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Gastric Carcinoma in Young Adults: An In-Depth Review

Rafael Fernandes de Sá

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Orientador: Dr. Pedro Miguel Ribeiro Marcos

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Declaração de Integridade

Eu, Rafael Fernandes de Sá, que abaixo assino, estudante com o número de inscrição 43414 de Medicina da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Rafael Fernandes de Sá

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Dedicatória

Esta tese é dedicada a todas as pessoas que sofrem com esta patologia e àqueles à sua volta, que oferecem o seu apoio.

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Abstract

Introduction: Early-onset gastric carcinoma (EOGC) is growing worldwide. Young adults display different clinicopathological characteristics resulting in unique prognostic implications. Therefore, we proposed to conduct a literature review about this condition.

Methods: Review of literature available on PubMed. Systematic reviews, metanalysis, case-control studies, case series, and cohort studies were preferred for analysis.

Results: EOGC is predominantly associated with diffuse histology, affecting more females. It is linked to modifiable risk factors, including high intake of processed and red meats, excessive salt consumption, smoking, alcohol use, and *Helicobacter pylori* infection, as well as genetic predispositions. While hereditary diffuse gastric cancer is the most studied syndrome, it accounts for only a small percentage of cases. Compared to older individuals, young adults are diagnosed with more advanced tumors and a higher rate of metastasis at diagnosis. Nevertheless, younger age is associated with a more favorable prognosis, likely attributable to better tolerance of surgical and other therapeutic interventions. Screening programs should target the general population, with particular emphasis on individuals with a family history of gastric carcinoma or related syndromes. Strategies like *Helicobacter pylori* testing and eradication in young adults and periodic endoscopic surveillance programs for at-risk individuals should be implemented.

Conclusion: EOGC exhibits distinct clinicopathological features and outcomes compared to late-onset gastric carcinoma. Prevention and education are key to reducing its burden. Early detection of familial syndromes and proper surveillance significantly improve outcomes.

Keywords

Gastric Cancer; Gastric Carcinoma; Young Adults; Early-Onset Gastric Carcinoma.

Resumo

Introdução: O carcinoma gástrico de início precoce (EOGC) está a crescer em todo o mundo. Os adultos jovens apresentam características clinicopatológicas distintas, com impacto prognóstico . Posto isto, propusemos-nos a realizar uma revisão da literatura sobre esta patologia.

Metodologia: Revisão da literatura disponível na PubMed. Revisões sistemáticas, meta-análises, estudos caso-controlo, série de casos e estudos de coorte foram priorizados para análise.

Resultados: O EOGC está predominantemente associado a histologia difusa, afetando mais mulheres. Está ligado a fatores de risco modificáveis, incluindo elevado consumo de carnes processadas e vermelhas, consumo excessivo de sal, tabagismo, consumo de álcool e infeção por *Helicobacter pylori*, bem como predisposições genéticas. Embora o cancro gástrico difuso hereditário seja a síndrome mais estudada, representa apenas uma pequena percentagem dos casos. Comparados com indivíduos mais velhos, os EOGC são diagnosticados geralmente em estadios mais avançados e com uma maior taxa de metástases no diagnóstico. No entanto, a idade jovem está associada a um prognóstico mais favorável, provavelmente devido a uma melhor tolerância a intervenções cirúrgicas e outras terapias. Os programas de rastreio devem abranger a população em geral, com ênfase especial em indivíduos com antecedentes familiares de cancro gástrico ou síndromes relacionadas. Estratégias como o diagnóstico da infeção e erradicação de *Helicobacter pylori* ou vigilância endoscópica periódica devem ser implementadas.

Conclusão: O EOGC apresenta características clinicopatológicas e resultados distintos em comparação com o cancro gástrico de início tardio. Prevenção e educação são fatores chave para reduzir o seu impacto. Deteção precoce de síndromes hereditárias e familiares e vigilância adequada melhoram significativamente os resultados.

