Review Article

CDH1 and hereditary diffuse gastric cancer: a narrative review

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Background and Objective: Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome that increases lifetime risk of diffuse-type gastric cancer which carries a dismal overall survival. Due to the high prevalence of cancer in patients with *CDH1* variants, early screening and prophylactic total gastrectomy (PTG) are recommended. This review aims to summarize the current understanding of *CDH1* and HDGC, highlighting its molecular and cellular implications as well as its clinical management and research efforts.

Methods: A review of PubMed and ClinicalTrials.gov was conducted. Articles published in English and with full text were considered. PubMed was searched using the terms 'CDH1' AND 'Hereditary Diffuse Gastric Cancer'.

Key Content and Findings: Loss-of-function mutations in the *CDH1* gene, which encodes the cell adhesion protein E-cadherin, have been identified as the primary cause of HDGC. The loss of E-cadherin expression disrupts cell-cell adhesion and activates oncogenic signaling pathways, ultimately promoting cancer cell growth and dissemination. Prophylactic total gastrectomy (PTG) is recommended for pathogenic *CDH1* variant carriers with a family history of diffuse gastric cancer (DGC). However, recent studies of endoscopic surveillance utilizing specific biopsy protocols have demonstrated the potential for surveillance as an alternative to total gastrectomy in selected patients. Researchers are actively investigating the consequences of E-cadherin loss in gastric epithelium and have identified potential molecular drivers of HDGC development using animal models and organoids. These discoveries provide promise for chemoprevention strategies, biomarker discovery, and targeted therapies for diffuse-type gastric cancer.

Conclusions: The understanding of HDGC has significantly advanced in recent years, with the loss of E-cadherin expression identified as a crucial factor in disease pathogenesis. The use of advanced *in vitro* models offers substantial promise for investigating the molecular mechanisms underlying HDGC and identifying novel therapeutic targets. By leveraging advanced models, continuing clinical trials, and improving clinical management of affected individuals, researchers can work towards the development of more effective treatment strategies for HDGC. The goal is to prevent cancers from developing in patients with *CDH1* gene variants and minimize the burden of cancer.

Keywords: *CDH1*; hereditary diffuse gastric cancer (HDGC); E-cadherin

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Introduction

Gastric cancer remains the fifth most common and fourth most lethal cancer worldwide in 2020, despite improvements in medical technology, food preservation, and *Helicobacter pylori* treatment (1). Majority of gastric cancers are sporadic with approximately 10% of gastric cancers having familial predilection. However, 1–3% of gastric cancers are the result of a hereditary cancer syndrome (2). Hereditary diffuse gastric cancer (HDGC) is a rare and autosomal dominant inherited syndrome that is characterized by early onset of diffuse gastric cancer (DGC) in affected individuals.

HDGC was first described by Jones *et al.* in 1964 when three separate Māori families from New Zealand were discovered to have multigenerational early onset familial gastric cancer (3). Thirty years later, Guilford *et al.* published his work detailing the families originally described by Jones. While the general population of New Zealand had 80% of gastric cancers occur in people over the age of 60, Guilford noted a stark contrast in the Māori families, with majority of gastric cancers occurring before the age of 40 (4) and the earliest arising in a 14-year-old who succumbed to the disease.

Today, germline *CDH1* variants have an estimated population frequency of approximately 5–10/100,000 births (5). Inactivating germline variants in the *CDH1* tumor suppressor gene, which codes for a cell adhesion glycoprotein E-cadherin, are the most common cause of HDGC, with *CTNNA1* gene mutations a more recently identified but less frequent cause (4,6,7). *CDH1* gene variants result in elevated lifetime risk of DGC, lobular breast cancer (LBC), and non-syndromic cleft lip and palate (6,8). Overall, *CDH1* loss of function variants are associated with up to a 70% lifetime risk of gastric cancer in males, and 56% lifetime risk in females who also have a 42% lifetime risk of developing LBC (6). HDGC is considered a highly aggressive form of gastric cancer occurring typically in young patients with a median age of diagnosis in the 30s (6,7). Early identification of *CDH1* mutations in HDGC patients has important implications for genetic counseling and management. However, HDGC has a peculiar and indolent clinical behavior with occult, microscopic foci of gastric signet ring cells (SRC) that are frequently detected in asymptomatic individuals before clinical diagnosis of advanced cancer (6,9). Symptomatic patients often present with American Joint Committee on Cancer (AJCC) stage III and IV disease, for which 5-year survival is particularly poor at approximately 3–19% (10,11). Due to limited survival associated with advanced stage gastric carcinoma, international consensus guidelines support early screening and prophylactic surgery to prevent advanced cancer and improve survival (5).

