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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Samy Azer, FACG, MD, PhD, Professor, Department of Medical Education, King Saud University College of Medicine, Riyadh 11461, Saudi Arabia. azer2000@optusnet.com.au

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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EDITORIAL

Dual primary gastric and colorectal cancer: The known hereditary causes and underlying mechanisms

Samy A Azer

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Samy A Azer, Medical Education and Medicine, King Saud University College of Medicine, Riyadh 11461, Saudi Arabia

Corresponding author: Samy A Azer, FACG, MD, PhD, Academic Editor, Medical Education and Medicine, King Saud University College of Medicine, P O Box 2925, Riyadh 11461, Saudi Arabia. azer2000@optusnet.com.au

Abstract

In this editorial, I commented on the paper by Lin *et al*, published in this issue of the *World Journal of Gastrointestinal Oncology*. The work aimed at analysing the clinicopathologic characteristics and prognosis of synchronous and metachronous cancers in patients with dual primary gastric and colorectal cancer (CRC). The authors concluded the necessity for regular surveillance for metachronous cancer during postoperative follow-up and reported the prognosis is influenced by the gastric cancer (GC) stage rather than the CRC stage. Although surveillance was recommended in the conclusion, the authors did not explore this area in their study and did not include tests used for such surveillance. This editorial focuses on the most characterized gastrointestinal cancer susceptibility syndromes concerning dual gastric and CRCs. These include hereditary diffuse GC, familial adenomatous polyposis, hereditary nonpolyposis colon cancer, Lynch syndrome, and three major hamartomatous polyposis syndromes associated with CRC and GC, namely Peutz-Jeghers syndrome, juvenile polyposis syndrome, and PTEN hamartoma syndrome. Careful assessment of these syndromes/conditions, including inheritance, risk of gastric and colorectal or other cancer development, genetic mutations and recommended genetic investigations, is crucial for optimum management of these patients.

Key Words: Dual gastric cancer and colorectal cancer; Hereditary; Hereditary diffuse gastric cancer; Familial adenomatous polyposis; Hereditary nonpolyposis colon cancer; Lynch syndrome; Other hamartomatous polyposis syndromes

Core Tip: Patients with dual primary synchronous and metachronous primary gastric and colorectal cancer should receive appropriate surveillance measures to minimize their risk of developing syndrome-specific cancers. The genetic testing of diffuse hereditary gastric cancer, familial adenomatous polyposis, hereditary nonpolyposis colon cancer, Lynch syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and Cowden syndrome should be considered to ensure optimum diagnosis and management.

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INTRODUCTION

Colorectal cancer (CRC) has an incidence of 6.4% in patients with gastric cancer (GC), making a prevalence of synchronous GC of 4.4%[1]. Most gastric carcinomas are sporadic; however, approximately 10%-15% show familial aggregation[2]. Therefore, patients with GC have a risk, either synchronously or metachronous, of developing a second primary cancer[3]. Although an improvement in the prognosis for GC has been observed, an increase in the incidence of second primary cancer, mainly CRC, has negatively affected the outcomes of GC. In patients with an increased risk of dual primary gastric and CRC, inherited cancer predisposition syndromes should be considered, including hereditary diffuse GC (HDGC), familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC), Lynch syndrome (LS) and the three major hamartomatous polyposis syndromes associated with CRC and GC, namely Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and PTEN hamartoma syndrome (PTHS). Therefore, careful assessment through preoperative and postoperative examinations and exploring genetic and molecular basis for second primary cancers is crucial. It is also essential to assess the extent of primary cancer and any other dual cancers as a fundamental part of managing these patients. Below, I discuss dual gastric and colorectal in inherited predisposition syndrome.

