based on previous studies of EOGC among younger patients, typically those aged <45 years, and to describe the recent clinical experience of patients with EOGC at the Department

of Surgical Oncology of Lanzhou University Second Hospital (Lanzhou, China).

2. Epidemiology

Diagnostic age range for EOGC. A literature search of previous studies to determine the age range considered definitive of EOGC indicated that an appropriate age at diagnosis was <50 years (4). Some studies have suggested an age of ≤40 years at diagnosis is the most appropriate for defining EOGC (5). However, in recent years, most studies have identified ≤45 years as the most appropriate age group for distinguishing EOGC from traditional GC (6), which is consistent with our clinical experience.

Incidence rate of EOGC. Medina-Franco *et al* (7) conducted a comparative study between young and elderly patients with GC in Mexico, and observed that the proportion of patients aged <40 years was 16.2% (7), and in subsequent studies this proportion increased to 30%, which is the highest proportion mentioned in the literature (8). Differences in the age range used to define EOGC may lead to significant differences in the incidence rate of EOGC reported among studies. Geographical location, as well as other factors including *Helicobacter pylori* (*H. pylori*) infection, genetic susceptibility and environmental factors, may also affect the incidence of EOGC (9). In 2011, it was reported that EOGC accounted for <10% of newly diagnosed cases of GC in the USA (10). Moreover, in the USA, the incidence of early EOGC is similar to that of late-onset gastric cancer (LOGC) and has been rising steadily since the late 1980s (8).

Disease prognosis of EOGC. The majority of young (<45 year old) patients present with late-stage clinical symptoms, similar to those observed in older patients, resulting in a poor prognosis (11). It has also been reported that the tumor stage at diagnosis and prognosis of younger patients are similar to those of older patients, with radical gastrectomy suggested to be a more important prognostic factor (12). By contrast, another study stated that young patients with gastric carcinoma do not have a worse prognosis compared with older patients (10). The important prognostic factor was whether the patients underwent curative resection (10).

Risk factors associated with EOGC. GC is a multifactorial disease resulting from hereditary or environmental factors, including *H. pylori* (13), which was classified as a class I carcinogen by the World Health Organization in 1994 (14,15). Smoking cessation may improve the medical management of acid reflux, and *H. pylori* treatment over the past few decades has resulted in a significant reduction in the incidence of conventional GC (16,17).

A study of EOGC in 20-39-year-old patients compared several risk factors with those observed in traditional GC based on an analysis of Surveillance, Epidemiology and End Results (SEER) and Behavioral Risk Factor Surveillance System (BRFSS) data (18). Regional and ethnic differences in disease trends were observed in the SEER analysis. The BRFSS analysis indicated that heavy alcohol consumption was positively correlated with EOGC, which is also a risk factor for traditional GC (P=0.027; 0.008). However, obesity and smoking were not found to be significantly correlated with either EOGC or traditional GC, and there was no evidence of any difference between the two GC groups with regard to their associations with various risk factors (18). Certain risk factors, including *H. pylori* infection, nitrites and food intake, were not included in the BRFSS risk assessment survey and, therefore, were not assessed. Additional investigations are necessary to identify risk factors in EOGC to provide risk reduction strategies for public health policies.

3. Etiology

The cause of GC remains unknown. However, various etiologies have been suggested and evaluated.

EOGC and heredity. It has been hypothesized that genetic factors are more important in EOGC compared with traditional GC. Therefore, molecular studies may be key in revealing genetic changes associated with EOGC (19). Notably, not all patients with EOGC have a family history of GC or hereditary GC genes. It has been reported that only 10% of patients aged ≤40 years have a positive family history, and up to 90% of EOGC cases are idiopathic and no specific cause can be identified (20).

There are two main histological types of GC: Diffuse gastric cancer (DGC) and intestinal type-gastric cancer (IGC) (21). These two types are considered to be caused by or directly associated with certain environmental factors and specific genetic changes, such as known carcinogenic gene mutations. In elderly patients, IGC is more common compared with DGC (22,23). In addition, patients with a family history of GC are more likely to develop IGC compared with those without a family history of GC (24). This is consistent with the DGC performance of EOGC described in previous studies (23,24), indicating that familial GC cannot completely explain the occurrence of EOGC.