Recent advances in genetic testing and risk assessment have facilitated the identification of *CDH1* mutation carriers and improved the management of HDGC. However, there is still much to be learned about the pathogenesis of HDGC and the specific mechanisms by which *CDH1* mutations contribute to tumorigenesis. Basic science research has shed light on the functional consequences of *CDH1* mutations on E-cadherin expression and cell adhesion, as well as the downstream signaling pathways that may be disrupted in the presence of *CDH1* mutations. Animal models and organoid cultures of diffuse-type gastric cancer have been developed to study pathogenesis and test potential preventive and therapeutic interventions.

This literature review provides an overview of the current understanding of the role of *CDH1* in HDGC, including the genetic and clinical features of the disease, the functional consequences of *CDH1* mutations, and the current approaches to prevention and treatment. This review also highlights ongoing research efforts aimed at elucidating the specific mechanisms of *CDH1*-mediated tumorigenesis and developing targeted therapies and clinical trials for HDGC. This review covers critical aspects of HDGC that include the molecular biology of *CDH1* loss and the prospect of secondary (extra-intestinal) cancers. We present the most up-to-date knowledge on the subject that is presented with clinical context for practical clinical applicability. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-36/rc).

Methods

A literature review was completed by searching PubMed and ClinicalTrials.gov from the first literature description of HDGC in 1964 up to March 31, 2023. Only articles published in English and with full text were considered. PubMed was searched using the terms "'CDH1' AND 'Hereditary Diffuse Gastric Cancer'". A total of 142 articles were captured (Figure S1). Types of studies included were case reports, clinical trials, comparative studies, meta-analyses, evaluation studies, guidelines, multicenter studies, observational studies, review articles, systemic reviews, and validation studies. Of the 142 articles, 62 articles were review papers, resulting in a total of 80 non-review papers.

Table 1 The search strategy summary

Items	Specification
Date of search	3/31/2023
Databases and other sources searched	PubMed
Search terms used	"CDH1" AND "Hereditary Diffuse Gastric Cancer"
Timeframe	01/01/1964–3/31/2023
Inclusion and exclusion criteria	Included
	English
	Full text articles
	Species: human & animal
	Types: case reports, clinical trials, comparative studies, meta-analyses, evaluation studies, guidelines, multicenter studies, observational studies, review articles, systemic reviews, and validation studies
	Excluded
	Not English
	Abstracts
Selection process	Both authors conducted the selection and review of material together

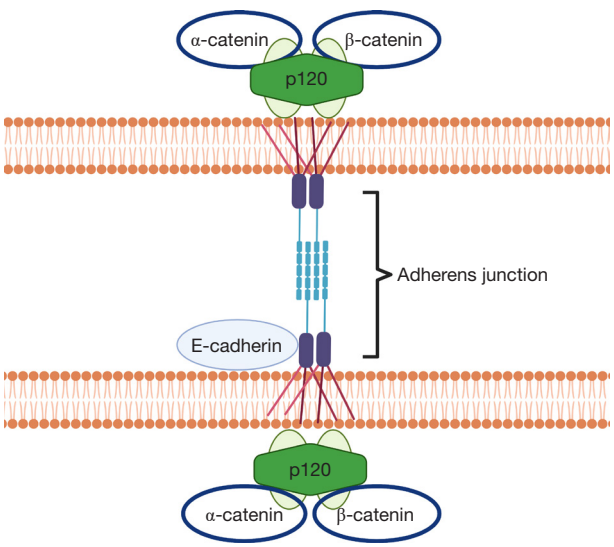

Figure 1 Extracellular and intracellular domain of E-cadherin. Created with BioRender.com.

All articles were reviewed and verified by both authors (*Table 1*).