HDGC

In patients with HDGC, a cancer with poor prognosis, it is inherited as an autosomal dominant trait and caused by the presence of a pathogenic germline variant in the cadherin 1 (CDH1)[4,5]. The *CDH1* gene encodes the E-cadherin protein responsible for cell-to-cell adhesion and responsible for signal transduction functions[6]. Mutations or silencing of CDH1 (E-cadherin) has been reported to initiate carcinogenesis in HDGC[7]. Interestingly, HDGC is responsible for only 1%-3% of diffuse GCs. A study of families with HDGC found that patients with truncating CDH1 germline variants in the PRE-PRO region were at a higher risk of having family members affected by CRC[8]. There is also evidence that patients with HDGC are at a higher risk of developing "signet ring cell colon cancer"[9].

FAP

Patients with FAP are usually asymptomatic for years. FAP, an autosomal-dominant condition, is defined as the presence of hundred or more synchronous colorectal adenomas. Symptoms may include rectal bleeding, anaemia or neoplasia, which will occur when the adenomas become larger and numerous. Most patients have a family history of colorectal polyps and cancer. Patients may present with extraintestinal manifestations, individually or in the family, including osteomas, unerupted teeth, congenital absence of teeth, desmoid tumours[10], and extracolonic cancers (thyroid, liver, bile ducts, duodenum, and central nervous system). It results from a germline mutation in the adenomatous polyposis (*APC*) gene. In a subset of patients, a *MUTYH* mutation causes a recessively inherited polyposis condition, known as "MUTYH-associated polyposis". The later condition is associated with a higher risk developing CRC and polyps in the gastrointestinal tract. Positive family history, clinical findings, and colonoscopy changes are the basis for making the diagnosis. To confirm the diagnosis, genetic testing is required. Identifying the *APC* mutation in the family necessitates performing genetic testing of all first-degree relatives. The differential diagnoses should include all disorders causing gastrointestinal multiple polyps. The primary goal of management is cancer prevention, with regular follow-up and providing supportive care to patients. CRC prophylactic surgery is recommended at the age of 20s[11]. Duodenal cancer and desmoids are the two fundamental causes of mortality after total colectomy. Therefore, upper endoscopy is necessary for surveillance to reduce the risk of ampullary, duodenal or GC[12]. Fundic gland polyps, dysplasia, and neoplasia have been reported in FAP[13,14].

HNPCC and LS

HNPCC carries an increased risk of intestinal-type GC caused by mutations in genes involved in DNA mismatch repair (MMR), mainly in the *hMLH1* and *hMSH2* genes[15]. Mutations in these genes increases the tendency of mutation in oncogenes and tumour suppressor genes, facilitating the process of cancer initiation and progression, including-instability of repeat nucleotide sequences, germline mutations in these genes, and short repeated sequences called "microsatellites" leading to "microsatellite instability (MSI)". GC appears to be a common extracolonic manifestation of this syndrome. Therefore, genetic testing and colonoscopic screening among *HNPCC* mutation carriers is recommended

[16]. Treating physicians should give more attention to assessing patients' family histories of colon cancer and provide appropriate referrals for genetic counselling and testing to target colonoscopic screening to high-risk individuals[17].

LS is the most common inherited cause of gastrointestinal cancers including various malignancies, particularly CRC and GC diagnosed before the age of 50 in the family[18]. LS is caused by autosomal dominant inheritance of pathogenic germline mutations in the DNA *MMR* genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or EPCAM, and LS carriers are associated with unusually high frequency of several extracolonic malignancies[19]. Uterine cancer is the most common, occurring in 54% of women with LS. Also, these women are at a higher risk for breast cancer. MSH6 and PMS2 immunohistochemistry are used as screening tests for LS in endometrial cancer patients[20]. Women with Lynch are also at an increased risk for ovarian cancer. In both sexes, LS is associated with GC[21]. The first family identified with LS, "family G", had a higher number of uterine and GCs[22]. Patients with LS also have an unusual higher risk for cancer of the pancreas, brain, kidney, and bile ducts than the general population[23]. A rare variant of LS, known as "Muir-Torre syndrome" has been identified. It is characterized by multiple sebaceous gland neoplasms together with the classic features of LS, including CRC[24].