Palavras-chave

Cancro Gástrico; Carcinoma Gástrico; Adultos Jovens; Cancro Gástrico de Início Precoce.

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Abbreviations List

aHR	Adjusted Hazard Ratio
AKT	Protein Kinase B
ASR	Age-Standardized Rate
CA 19-9	Carbohydrate Antigen 19-9
CDH1	Cadherin 1
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CIN	Chromosomal Instability
CLDN18-ARHGAP	Claudin 18-ADP-Ribosylation Factor GTPase Activating Protein Fusion Gene
CTNNA1	Catenin Alpha 1
EBV	Epstein-Barr Virus
EGFR	Epidermal Growth Factor Receptor
EOGC	Early-Onset Gastric Cancer
Erβ	Estrogen Receptor Beta-Isoform
ESGE	European Society of Gastrointestinal Endoscopy
GC	Gastric Carcinoma
GCO	Global Cancer Observatory
GS	Genomically Stable
HDGC	Hereditary Diffuse Gastric Cancer
HER2	Human Epidermal Growth Factor Receptor 2
HP	Helicobacter Pylori
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
MLPA	Multiplex Ligation-dependent Probe Amplification
MSI	Microsatellite Instability
mTOR	Mechanistic Target of Rapamycin
PCR	Polymerase Chain Reaction
PD-L1	Programmed Death-Ligand 1
PI3K	Phosphoinositide 3-Kinase
RAS	Rat Sarcoma Virus
RHOA	Rho-Associated Coiled-Coil Kinase
RTK	Receptor Tyrosine Kinase
SEER	Surveillance, Epidemiology, and End Results
TCGA	The Cancer Genome Atlas

Introduction

Gastric carcinoma (GC) remains a significant global health issue, ranking fifth among the most diagnosed malignancies and also fifth among the leading causes of cancer-related mortality worldwide. Despite an overall declining trend in incidence globally, GC continues to impose a considerable burden, particularly in regions such as Eastern Asia, Eastern Europe, and South America (1).

As classified by Lauren, the primary histological subtypes of GC include the intestinal type, the most common, which is usually well-differentiated and often associated with environmental factors, and the diffuse type, which is more commonly poorly differentiated with worse prognosis and more frequently linked to genetic predispositions. Most GC cases are sporadic, with approximately 10% showing familial aggregation (2).

Historically, GC has been considered a disease of older individuals, most commonly diagnosed after the age of 50. Conversely, an estimated 2-8% of cases occur in younger patients, often referred to as early-onset gastric carcinoma (EOGC). This trend is concerning, as younger patients frequently present with more advanced disease at diagnosis and may exhibit distinct biological and clinical characteristics compared to older populations (3). EOGC lacks a fully established standard age cut-off, with studies indicating a range from under 30 to 60 years; most consider it as GC occurring before the age of 45 or 50. Standardizing this age range should be a priority for major organizations (4).

The increasing incidence of EOGC raises critical questions about its etiology, as younger patients are less likely to have accumulated environmental exposures traditionally linked to GC, such as *Helicobacter pylori* (HP) infection, high salt intake, or smoking. Instead, non-modifiable factors may play a more prominent role in this subgroup, and understanding these distinct patterns is important (2). To gather relevant information about EOGC, we proposed conducting a literature review. Studies published in MEDLINE until October 2024 were searched via PubMed using the following query: ("gastric cancer"[Title/Abstract] OR "stomach cancer"[Title/Abstract] OR "gastric carcinoma"[Title/Abstract]) AND ("young adults"[Title/Abstract] OR "adolescents"[Title/Abstract] OR "under 45"[Title/Abstract] OR "under 50"[Title/Abstract] OR "early onset"[Title/Abstract]). Studies of interest for full-text analysis were selected according to the information in titles and abstracts. Only articles written in English, Spanish, and Portuguese were considered. Systematic reviews, metanalysis, case-control studies, case series, and cohort studies were preferred for analysis.