CDH1-induced gastric carcinogenesis

HDGC is most often the result of a truncating mutation in the *CDH1* gene located on chromosome 16q22.1, which encodes E-cadherin (4,12). E-cadherin is an important transmembrane glycoprotein involved in cell adhesion, signal transduction, and maintaining normal tissue architecture (4,6,7). E-cadherin consists of three domains: an extracellular domain with 5 cadherin repeats, a transmembrane domain, and a highly conserved intracellular cytoplasmic tail (13). The extracellular domain is important for cell-cell adhesion (14,15). The intracellular domain interacts with several catenins (α, β, and p120) to perform important cell functions such as autophagy, endo- and exocytosis, and receptor and transmembrane channel recycling (16,17) (*Figure 1*). E-cadherin also participates in cell differentiation, epithelium maintenance, and alteration of gene expressions in the nucleus through transduction of signals that originate from its extracellular domain (17-19). Loss of E-cadherin leads to cell detachment and disruption of tissue organization. Majority of mutations consist of small insertions and deletions; however, loss of *CDH1* has resulted from nonsense mutations, missense mutations, exon/intro splice site mutations, as well as frameshift mutations (6,20-22). *CDH1* germline variants have been discovered throughout the entire gene length, including entire gene deletions, with no apparent correlation of genotype with phenotype (23).

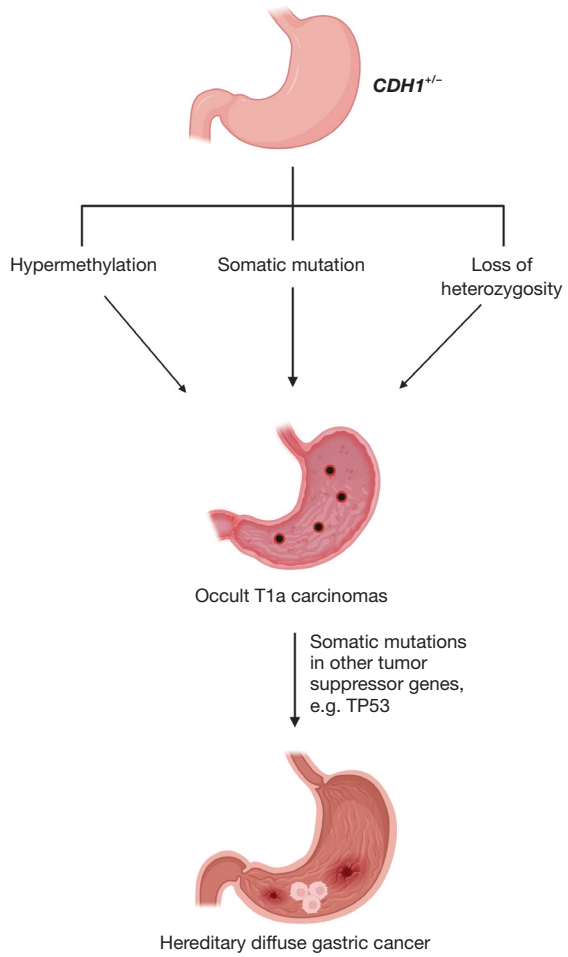

Figure 2 Mechanism of patients with *CDH1* mutations progression to diffuse gastric cancer. Created with BioRender.com.

Germline *CDH1* variants in one allele are inherited in an autosomal-dominant manner. In order to initiate the neoplastic process, the second copy of *CDH1* gene must become inactivated (21). Several mechanisms have demonstrated inactivation of the second *CDH1* allele, including promoter hypermethylation, somatic mutation, and loss of heterozygosity (21,24) (*Figure 2*). *CDH1* acts as a tumor suppressor gene, and the loss of function of the second allele promotes tumor initiation through uninhibited cell adhesion and cell proliferation (13,25,26). Despite these established mechanisms, an explanation for why some patients with *CDH1* variants will develop HDGC whereas others will not is unknown. Interestingly, both *in situ* and invasive HDGC have either reduced or absent E-cadherin expression, signifying that E-cadherin inactivation is an early event in the disease process (27). In addition, multifocal lesions appear to arise as independent events given tumor heterogeneity and complex somatic inactivating mechanisms (24).

This loss of E-cadherin function also leads to the activation of oncogenic signaling pathways, such as the Wnt/beta-catenin pathway which contributes to the uncontrolled growth and survival of cancer cells. The Wnt/beta-catenin pathway is a vital signaling cascade involved in cell proliferation, differentiation, migration, and homeostasis of intestinal stem cell function (28). In normal conditions, E-cadherin sequesters Beta-catenin at the cell membrane, preventing its translocation to the nucleus and thus maintaining the pathway's regulation. However, the loss of E-cadherin liberates beta-catenin, allowing it to translocate to the nucleus and activate downstream target genes involved in cellular proliferation, survival, and invasion (28,29). Consequently, the aberrant activation of the Wnt/beta-catenin pathway promotes tumorigenesis in HDGC. These interconnected pathways contribute to the uncontrolled growth, survival, and invasive properties of cancer cells, ultimately driving the development and progression of HDGC. A sophisticated understanding of these pathways and their interplay is crucial for the development of targeted therapeutic strategies aimed at combating this aggressive malignancy.

