

# Prophylactic total gastrectomy for individuals with germline *CDH1* mutation

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**Background.** Germline mutation of the *CDH1* gene, which encodes for the E-cadherin adhesion protein, is rare but confers an estimated lifetime risk of hereditary diffuse gastric cancer of 87%. Fewer than 100 prophylactic total gastrectomies have been reported for this condition.

**Methods.** Patients with germline *CDH1* mutation who underwent multidisciplinary counseling followed by prophylactic total gastrectomy were reviewed.

**Results.** Ten patients (6 male, 4 female) with a median age of 42 years (range, 26–51) underwent prophylactic total gastrectomy between 2006 and 2009. Of the 6 families represented, there were 4 missense, 1 frameshift, and 1 splice site mutation. Median time from genetic testing to surgery was 3 months (range, 1–7). All patients had an upper endoscopy before surgery, identifying only 1 patient with a focus of diffuse gastric cancer. After prophylactic total gastrectomy, extensive pathologic analysis demonstrated that 9 patients had up to 77 foci of noninvasive cancer, and 2 of these patients had 4–12 foci of T1 invasive cancer. Median operative time was 213 minutes; there were no anastomotic leaks, and the length of stay was 7–8 days. One patient had a complication within 30 days (pulmonary embolism), and 3 patients had late complications (2 small bowel obstructions and 1 anastomotic stricture). Median weight loss at 6 months was 19%.

**Conclusion.** The majority of patients with germline *CDH1* mutation have foci of noninvasive or invasive gastric cancer by middle age. Serial upper endoscopies provide inadequate screening. Prophylactic total gastrectomy is the procedure of choice for definitive treatment. (*Surgery* 2011;149:347-55.)

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WORLDWIDE, THERE are approximately 930,000 new cases of gastric cancer per year leading to >700,000 deaths, thus making gastric cancer the second highest cause of cancer death.<sup>1</sup> It is estimated that 90% of gastric cancer cases arise in the sporadic setting, whereas familial clustering is observed in the remaining 10%.<sup>2</sup> Early onset familial gastric cancer was first described in 3 families of Maori descent from New Zealand in 1964.<sup>3</sup> In 1998, Guilford et al<sup>4</sup> carried out a genetic linkage analysis with microsatellite markers in a large Maori kindred and found significant linkage to

markers flanking the gene for E-cadherin, *CDH1*. This group subsequently identified germline mutations in the *CDH1* gene associated with familial gastric cancer. Inactivating *CDH1* germline mutations have subsequently been identified in diffuse gastric cancer families from multiple different countries.<sup>5-7</sup>

The International Gastric Cancer Linkage Consortium (IGCLC) defined hereditary diffuse gastric cancer (HDGC) as an autosomal-dominant cancer susceptibility syndrome characterized by the following criteria: (1)  $\geq 2$  documented cases of diffuse GC in first- or second-degree relatives, with  $\geq 1$  diagnosed before age 50; or (2)  $\geq 3$  cases of diffuse GC in first- or second-degree relatives, independent of age of onset.<sup>8</sup> It is estimated based on limited data that up to 25% of families that fit the IGCLC criteria will have germline *CDH1* mutations.<sup>9</sup> The lifetime penetrance of diffuse GC in patients who carry *CDH1* mutation is estimated overall at 40–67% for men and 63–87% for women.<sup>7,10</sup>

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Of the 2 Lauren histologic types of GC, HDGC is characterized by the diffuse type (rather than the intestinal type) exclusively. Pathologic evaluation of gastrectomy specimens in HDGC patients have been characterized by multiple small infiltrates of signet ring cell carcinoma that underlie normal-appearing mucosa.<sup>11-14</sup> This characteristic makes traditional white-light endoscopy with random biopsies an unreliable screening modality in this high-risk patient population.