Epidemiologic Data

In 2022, according to the Global Cancer Observatory (GCO), 968,784 new GC cases were reported worldwide, along with 660,175 deaths attributable to this disease. Portugal, in particular, had 3,668 new cases and 2,578 deaths in the same year (1).

EOGC shows an upward trend, growing in both total numbers and its proportion of overall GC cases. Data from the GCO indicates that globally, in 2022, there were 82,146 cases of GC in individuals aged 0–49, yielding an age-standardized rate (ASR) of 1.2 per 100,000 population. Within this same age bracket, the mortality count was 51,963 deaths, equating to an ASR of 0.79 per 100,000 population. In 2022, Portugal documented 174 cases for this age group, leading to an ASR of 1.8 per 100,000 population. Mortality figures for this group stood at 88 deaths, with an ASR of 0.87 per 100,000 population (1).

Data from the Surveillance, Epidemiology, and End Results (SEER) database in the United States revealed a significant increase in the proportion of GC patients under 50 years old, rising from 6% in 1982 to 12.5% in 2015. The proportion of EOGC under the age of 40 increased from 1.7% in 1973 to 3.5% in 2015 (5). Overall, EOGC appears to represent around 2-10% of all GC, obviously varying due to the lack of age standardization (2,3,6).

Risk Factors Associated With EOGC

Non-Modifiable Risk Factors

Women experience incidence and mortality rates 1.64 and 1.58 times greater than those in men, respectively. Estrogen is thought to encourage the development of diffuse-type GC that expresses estrogen receptors (7).

While most GC cases across all age groups are sporadic, familial clustering is observed in approximately 10%. Among these, only 1-3% are hereditary, and the vast majority is diffuse, commonly referred to as Hereditary Diffuse Gastric Cancer (HDGC), which is more commonly observed in young adults (8).

Family history of GC in first-degree relatives is associated with an approximately threefold increase in risk for both diffuse and intestinal subtypes of the disease (2,4). This elevated risk is thought to result from a complex interplay between inherited genetic mutations and alterations in host-environment interactions (4,9,10). Notably, relatives of GC patients exhibit an elevated susceptibility to HP infection, likely due to interpersonal transmission and shared environmental or living conditions. Furthermore, these individuals show a higher prevalence of gastric precancerous conditions, such as gastric atrophy and gastric intestinal

metaplasia, even at a younger age (4).

The genetic component may extend beyond HP susceptibility, as evidence suggests that altered immune responses to HP could have a hereditary basis (4). The role of inherited genetic factors in EOGC is considered more pronounced compared to late-onset cases, as younger individuals generally have reduced exposure to environmental carcinogens, further emphasizing the importance of genetic predisposition in this population (11,12).

Genetic Syndromes

Several syndromes increase the risk of EOGC, with HDGC being the most notable (2,13). The lifetime risk of developing GC differs among these syndromes. Lynch Syndrome carries a lifetime risk of 1–13%, with 85% of cases being the intestinal type of GC. Peutz-Jeghers Syndrome presents a 29% lifetime risk, whereas Juvenile Polyposis Syndrome has a risk varying from 11% to 21%. In the case of Li-Fraumeni Syndrome, the lifetime risk ranges from 1.3% to 22.6%. Familial Adenomatous Polyposis has a risk of 0.6% to 1.3%, and Gastric Adenocarcinoma with Proximal Polyposis of the Stomach is associated with a 13% lifetime risk. Additional syndromes linked to higher risk include MUTYH-Associated Adenomatous Polyposis, Cowden Syndrome, and Hereditary Breast and Ovarian Cancer Syndrome. Among these, the BRCA2 mutation presents a relative risk of 2.15 for GC (14–19).