To further elucidate these pathways and mechanisms of HDGC, animal models have been utilized. One study by Humar *et al.* used N-methyl-N-nitrosourea (MNU) to induce gastric carcinogenesis in cdh1$^{+/-}$ mice (30). These mice were shown to have an 11× higher incidence in developing intramucosal signet-ring cell carcinoma (SRCC) compared to their wild-type counterparts, which supports the known importance of E-cadherin loss in the development of malignancy. Similar to humans, this mouse model demonstrated early detection of SRCC indicating that E-cadherin is an early mechanism, and the tumors also revealed a transition to poorly differentiated tumors once invading beyond the mucosa. Additionally, *CDH1* knockout mice have demonstrated a significant increase in SRCs and the development of more advanced tumors with the additional loss of *TP53*, further promoting the two-hit hypothesis (31). While convenient, mice are genetically different from humans and the SRCC found in mice are restricted to only the gastric antrum compared to the diffuse and unpredictable gastric distribution of SRCC in humans (30). To counteract the differences in microenvironments seen in animal models, organoids have emerged as a promising tool for the study of *CDH1* and

HDGC. Organoids are three-dimensional multi-cellular *in vitro* models that recapitulate the architecture and functionality of native tissues, such as the stomach. Both murine and human organoids have been utilized to further understand the mechanisms of HDGC to develop treatment and screening modalities. Using the stomachs from *CD44-Cre/CDH1*$^{loxP/loxP}$ mice that underwent subsequent *CDH1* deletion to create organoids, Dixon *et al.* discovered that cytokeratin 7 (CK7) and its respective differentiation gene Krt7 were markers for early neoplastic lesions in *CDH1* carriers (32). The authors recommend the use of CK7 immunohistochemistry analysis on suspicious endoscopic biopsies to aid in the detection of early malignancy. Caution should be noted as published data using human derived organoids is not available to validate these findings. Similar to *CDH1* knockout mice, patient-derived organoids that have combined loss of both *TP53* and *CDH1* have been shown to form highly invasive tumors and grown independently of their required growth factor, R-spondin (33,34). This emphasizes the accumulation of additional mutations in helping the early stages of SRC progress into a more aggressive form. Additionally, emerging evidence has revealed that DGC organoids differentiate into SRC-like cells when Wnt pathway factors are absent (35). However, additional factors are needed to enable the early-stage lesion to grow and progress. In conclusion, the use of organoids and animal models to study *CDH1* and HDGC has opened new avenues for understanding the intricate molecular mechanisms underlying this aggressive malignancy. By leveraging these advanced *in vitro* models, researchers can elucidate the consequences of E-cadherin loss and identify novel therapeutic targets, ultimately paving the way for improved clinical management of HDGC.

Guidelines and diagnosis

Individuals with pathogenic or likely pathogenic germline *CDH1* variants are at increased risk of developing DGC and LBC (6,8). For early detection and diagnosis, the International Gastric Cancer Linkage Consortium (IGCLC) established guidelines for germline genetic testing for individuals who meet specific criteria (5). These are separated into individual and family criteria. Individual criteria include DGC in an individual aged <50 years old, DGC at any age in individuals with a personal or family history of cleft lip/palate, history of DGC and LBC in an individual <70 years old, bilateral LBC/lobular carcinoma in situ (LCIS) in individuals <70 years old, or gastric biopsy with *in-situ* SRCs and/or pagetoid spread of SRCs in individuals <50 years old. Family criteria include ≥2 cases of gastric cancer in family (any age) with a least 1 confirmed DGC, ≥2 cases of family members aged <50 years old, or ≥1 case of DGC any age and ≥1 case of LBC in different family members aged <70 years old. Of note, to meet criteria all diagnoses of DGC and LBC must be histologically confirmed and family members must be first- or second-degree blood relatives of each other.