Other major polyposis syndromes

These hamartomatous syndromes include - PJS, JPS, and PTHS[25]; they are rare and accounting for less than 1% of CRC.

PJS: PJS is a rare autosomal dominant genetic disease that falls into the hereditary CRC category. The prevalence of PJS is estimated from 1 in 8300 to 1 in 280000 individuals. It is linked to serine threonine kinase 11 (STK11) located on chromosome 19, a tumour suppressor gene involved in cell polarization, regulation of apoptosis, and DNA damage response[26]. There are about 7000 new cases of PJS in China every year, and 170000 PJS patients may survive for a long time in society[27]. PJS patients typically develop characteristic skin pigmentation of the mucosa around the mouth and inside the lips with intestinal polyposis. PJS, although rare, it significantly increases individual predisposition to cancer including colorectal, pancreatic, and GCs. Also, non-gastrointestinal cancers such as breast, uterine, cervical, ovarian, and lung may develop[28].

JPS: JPS is an autosomal dominantly inherited condition in 75% of cases and sporadic in the remaining 25%. It is related to mutations of the *SMAD4* gene (also called the MADH4 gene) and the *BMPR1A* gene. It is associated with gene mutations related to the transforming growth factor (TGF)-β/SMAD signalling pathway[29,30]. JPS is characterized by multiple hamartomatous polyps within the gastrointestinal tract, found in - mainly in the colorectum, and could be found in the stomach, jejunum and, ileum, and duodenum[31]. Although juvenile polyps are more common in childhood, JPS can occur at any age. Patients with JPS have 10%-38% lifetime risk of CRC and an increased risk for gastric, duodenal and pancreatic cancers[32]. The incidence of JPS is approximately 1 in 100000 individuals. The criteria for JPS diagnosis include: (1) Five or more juvenile polyps in the colorectum; (2) Juvenile polyps detected in other parts of the gastrointestinal tract; or (3) The presence of juvenile polyps in a person with a family history of the condition[33]. Other inherited syndromes that exhibit the gastrointestinal phenotype of JPS must also be ruled out[34]. The cancer risk arises within the juvenile polyp adenomatous change.

PHTS: PHTS comprise hamartomatous overgrowth syndromes associated with *PTEN* germline mutations. PTEN is inherited in an autosomal dominant manner. It includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and PTEN-related Proteus-like syndrome. CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumours of the breast, thyroid, kidney, and endometrium. PTEN patients are at higher risk of developing polyps throughout their gastrointestinal tract. Colorectal and GCs are rarely found in these patients. Affected individuals usually have macrocephaly and papillomatous papules. They are at a higher risk of developing breast cancer (85%) and follicular thyroid cancer (35%). The lifetime risk for renal cell cancer is 34%. The risk for endometrial cancer may approach 28%. The diagnosis is established by molecular genetic testing and identifying a heterozygous germline PTEN pathogenic variant[35].

UNDERLYING MOLECULAR MECHANISMS

The mechanisms underlying the development of dual GC and CRC remain controversial. Some explanations have been proposed, including both neoplasms are related to the same genetic alterations, such as APC, p53, CDH1, MSH1 and MLH1, STK11, TGF-β/SMAD, SMAD4, BMPR1A, and K-ras[8,15,29,30,36,37]. MSI is proposed to play a crucial role in colorectal carcinogenesis[38]. However, p53 overexpression or MSI could not predict synchronous and metachronous CRC in GC. Further studies are needed to examine the molecular pathogenesis of dual GC and CRC and if there are specific markers to diagnose synchronous and metachronous cancers[1] (Table 1). Also, environmental factors play a role, including *Helicobacter pylori* (*H. pylori*) infection. Chronic gastric infection with *H. pylori* is responsible for increased serum gastrin levels in these patients, which may act as a growth-promoting hormone, initiating gastric mucosal dysplasia[39]. However, the association between chronic *H. pylori* infection and CRC was not confirmed[1]. Also, GC and CRC are biologically heterogeneous diseases and develop *via* distinct and non-identical pathophysiological mechanisms.