HDGC is an autosomal dominant syndrome characterized by an increased risk of diffuse GC and lobular breast cancer. It was first described in 1998 in a New Zealand Māori family (14). It is the most frequent form of hereditary GC. The prevalence of HDGC is less than 0.1 per 100,000 in the general population and less than 1% of patients with GC. HDGC exhibits a mean penetrance of about 70-80% (15,20–22). Between 25% and 50% of all confirmed cases are attributed to inactivating germline mutations in the CDH1 tumor suppressor gene, resulting in the loss of E-cadherin protein, a cellular adhesion protein (10,15,21). Since 2020, mutation on the CTTNA also accounts for this syndrome, with a penetrance of about 49-57% (23–25). CTNNA1 encodes α-E-catenin, which binds the cytoplasmic domain of E-cadherin to the cytoskeleton alongside β-catenin (26).

The International Gastric Linkage Consortium recommends genetic testing for individuals who satisfy at least one of these criteria in addition to several supplementary criteria not explicitly listed here: (a) having two or more family cases of GC, irrespective of age, with at least one confirmed as diffuse type; (b) a confirmed diagnosis of diffuse-type GC before the age of 50; (c) a history of both diffuse gastric cancer and lobular breast cancer diagnosed before age 70; (d) gastric signet ring cells found in individuals under 50 years old (14). Patients should be tested for CHD1, and if the results are negative, they should undergo testing for CTNNA1 or investigate potential rearrangements of the CDH1 locus that Polymerase Chain

Reaction (PCR)-based sequencing may not have detected. Additionally, full genetic analysis can be performed using Multiplex Ligation-dependent Probe Amplification (MLPA) (23,27). Prophylactic total gastrectomy is the most effective preventive measure for CDH1 mutation carriers and is recommended for individuals aged 20 to 30 (21,22,24). Alternatively, annual surveillance endoscopy may be conducted following the Cambridge protocol, though it has limitations since many patients present with cancer foci despite having normal macroscopic findings (14,28,29).

Modifiable Risk Factors

Preventable risk factors are common in individuals with EOGC but likely less prevalent than in older individuals, as they have not had as long of exposure (16). Diet, lifestyle, infections and hormonal factors have all been implicated. A 2018 study found that patients with EOGC had significantly higher consumption of red meat (odds ratio [OR] 2.6, 95% CI [confidence interval] 1.4–4.9) and processed meat (OR 3.1, 95% CI 1.6–6.0) compared to the general population. They also had increased intake of food preserved with salt (OR 1.7, 95% CI 1.0–3.0) (30). Highly processed or smoked foods and preservatives have also been associated. In contrast, due to their antioxidant properties, the consumption of fresh foods and vegetables is associated with a reduced risk (2,5,30,31).

A cohort study involving 6,793,699 individuals aged 20 to 39 years with a mean follow-up of 9.4 years identified 9,893 cases of EOGC. Increased risk was significantly associated with smoking and alcohol consumption. Compared to never-smokers, former smokers had an adjusted hazard ratio (aHR) of 1.1 (95% CI 1.0–1.2), while current smokers had an aHR of 1.3 (95% CI 1.2–1.4). Low-to-moderate-risk alcohol consumers had an aHR of 1.1 (95% CI 1.0–1.1), whereas high-risk consumers had an aHR of 1.2 (95% CI 1.1–1.3). The highest GC risk was observed in current smokers and high-risk alcohol consumers (aHR 1.4, 95% CI 1.3–1.6) (32). Furthermore, starting smoking at a younger age increases the total duration of exposure to harmful carcinogens, which, in turn, raises the likelihood of developing EOGC (2,32). Additionally, HP has the ability to convert ethanol (present in alcoholic beverages) into acetaldehyde, a substance that is considered a potential carcinogen (17,33). Occupational exposure to metal dust has also been associated with a significant 70% increase in the risk of GC among younger male populations (17).