It is important that individuals who meet testing criteria are provided with both genetic counseling and genetic testing at certified molecular diagnostic laboratories (5). Positive tests from direct-to-consumer testing may be used only if validated by a certified molecular diagnostic laboratory (5). Genetic testing should include *CDH1* variants as well as *CTNNA1* and other gene variants that have been linked not only to DGC but increased gastric carcinoma risk in general (6,36,37).

Endoscopic cancer surveillance

The most recent clinical practice guidelines for HDGC advocate PTG for carriers of pathogenic *CDH1* variants with a family history of DGC. For patients meeting these criteria who either decline PTG or present with contraindications to surgery, annual surveillance endoscopy is recommended (5). The Cambridge method, a consensus approach, is advised to guide endoscopic surveillance in HDGC, primarily aiming to assess early cancer signs through meticulous inspection of the gastric mucosa and evaluation of distensibility. Subsequently, targeted biopsies of visible abnormalities are performed, followed by non-targeted (random) sampling of the gastric mucosa (32-35). Using the Cambridge method, a minimum of 30 random gastric mucosal biopsies are collected, partly due to the presence of intramucosal, occult SRC carcinoma foci in nearly all *CDH1* variant carriers (5,38). Historically, detection of SRC lesions in gastric biopsies during endoscopy has reported to be between 9–24% (9,39-41); however, more recent surveillance endoscopies in expert HDGC centers have detected SRC lesions in up to 40–61% (5,38,42-45). While endoscopic detection of SRCs has varied, it remains an insensitive method for occult SRC carcinoma detection when compared to PTG (39,46,47). In fact, gastrectomy explants from *CDH1* variant carriers are reported to harbor SRC in 80–100% of specimens, even those with negative endoscopic surveillance biopsies (48-53). The high false-negative rate of SRC detection with

Cambridge method of surveillance was addressed using the Bethesda protocol developed by Curtin *et al.* (46). This protocol utilizes 88 non-targeted biopsies total, which are obtained from twenty-two individual anatomic sites (46). While the cohort reported initially was small, the Bethesda method resulted in a 38% false-negative SRC detection rate compared to 80% with the Cambridge method (46,54). The Cambridge group recently reported their 16-year experience with surveillance endoscopy and reported a sensitivity of 67.3% and a specificity of 90.2% for detecting occult gastric SRC carcinoma (38). Another study by Benesch et al revealed no difference between cancer rates in biopsy positive and biopsy negative groups, although the median number of biopsies was greater in the biopsy positive group (41). Adjuncts to white light endoscopy have been explored but have not proved useful to date. A single-institution phase II clinical trial evaluated the use of a probe-based confocal endomicroscopy (pCLE) compared to the Cambridge method with the aim of improving detection of occult SRC. This study demonstrated an improvement of false-negative SRC detection rate of 67% using pCLE compared to 87% when using the original Cambridge method, however the study was small and did not show clinically meaningful differences in detection (53).

The only comparatively large study of endoscopic surveillance to date demonstrated that endoscopic surveillance can be safe for patients who decline PTG (55). This prospective study challenges the urgency of upfront gastrectomy in patients with *CDH1* variants and SRC detected on random biopsy. However, despite this recent evidence supporting the potential efficacy of endoscopic surveillance, PTG remains the recommendation for *CDH1* pathogenic variant carriers with a family history of DGC.

PTG

Before undertaking PTG, patients deserve comprehensive consultation and evaluation of operative risks, long-term consequences, and thorough examination of psychosocial and medical comorbidities. The prevailing consensus advises patients with *CDH1* pathologic variants to undergo prophylactic gastrectomy as early as age 20, with attention given to social and psychological factors potentially influencing the surgical decision. Total gastrectomy constitutes a life-altering intervention, as it imposes considerable dietary restrictions and necessitates lifelong nutritional supplementation. Consequently, it is paramount that patients receive dietary counseling, maintain a family or peer support network, and comprehend the surgery's repercussions fully.

Acute perioperative risks of total gastrectomy include anastomotic leaks and intra-abdominal abscesses, among others, whereas mortality remains a rare occurrence. Chronic sequelae encompass weight loss, micronutrient deficiencies, bile acid reflux, dumping syndrome, osteopenia/osteoporosis, and esophageal dysmotility. One cohort study disclosed that approximately 60% of patients reported bile reflux within two years post-operatively: with more patients experiencing bile reflux at 1 year than 3 months post-operatively (56). Weight loss typically reaches a plateau at six months post-gastrectomy; however, patients typically weigh 20% less than their preoperative weight one-year post-gastrectomy (43,57-59). One study demonstrated a supplementary 4% weight gain for patients with extended follow-up, resulting in an overall median weight loss of 15% from preoperative weight (59). Consequently, it is crucial to screen patients for eating disorders before undergoing gastrectomy.