Table 1 Inherited cancer predisposition syndromes related to dual primary gastric and colorectal cancer

Inherited syndrome/condition	Presentation	Clinical features	Inheritance type	Molecular/genetic defect/mutation	Ref.
Hereditary diffuse gastric cancer	Late presentation	GC and CRC	Autosomal dominant	Cadherin 1. Alpha-1 catenin. *CTNNA1* gene	[8]
Familial adenomatous polyposis	Early (20s) asymptomatic, then diarrhoea, rectal bleeding, anaemia, CRC. GC (the proximal stomach)	Family history of colorectal polyps and CRC. Extraintestinal manifestations-osteoma, unruptured teeth. Extracolonic cancer (thyroid, duodenum, stomach, liver, bile ducts)	Autosomal dominant	*APC* gene. *MUTYH* mutation (MUTYH-associated polyposis)	[13, 14]
Hereditary nonpolyposis colon cancer	Over the age of 50 yr	GC. CRC	Autosomal dominant	*hMLH1* and *hMSH2* genes. Instability of repeat nucleotide sequences or (microsatellites instability)	[15, 17]
Lynch syndrome	Diagnosed at the age of 50-60 yr	GC. CRC. Others [endometrial cancer (54%)]. Ovarian cancer. Also, cancer of the pancreas, brain, kidney, and bile duct	Autosomal dominant	*MMR* genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*)	[18, 19]
Peutz-Jeghers syndrome	At their 20s	CRC. Pancreatic, and gastric cancers. Others: Uterine, breast, ovarian, and lung	Autosomal dominant	*STK11*	[25, 27]
Juvenile polyposis syndrome	In childhood but can occur at any age	Multiple hamartomas in the gastrointestinal tract. CRC. Duodenal, gastric, pancreatic cancers	Autosomal dominant in 75% and sporadic in 25%	*SMAD4* gene (*MADH4* gene) and the *BMPR1A* gene	[29-32]
PTEN hamartoma tumour syndrome and Cowden syndrome and others	Cancers are usually diagnosed at the age of 30-50 yr	Multiple hamartomas in the gastrointestinal tract. CRC. Breast, thyroid, kidney, endometrium, and gastric cancer (not common)	Autosomal dominant	*PTEN* germline mutations	[35]

GC: Gastric cancer; CRC: Colorectal cancer; STK11: Serine/threonine-protein kinase 11; APC: Adenomatous polyposis.

DISCUSSION AND CLINICAL IMPLICATIONS

Firstly, a genetic evaluation for HDGC is indicated for families having individuals with: (1) Two or more cases of diffuse GC, with at least one diagnosed before the age of 50 years; (2) Three or more cases of documented diffuse cancer in first- or second-degree relatives; (3) Diffuse GC diagnosed before the age of 40 years; and (4) A family history of diffuse GC and lobular breast cancer with one diagnosed before the age of 50 years[40]. Genetic testing of individuals who fulfil HDGC clinical criteria should include analysis of *CDH1* mutations. The identification of a mutation in a family should trigger further actions, including testing all family members at risk at the age of 16[41]. Prophylactic gastrectomy in a mutation-positive patient is recommended in managing HDGC[40]. It is recommended that gastrectomy be offered by a multi-disciplinary team in a centre specialized in managing such conditions[42].

Secondly, patients who have a history of more than ten cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations should undergo assessment for the adenomatous polyposis syndromes. The genetic testing of suspected patients includes *APC* and *MUTYH* gene mutation analysis[43] (Table 1). FAP patients usually present with multiple gastric polyps, both fundic gland and adenomatous types on histology. Fundic gland polyps occur in almost 90% of patients with FAP, and around half may be dysplastic[13]. However, progression to high-grade dysplasia or adenocarcinoma was reported to be low in these polyps[44]. Management should be based on individual assessment, including colonoscopic findings, rather than on the site of mutation only[43].