The rise in EOGC prevalence might also be attributed to the growing occurrences of autoimmune gastritis (34). Additionally, the increased use of antibiotics could lead to dysbiosis in the gastric microbiome, which may further drive up the rates of EOGC (5,16,35). In a retrospective study involving 96 EOGC cases, statins (OR 1.1, 95% CI 0.5-2.6), proton pump inhibitors (OR 0.6, 95% CI 0.2-2.2), and metformin (OR 0.5, 95% CI 0.2-1.9) were evaluated,

but none showed a significant association (16).

HP infection is a critical factor in EOGC etiology. Infection rates among EOGC patients are notably higher than in the general population, as evidenced by studies reporting ratios of 72.5% versus 27.5% and 70.5% versus 41.9%, respectively (5,36). The World Health Organization categorizes HP as a Group 1 carcinogen with a strong link to intestinal GC (2). Particularly virulent strains, such as CagA and VacA (m1 and s1), significantly contribute to gastric carcinogenesis (12).

As stated previously, EOGC predominantly affects females. The expression of Erβ (estrogen receptor beta-isoform) in GC is correlated with younger age and advanced cancer stages, as it is believed to promote tumor cell survival and proliferation (17). A comprehensive retrospective case-control study involving 3,242 patients aged 18-45 identified several factors significantly linked to an increased risk of EOGC. Frequent use of oral contraceptives lacking progesterone (OR 2.5, 95% CI 2.1-3.0), older age at first delivery (OR 2.3, 95% CI 1.9-2.7), no history of lactation (breastfeeders had an OR of 0.7, 95% CI 0.6-0.8), and having no children or only 1-2 children (OR 2.1, 95% CI 1.8-2.5) all contribute to longer estrogen exposure. Additionally, there was a notable increase in bone metastases among younger women, potentially linked to estrogen receptor positivity in this tissue (37). Furthermore, a pregnancy history within the past two years also elevates the risk (6).

Carcinogenesis

The intestinal subtype GC typically evolves through a series of gradual transformations called the Correa cascade, beginning with chronic gastritis, moving on to gastric atrophy, followed by gastric intestinal metaplasia, dysplasia, and, eventually, culminating in carcinoma. In contrast, diffuse GC does not follow a defined cascade and typically appears as a widespread infiltration beneath the normal mucosa. This form arises from multiple malignant foci instead of creating a distinct mass, often displaying signet ring cells and linitis plastica (2,5,38).

Although intestinal and diffuse GC carcinogenesis follow distinct pathways, carcinogenic processes between EOGC and late-onset GC are not fully understood. A 2024 review summarizes the molecular mechanisms and pathways that may explain the difference (5). The molecular signaling characteristics of EOGC differ from those of late-onset GC, which may contribute to the faster progression observed in EOGC. Based on The Cancer Genome Atlas (TCGA) data, GC is classified into four molecular subtypes.

The *Epstein–Barr virus (EBV) subtype* is observed more frequently in EOGC, with rates of 7.7% compared to 5.1% ($p<0.01$). This subtype is linked to mutations in the PI3K/AKT/mTOR signaling pathway, which facilitates tumor progression by inhibiting apoptosis and enhancing angiogenesis. Furthermore, EOGC shows elevated PD-L1 expression

(31.0% vs. 2.9%, $p<0.01$), indicating a potential for immune evasion. The *microsatellite instable (MSI) subtype*, often resulting from inadequate mismatch repair, is associated with improved survival rates; however, its occurrence is lower in EOGC (5.6% versus 18.6%, $p<0.01$). The *genomically stable (GS) subtype* possesses mutations in CDH1, RHOA, and the CLDN18-ARHGAP fusion gene, correlating with a worse prognosis. This subtype occurs more frequently in EOGC (22.5% vs. 8.8%, $p<0.05$). The *chromosomal unstable (CIN) subtype* features mutations in the RTK/RAS signaling pathway (such as EGFR, HER2, KRAS) but does not exhibit significant differences between the groups (5).

Moreover, EOGC patients are more prone to testing negative for traditional tumor markers like CEA and CA19-9 (5).