Laszkowska *et al.* investigated the optimal timing of total gastrectomy to prevent DGC, estimating the optimal age for PTG at 39 years for men and 30 years for women when comparing quality-adjusted life-years, cancer mortality, and life expectancy (60). However, caution is advised when interpreting this study, as it employed mathematical modeling based on cancer penetrance estimates affected by ascertainment bias. The onset of advanced DGC in individuals with *CDH1* variants can happen at almost any age, the causes of which are still unknown.

Once the decision to pursue PTG is solidified, *CDH1* variant carriers should be directed to high-volume gastrectomy centers under the guidance of a surgical oncologist. Total gastrectomy may be executed laparoscopically or via open surgery, depending on the surgeon's preference. Laparoscopic surgery may afford patients a shorter initial hospital stay, but no approach has demonstrated long-term outcome superiority (61). For complete gastric cancer risk reduction, total stomach removal is essential. Intraoperative biopsies of the esophageal and duodenal margins must be confirmed free of gastric mucosa before concluding the procedure to verify complete resection of gastric mucosa. It is important to note that while the gastric explant may appear grossly normal, 89–95% of patients are found to harbor multi-focal superficial diffuse invasive SRCC (62,63).

Post-operatively, patients adhere to stringent dietary practices with specific micronutrient supplementation and

should have access to a knowledgeable dietitian following hospital discharge. Close clinical follow-up is imperative, with the author's recommending clinical assessments at 3-month intervals post-gastrectomy for the first year, biannually the subsequent year, and annually thereafter. However, no official follow-up guidelines exist. Patients should be evaluated for common functional complaints, such as bile reflux, dumping, and signs of pancreatic insufficiency, which may necessitate pancreatic enzyme supplementation (56). Despite post-operative symptom burden, a quality-of-life study in British Columbia and Newfoundland uncovered a cohort of *CDH1* patients largely satisfied with their quality of life (QOL) following prophylactic gastrectomy (64). In fact, the mean QOL was 70.6, which was comparable to the QOL of the general population of Sweden and Norway (71.2), and remarkably better than patients with gastric cancer (65,66). A detailed pre-operative assessment of individual risks is essential due to the risks associated with surgery. Nevertheless, prophylactic gastrectomy remains the recommendation for individuals with pathologic *CDH1* variants and a family history of DGC.

Advanced-stage HDGC

Advanced stages of HDGC carry poor prognosis due to the relative resistance of diffuse-type gastric cancers to existing systemic therapies. Although the overall 5-year survival rate for patients with advanced HDGC is reported at 4%, compared to 13% in patients with sporadic disease, the overall prognosis and treatment options remain the same (10,67). Just as with sporadic cases of diffuse-type gastric cancer, advanced stages of HGDC manifest as *linitis plastica*, characterized by diffuse infiltration of the stomach with poorly cohesive cancer cells with occasional SRC morphology (66). Interestingly, mutations in RHOA are predominantly found in advanced DGC (33,68). RHOA mutations are responsible for dysregulation of the actomyosin cytoskeleton during early DGC development and have a cumulative malignant effect when occurring with a *CDH1* mutation (33,69). For patients without metastases, surgical resection with perioperative or adjuvant chemotherapy is recommended. Metastatic HDGC should be treated according to current treatment guidelines as for sporadic gastric carcinoma (21,70). Notably, HDGC, like many sporadic diffuse-type gastric cancers, rarely overexpresses human epidermal growth factor receptor 2 (HER2) and is considered genomically stable with a low tumor mutational burden (71). Furthermore, these cancers often lack markers indicative of response to current immunotherapy regimens. Clinical trials investigating treatments for isolated peritoneal metastases such as normothermic intraperitoneal chemotherapy, hyperthermic intraperitoneal chemotherapy, and pressurized intraperitoneal aerosolized chemotherapy have been employed for sporadic DGC and HDGC (72-75). Overall, the prognosis for advanced HDGC is dismal, emphasizing the importance of early recognition and genetic testing, enhanced surveillance, and risk-reducing surgery.