Thirdly, all newly diagnosed CRCs should be evaluated for MMR deficiency. Analysis may include immunohistochemical testing and testing for microsatellite instability (Table 1). Tumours that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation. Individuals who have a personal history of a tumour showing evidence of MMR deficiency, a known family mutation associated with LS should undergo genetic evaluation for LS[45] (Table 1). Colonoscopic surveillance is recommended every 1-2 years. The recommended management of patients with confirmed LS is colectomy with ileorectal anastomosis. Segmental colectomy may be considered unsuitable for total colectomy with postoperative surveillance in patients[45].

Screening and treatment of *H. pylori* infection is recommended in LS patients to decrease the risk of GC[16]. A study from the Netherlands reported *H. Pylori* screening outcomes in 184 patients with LS mutation carriers; they found *H. Pylori* prevalence was similar to the general population in carriers and patients with a first-degree relative with GC[46]. Current ACG recommendations suggest performing a baseline upper endoscopy by age 30-35 and gastric biopsy in patients with or at risk for LS. Surveillance may be considered every 3-5 years in LS patients with a family history of gastric or duodenal cancer, although there is little supportive evidence[45]. Currently, there are no guidelines on gastric

mapping biopsies for evaluating GC or pre-malignant changes in these patients.

Fourthly, individuals suspected to have PJS or have a family history of the syndrome should undergo a genetic evaluation, including testing for *STK11* mutations[47]. Individuals with five or more colorectal juvenile polyps or any juvenile polyps in the gastrointestinal tract should undergo further evaluation for JPS. The genetic testing should include testing for *SMAD4* and *BMPR1A* mutations[48]. Individuals with multiple gastrointestinal hamartomas should be further evaluated for CS and related conditions by geniting testing[49] (Table 1).

CONCLUSION

Assessment of synchronous and metachronous dual colorectal and GC should not just aim at surgical treatment. Still, it should aim at the further assessment of these patients to detect if they are part of familial cancer syndromes and at a higher risk of developing gastrointestinal and non-gastrointestinal cancers. The advances in molecular medicine and genomics, routine registration of cases in most countries' familial cancer registries, progressive research in the field, and clinical guidelines have added evidence-based criteria and recommendations for managing these patients as well as the discovery of multiple genes in which germline mutations predispose to syndrome-associated neoplastic manifestations. This editorial focuses on the most characterized gastrointestinal cancer susceptibility syndromes, including HDGC, FAP, HNPCC, LS, and three major hamartomatous polyposis syndromes associated with CRC and GC, namely PJS, JPS, and PTHS. I discussed each of these. Syndromes regarding inheritance, risk of gastric and colorectal or other cancer development, genetic mutations and recommended genetic investigations. In this issue, Lin *et al*[50], in an elegant study, present three crucial findings that add value to our clinical practice and understanding of this area. First, the authors found that most second primary cancers in participating patients were observed within five years, suggesting that patients and family members' surveillance for metachronous cancer is necessary as part of postoperative care. Second, the authors found that patients with metachronous cancers had a better prognosis than those with synchronous cancers. However, the authors did not explain the possible mechanisms underlying such phenomena. Finally, the authors concluded that the prognosis appears to be influenced by the stage of GC rather than the stage of CRC. Therefore, the management strategy for synchronous cancers is worth further exploration and studies. While the work by Lin *et al*[50] focuses on the characteristics of dual gastric and CRC regarding relationship patterns (synchronous versus metachronous) and prognosis, this area should be further studied with a focus on related inherited syndromes and molecular and genetic pathological changes involved and their roles in adding a new feature to synchronous and metachronous dual gastric and CRCs.

FOOTNOTES

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Country/Territory of origin: Saudi Arabia

ORCID number: Samy A Azer 0000-0001-5638-3256.

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