Phenotypes

Across various studies, diffuse GC accounts for double or more cases compared to intestinal GC in younger populations (31,36,39–41). A study of 115 individuals aged 21 to 45 found 70% had diffuse GC, 22% intestinal-type GC, and 9% mixed carcinoma (31). This pattern is seen in other studies. One analysis of ages 16 to 45 revealed that 79.8% had diffuse GC (42). Another reported a 25.7% prevalence of diffuse GC in young adults, compared to 15.0% in older individuals (5). Another study showed 79% of young patients had diffuse GC, with only 21% having intestinal type (6). Additionally, diffuse GC was 47.3% in younger adults versus 22.9% in older groups (39). Another showed a ratio of 70% diffuse to 30% intestinal GC (36). Lastly, a comparison found that 77% of younger patients had diffuse GC versus 23% with intestinal GC, while older individuals had 49% diffuse GC (40). These findings highlight the greater prevalence of diffuse GC in EOGC.

Additionally, patients with EOGC typically exhibit more advanced tumor stages than those with late-onset GC (42). This group also has a higher incidence of signet ring cell carcinoma, with rates of 19.0% compared to 10.4% (42). Regarding cell differentiation, EOGC shows a greater prevalence of poorly differentiated cancers at 57.7%, in contrast to 35.4% in older individuals. Moreover, the occurrences of moderately differentiated (12.4% vs. 37.3%) and well-differentiated cancers (0.3% vs. 2.2%) are notably lower among younger patients (5). Another study reported similar findings, indicating that EOGC is more frequently poorly differentiated, at 62.4% compared to 48.3% (39).

Traditionally, EOGC is predominantly located in the middle to distal regions, with the antrum being the most frequently affected site (39.8%). Less than 20% typically impacts the cardia, while diffuse GC is spread throughout the stomach, affecting multiple areas (6,11,31,40–44). However, recent studies indicate a shift from distal to proximal EOGC (as for

all GCs in general), likely linked to improved hygiene standards and successful HP eradication, which primarily impacts the distal stomach. This trend underscores the need for ongoing monitoring (40).

Prognosis

EOGC typically faces delayed diagnosis in the general population, particularly among younger individuals, because its lower incidence leads to diminished clinical suspicion, which in turn impacts prognosis (45). EOGC is typically diagnosed at more advanced stages (notably stage IV) compared to late-onset GC (39.3% vs. 29.8% and 42.9% vs. 21.4–36.7%, $p<0.0001$, respectively, according to two different studies) and presents with fewer cases of resectable disease (52.7% vs. 61.3%) (41,42). Although some research indicates that late-onset GC shows overall better survival rates, stage-by-stage analyses reveal that EOGC often has more favorable outcomes (3,5,40,42,43,45,46). For instance, a cohort study indicated an average survival of 58.6 months for EOGC patients, compared to 35.2 months for those with late-onset GC (43). Additionally, the 5-year survival rate stands at 44% for EOGC compared to 31% for late-onset GC (3). Younger individuals with EOGC face this challenge, yet they have a better prognosis than older patients at the same treatable stages. This is mainly due to their greater recovery ability from surgery and better tolerance for other therapies (3,40,42,43). For this reason, younger age has been identified as an independent predictor of better survival despite the more aggressive and advanced nature of tumors in this group (3).

The treatment approach to EOGC aligns with that for GC in older patients, being stage-dependent (47). However, as already mentioned, after surgery, patients with EOGC demonstrate better outcomes than older patients (31).

The liver is the primary site for distant metastases in GC. Interestingly, young age appears to be a protective factor against liver metastases when compared with late-onset GC (13.6 %vs. 15.7%, $p<0.001$), according to a study that included 2,684 EOGC patients and 33,289 late-onset GC patients. In contrast, EOGC has a greater propensity for metastasizing the bone (8.4% vs. 4.4%, $p<0.001$), lungs (6.6% vs. % 5.2%, $p<0.001$), and brain (1.2% vs. 0.7%, $p<0.001$) (39,46). Gender does not seem to influence the metastatic pattern in EOGC significantly (39). Additionally, EOGC in the fundus and body were more likely to develop distant metastases compared to those in the cardia, antrum, pylorus, and lesser curvature (39).