EOGC and DNA methylation. Age-associated methylation transformations have been identified in various organs and tissues as a result of abnormalities in DNA methylation caused by *H. pylori* and Epstein-Barr virus infection (25,26). The abnormal DNA methylation of gene promoters has been demonstrated to play a key role in the development of GC (27-29). Studies have used methylation chip to explore patients with EOGC and LOGC overall DNA methylation differences, results demonstrated that the pattern of genome-wide methylation expression was significantly different between early onset and elderly GC (30). The hypermethylation of cg11037477, located at the promoter of EIF4E, was significantly associated with age at diagnosis and the expression of Eukaryotic initiation factor 4E (EIF4E) (30). Besides, patients with GC with high level of cg11037477 were more likely to have advance disease with T3/T4 invasion and III/IV stage (30). The cg11037477 hypermethylation and EIF4E downregulation were significantly related to poor survival of patients with GC (30). EIF4E is a member of the PI3K-Akt signaling pathway, whose activation and expression are related to the occurrence and development of GC (31).

4. Diagnostic criteria of EOGC

Clinicopathological characteristics. EOGC is currently a matter of debate among researchers. Previous studies have

reported that, compared with young patients with GC, elderly patients are more likely to have distant metastasis, high tumor grade, invasion of adjacent organs and poor survival rate (32-34). Given the rarity of GC in young individuals, the reduced clinical suspicion of GC may delay examination and the final diagnosis of the disease, leading to a higher incidence of advanced cancer in these patients. In certain retrospective studies, it was shown that the proportion of young patients with GC who were female was higher than that of older patients, and the young patients exhibited poor histological tumor differentiation and rapid disease progression (3,35-38).

A retrospective study was conducted on 121 patients with EOGC aged ≤45 years. Compared with LOGC, EOGC was associated with a higher incidence of stage III/IV lesions (86.8 vs. 57.9%; P<0.001), low differentiation (95.9 vs. 74.4%; P<0.001) and signet-ring cell tumors (88.4 vs. 32.2%; P<0.001). Most of the tumors in the two groups were located in the middle third of the stomach (P=0.108) (39).

In order to evaluate the pathological and clinical characteristics of EOGC, a study searched the SEER database of tropical diseases for GC in patients aged 20-39 years and compared them with patients with traditional LOGC. The results indicated that EOGC was more common than LOGC among women (48.9 vs. 39.0%; P<0.0001), more frequently presented with poor tumor differentiation (55.3 vs. 48.0%; P<0.0001) and was more aggressive and more prone to generate lymph node and distant metastases (48.3 vs. 32.5%; P<0.0001) (18). This is consistent with other earlier findings based on the SEER database (9). The reasons for these differences between young and older patients with GC may include biological dissimilarities, as well as the risk of delayed diagnosis of GC in young patients, as practitioners generally are less likely to consider a diagnosis of GC in young patients compared with elderly patients (40).

A recent investigation of 75,225 cases of GC, including 18,608 cases of EOGC and 56,617 cases of LOGC, indicated that patients with EOGC were more likely than those with LOGC to exhibit poor histological differentiation (55.2 vs. 46.9%), signet-ring cells (19.0 vs. 10.4%), diffuse histological type (25.7 vs. 15.0%) and local or distant metastasis (49.5 vs. 40.9%; all P<0.01) (8).

The clinicopathological characteristics of EOGC and LOGC are markedly different from each other (41). Specifically, EOGC lesions are more likely to be multifocal (42). In addition, the prevalence of diffuse lesions is higher and that of intestinal metaplasia is lower in EOGC (20,43,44). Female patients are more commonly affected by EOGC than LOGC, which has been suggested to be due to hormonal factors (45). Female EOGC is characterized by poor differentiation, strong invasiveness and a propensity for lymph node and distant metastasis (9,18,43). Furthermore, recent studies have shown that the majority of patients are male for both EOGC and LOGC (8,46,47).

EOGC and gene expression. EOGC and LOGC have different molecular expression profiles (11,46,48), and their underlying molecular genetic mechanisms are also markedly different (11,49). One study revealed that heterozygous loss most frequently occurs near the Runt-related transcription factor 3, TP53 and cadherin-1 (CDH1) genes in patients with EOGC, indicating that the characteristics of EOGC are different from those of LOGC (11). Another study suggested an association between different patterns of DNA copy number alterations and the age at which GC progression began, and suggested that chromosomal regions 19p13.3 and 11q23.3 may be associated with age-related differences in tumors (49).

EOGC exhibits different clinicopathological and molecular characteristics from those of traditional GC, indicating that it is an independent GC entity. South Korea has been reported to have one of the highest incidences of GC among young patients worldwide, with 15% of cases of GC being diagnosed in individuals <45 years old (50). Korean researchers studied the protein genome of EOGC in younger patients, collecting matching tumors and adjacent normal tissues as well as blood samples from 80 patients aged <45 years with EOGC. Exome sequencing was performed on tumor and peripheral blood mononuclear cells from each patient, and mRNA sequencing was performed on tumors and the adjacent normal tissues. In addition, the entire proteome, phosphoproteome and the N-glycoproteome of paired tumors and adjacent normal tissues were analyzed by liquid chromatography tandem mass spectrometry. The results revealed that, compared with LOGC, EOGC had different gene expression profiles and six significantly mutated genes, namely CDH1, TP53, protein BANP, mucin 5B, transforming protein RhoA and AT-rich interactive domain-containing protein 1A. However, no difference in mRNA expression patterns was detected between EOGC and LOGC. Since no comparable protein data are available for LOGC samples, it remains unclear whether the protein levels, phosphorylation levels and N-glycosylation levels differ between EOGC and LOGC (6).