Secondary cancers

Germline *CDH1* variants also carry an estimated 42% lifetime risk of invasive LBC in women (6). Hereditary lobular breast cancer (HLBC) is defined in patients with a *CDH1* variant and LBC, and/or a positive family history of LBC, but without a family history of DGC. The most recent clinical management guidelines for HDGC included specific guidance for women with *CDH1* variants at risk for LBC (6). Breast cancer surveillance is advised to commence at age 30 with an annual breast magnetic resonance imaging (MRI). E-cadherin deficient invasive lobular carcinoma does not form well-defined masses or reliable microcalcifications that can be easily picked up on mammography, but rather infiltrates the tissue in single file sheets or cords (8,76). When patients reach 35 years of age, a breast MRI should be continued alongside standard mammography (77). Although bilateral risk-reducing mastectomy can be considered for patients with *CDH1*, recent guidelines suggest breast-conserving therapy may be sufficient for this patient population (5). However, the appropriateness of breast-conserving therapy for women at risk for multicentric and bilateral breast cancers remains to be determined. For women with *CDH1* germline variants, the average age onset for LBC is 53 years of age (78). Interestingly, two studies by Benusiglio *et al.* and Silva *et al.* suggest that early-onset LBC might be the first manifestation of HDGC, making early surveillance crucial (79,80). Another report by Benesch *et al.* examined cases of sporadic gastric SRC in the Surveillance, Epidemiology, and End Results (SEER) data set to estimate the secondary cancer risk in *CDH1* variant carriers and described an increased rate of LBC. Nonetheless, it is important to note that HDGC accounts for approximately 1–3% of all gastric cancers, therefore patients with SRC gastric cancers, regardless of *CDH1* mutation status, may be at increased risk for LBC due to as yet unknown causes (41).

In addition to HLBC, other cancers associated with germline *CDH1* variants have been investigated. One case report by Hamilton *et al.* described a synchronous SRC carcinoma of the appendix in a patient with *CDH1* and gastric cancer (81). Another study reported signet ring colon cancer in 3 out of 79 patients with *CDH1* pathogenic variants (23). However, using SEER data, no difference in colon cancer risk for *CDH1* carriers was identified (82). Although there is no direct evidence linking colorectal cancer with an increased risk in *CDH1* variant carriers, families should receive individualized counseling. In families with *CDH1* pathogenic variants and a clustering of colon cancer cases, screening colonoscopy at a younger age may be advised.

Strengths and limitations

This review presents several strengths and limitations in its synthesis of the literature surrounding *CDH1* and HDGC. A key limitation is that most existing literature is based on small case series, many of which have been updated more than once. Many reviews exist and likely outnumber original research articles. A strength of this review is the examination of the diverse aspects of HDGC, encompassing genetic factors, surveillance methods, surgical interventions, secondary malignancies, and clinical management guidelines. However, this review does not offer a systematic evaluation of the quality of the included studies because high-quality research is lacking in for this rare disease. Despite these limitations, this review provides a valuable overview of the role of *CDH1* in HDGC, emphasizing the importance of early recognition, genetic testing, and tailored clinical management for affected individuals.

Conclusions

In conclusion, germline *CDH1* variants are the primary cause of elevated lifetime risk of DGC and LBC. The aggressive biology and poor prognosis of HDGC necessitate accurate diagnosis with genetic testing and appropriate clinical intervention. PTG for *CDH1* variant carriers who have a family history of DGC is recommended. While endoscopic surveillance offers a viable alternative for those who are unable or unwilling to undergo surgery, further studies are needed to apply this strategy more broadly. Furthermore, breast cancer risk is significantly elevated in women with *CDH1* variants, therefore enhanced breast cancer surveillance and risk-reducing mastectomy should be discussed with affected individuals. As our understanding of *CDH1*-associated malignancies evolves, it is vital to continue refining clinical management guidelines to optimize outcomes for individuals carrying pathogenic variants. Advances in research methodologies, such as the use of organoids to model HDGC, have expanded our knowledge of the disease and provided invaluable insights into the underlying cancer biology.

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Footnote

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Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-36/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-36/coif). The series "Multimodal Management of Gastric and Gastroesophageal Cancers" was commissioned by the editorial office without any funding or sponsorship. SNG and JLD report that this research was supported in part by the Intramural Research Program of the NIH. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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