Prevention and Screening

In general, GC incidence can be lowered through HP testing and eradication, reducing risk factors like salt, alcohol, and red or processed meat consumption, quitting tobacco, and conducting genetic tests for those with a family history. Careful monitoring of individuals with known syndromes that elevate the risk for GC is also crucial (12).

Countries such as South Korea and Japan recognized as high-risk for GC, have put in place screening programs, HP eradication efforts, and various other measures that facilitated earlier diagnoses, leading to a notable reduction in mortality rates. In contrast, nations like the United States, which lack screening programs and face heightened exposure to risk factors, have seen a rise in the incidence of EOGC (7). Japan's extensive screening initiatives and prompt diagnosis through gastroscopy have led to the highest five-year survival rates worldwide, primarily attributed to the early identification and removal of cancer (2). Indeed, the European Society of Gastrointestinal Endoscopy (ESGE) recommends that in high-risk populations, endoscopic screening for GC should be considered for individuals aged more than 40 years (48). In countries/regions with intermediate risk, this endoscopic screening may be considered based on local settings and the availability of endoscopic resources (48). Implementing a GC screening program in countries with intermediate risk for GC starting at the age of 45, or even earlier, could be a meaningful strategy, but it requires careful evaluation based on epidemiological evidence, cost-effectiveness, and available resources. For instance, Portugal (a country with intermediate risk for GC) has a high prevalence of HP infection, affecting over half of the adult population, which is a significant risk factor for GC (49). Early screening and eradication of HP in the general population (mainly in young adults) could be a cost-effective measure (49). Conversely, upper digestive endoscopy enables the detection of HP infection through biopsies and allows diagnosing patients with precancerous conditions (atrophy and intestinal metaplasia) requiring regular endoscopic surveillance. Additionally, it identifies precancerous lesions (dysplasia) that require resection, ideally via endoscopy, to minimize the morbidity and mortality associated with open or laparoscopic surgeries. Moreover, it is already demonstrated that endoscopic GC screening in Europe can be cost-effective if combined with a screening colonoscopy in countries with a GC risk of 10 or more per 100,000 (50).

Conclusion

There is a growing interest in the origins contributing to the rising incidence of EOGC. While numerous studies have investigated the clinical features, prognosis, and treatment of EOGC, many have been limited by small cohort sizes and a predominant focus on HDGC often neglecting other syndromes and sporadic forms of the disease, which may influence the reliability of the analyzed outcomes. This review compiles and summarizes the most relevant evidence on EOGC.

The increasing cases of EOGC in Western populations can be linked to environmental and genetic influences and the absence of effective screening initiatives. This highlights the necessity for preventive approaches, including HP eradication and dietary modifications. In addition, implementing endoscopic screenings in countries at intermediate and high risk for GC could significantly reduce the incidence of this disease, and its related morbidity and mortality rates. EOGC exhibits distinct characteristics compared to late-onset GC, with a higher prevalence in females and a predominant diffuse-type histology. EOGCs are often associated with more aggressive behavior and a higher stage at diagnosis. Despite the increased aggressiveness of the disease, younger age has been an independent predictor of better surgical outcomes and survival rates and more favorable overall responses to therapy.

Future studies ought to concentrate on extensive, multicenter research to more accurately define the genetic and environmental factors contributing to EOGC while also filling the existing gaps in sporadic and syndrome-related cases. Standardizing age is crucial as it establishes a framework for study comparisons and consistency. Progress in understanding this condition, paired with effective prevention and early diagnosis methods, will be essential in tackling the challenges presented by this growing condition.

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