EOGC and chromosome instability (CIN). Genome-wide association studies (GWAS) have confirmed that genetic variations on chromosome 5p15 are associated with multiple cancer risk factors. The 5p15 locus has been demonstrated to exert a pleotropic effect on a variety of cancers, but the effects of its mutation on GC has not been elucidated (51).

The successful application of GWAS on the basis of the inheritance of complex diseases or traits has identified GC susceptibility sites on chromosomes 1q22, 3q13, 5p13, 8q24 and 10q23 (52-56). However, these results explain only a small part of the heritability of GC, as often only the strongest associations are the focus of subsequent replication studies. Based on an existing GWAS dataset comprising 1,006 cases and 2,273 controls, one study evaluated the association between 5p15 gene variations and GC, and then replicated the evaluation of two promising loci in a case-control analysis in a Chinese population. A novel 5p15 mutation (rs10052016) was found to be significantly associated with GC risk and age of onset, as well as EOGC, in that Chinese population (57).

EOGC and HER2. Since HER2 expression in IGC is more common compared with that in DGC (2,19) and it is generally considered that GC cases in young patients are more commonly of the DGC type, the expression of HER2 in young patients is expected to be low. Several studies have

demonstrated that HER2 positivity is associated with a poor prognosis in GC and more severe disease progression (58-60). However, it has also been indicated that as younger patients have a poorer prognosis and more aggressive disease course, patients with EOGC may have high HER2 expression. A study evaluated the expression of HER2 in GC tissue, and found that the rates of HER2 amplification (2%) and overexpression (0%) in EOGC were lower compared with those in LOGC (amplification rate, 8%; overexpression rate, 7%). In addition, HER2 showed higher amplification and overexpression in IGC compared with DGC (61). However, at present, no further theories have been proposed to explain this, and no follow-up studies have been performed for confirmation.

5. Therapeutic strategies of EOGC

A literature search of the database (PubMed) did not identify any differences in the treatment of EOGC and ordinary GC. The current treatment is still mainly surgical treatment, supplemented by chemotherapy/targeted therapy and immunotherapy (62).

6. Discussion

The cause of EOGC has been extensively investigated in numerous studies. Although younger patients may be exposed to fewer environmental carcinogens and the same environmental factors as the rest of the population, they tend to present with earlier development of GC for unknown reasons. Moreover, there is a possibility that the tumors in patients with EOGC are more dependent on genetic and molecular factors. In particular, they may be associated with multiple acquired mutations, such as genetic susceptibility to single-nucleotide polymorphisms, CIN, microsatellite instability, somatic gene mutations and epigenetic changes.

The early development of GC may not necessarily be an issue for the affected individual. The main concern arises when the GC metastasizes and treatment is compromised, resulting in a high mortality rate. In addition, tumors that remain dormant for several years and then develop rapidly after undergoing a change or mutation may cause additional challenges in young patients with EOGC.

EOGC sometimes develops in patients with a family history of GC. As these patients are screened earlier, they exhibit different characteristics from those of the general population. However, the screening standards vary among countries due to differences in health care systems and guidelines.

The current clinical challenge is to compare the differences between EOGC and traditional GC in various aspects in order to understand which changes are important, determine the associations between these changes, and design strategies to prevent them. This can assist practitioners in the identification of specific GC markers and therapeutic targets.

7. Conclusions

In the absence of clear data on EOGC epidemiology, histopathology, risk factors and genomic characteristics, the present review aimed to better define these attributes on the basis of the currently available literature and experimental research. The main goal of this review was to improve clinical awareness of EOGC and highlight opportunities for the diagnosis and treatment of younger patients with GC, ultimately, in order to improve patient prognosis and prevent disease progression.

To the best of our knowledge, no studies have yet reported on the association between the occurrence of EOGC and known risk factors. Since no clear trend has been identified in the association of EOGC with either sex, known mutations are currently the focus of targeted therapy. However, additional studies are required to further assess the impact of EOGC on younger patients.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

ZM and HC completed the conception and revision of the whole review. XL completed the structural framework and adjustment of the whole review. MEP completed the modification and adjustment of the English version of the review. MC and PZ have revised the manuscript for important intellectual content. ZM and HC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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