Prophylactic total gastrectomy eliminates the high risk of developing diffuse gastric cancer in patients with germline *CDH1* mutations. Given the rarity of this germline mutation and the magnitude of the surgery, there have been <100 reported cases of prophylactic total gastrectomy in the English literature.<sup>15</sup> Not all these studies examined the entire mucosa of the surgical specimen microscopically or reported on the degree of weight loss after surgery. Herein we report our single institutional experience with 10 *CDH1* mutation carriers undergoing prophylactic total gastrectomy by 1 surgeon after multidisciplinary counseling at a tertiary referral center.

## METHODS

**Patients.** All patients with germline *CDH1* mutations who were referred to our institution for prophylactic total gastrectomy between April 2006 and March 2009 are included in this report. Patients were evaluated preoperatively by a multidisciplinary team that included a genetic counselor, gastroenterologist, surgical oncologist, and nutritionist. A complete history and physical examination were performed, *CDH1* mutation testing records were obtained, and prior endoscopy reports and other relevant diagnostic studies were reviewed. Patient information was entered into a prospective database and included demographics, preoperative body mass index, detailed family history of gastric and breast cancer, preoperative clinical investigations, operative details, pathologic assessment, length of stay, and complications ( $\leq 30$  and  $>30$  days).

**Prophylactic total gastrectomy.** Prophylactic total gastrectomy was performed via an upper midline incision. To ensure complete removal of all gastric mucosa at risk for malignant transformation, the proximal gastric division was performed  $\geq 1$  cm above the squamocolumnar junction and the distal division across the duodenum was performed  $\geq 1$  cm beyond the pylorus. The total gastrectomy specimen was sent intraoperatively for frozen section evaluation of the proximal and distal margins to confirm resection of all gastric

mucosa. A formal lymph node dissection was not performed, but total gastrectomy generally incorporated perigastric lymph node stations 1-6.<sup>16-19</sup> Reconstruction was performed with a Roux-en-Y esophagojejunostomy with an anastomosis between the end of the esophagus and the side of the jejunum. This anastomosis was hand-sewn in 2 layers as previously described.<sup>20</sup> The retrocolic Roux limb was made 50-60 cm in length to prevent bile reflux. The jejunojunctionostomy was hand-sewn or stapled in a side-to-side fashion.

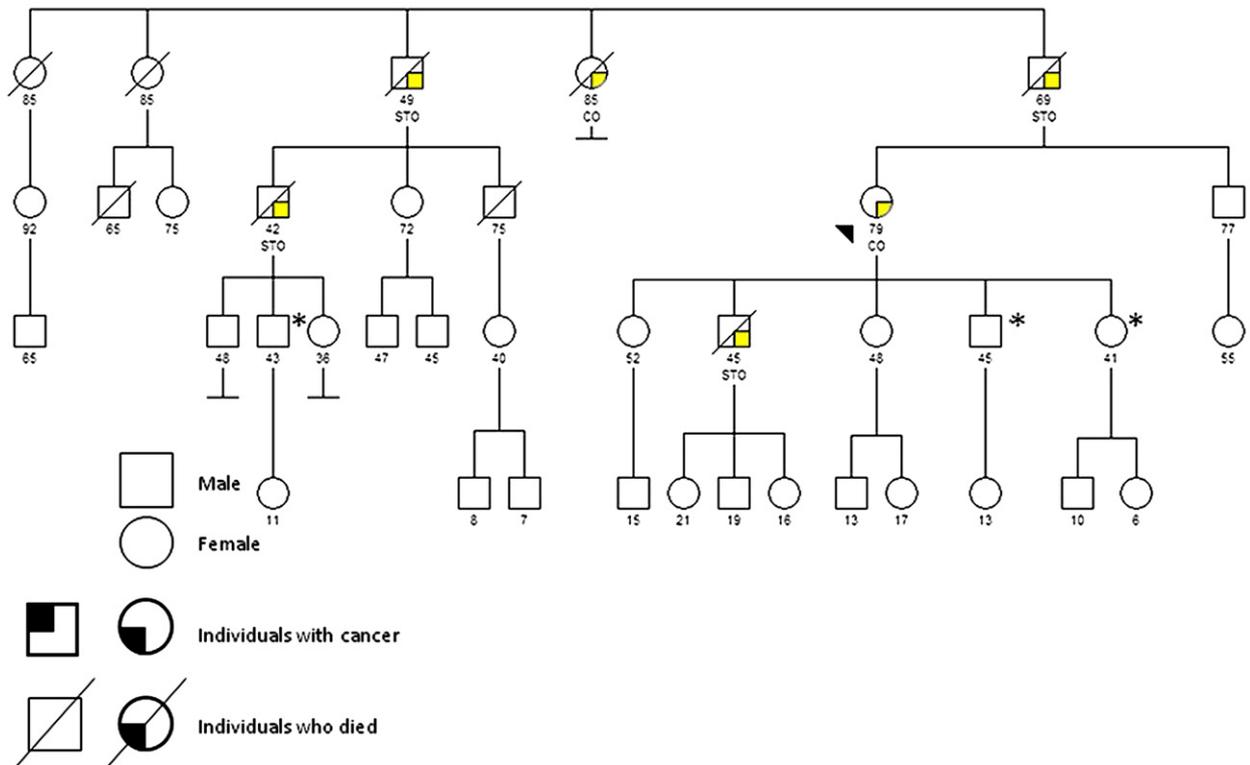
For pathologic analysis, the entire stomach was fixed in formaldehyde, and the entire mucosa was mapped and examined microscopically. This required a median of 340 sections and up to 470 sections. Noninvasive cancer refers to carcinoma in situ or intraepithelial tumor without invasion of the lamina propria. T1 tumor refers to tumor invading the lamina propria, muscularis mucosae, or submucosa.

**Follow-up.** All patients were started postoperatively on a daily multivitamin with ferrous sulfate. Monthly vitamin B<sub>12</sub> injections were also given to counter the loss of intrinsic factor production. All patients were followed every 3 months for  $\geq 12$  months. At each visit, patients had their weight recorded. A complete blood count, chemistry panel, vitamin B<sub>12</sub> level, vitamin D, and iron studies were obtained at 3-6 months and as indicated.

## RESULTS

Ten patients (6 male, 4 female) from 6 different families with known *CDH1* mutation were referred to our institution for surgical evaluation from April 2006 to March 2009. There were 6 males and 4 females. The median age was 42 years (range, 27-51).

All 6 families had a strong family history of GC and 5 of 6 families met IGCLC criteria.<sup>8</sup> The first patient to undergo prophylactic total gastrectomy for germline *CDH1* mutation at our institution has been previously described.<sup>21</sup> Figure 1 demonstrates the pedigree of a *CDH1* kindred (permission granted) of which 3 members underwent prophylactic total gastrectomy for germline *CDH1* mutation at our institution. Two of these individuals were siblings whose brother had recently died of diffuse signet cell cancer of the stomach at the age of 45. Shortly thereafter, their mother was diagnosed with signet cell carcinoma of the cecum and subsequently she underwent genetic testing for the E-cadherin (*CDH1*) gene. She tested positive for the 48+1 G→A splice site mutation. These 2 patients then underwent testing, which confirmed they harbored the same mutation. Both patients then underwent upper and lower endoscopies, which were unremarkable, followed by



**Fig 1.** Pedigree of *CDH1* kindred. The *arrowhead* represents presenting proband. Individuals with asterisks have had prophylactic total gastrectomies at Massachusetts General Hospital. The number beneath the circle/square is age at death or current age. *CO*, Signet cell colon cancer; *STO*, diffuse gastric cancer. Pedigree has been anonymized. (Color version of figure is available online.)

prophylactic total gastrectomy on the same day. Final pathologic analysis of their gastrectomy specimens revealed 5 and 1 foci of noninvasive cancer, respectively, and no invasive foci of cancer. One additional member of this kindred underwent prophylactic total gastrectomy and had 12 invasive foci of cancer on final analysis.

Table I summarizes the mutation status and family history of all 10 patients. These 10 patients were from 6 families. Missense mutations were seen in 4 families, splice site mutation in 1 family, and frameshift mutation in 1 family. The missense mutations included an arginine to glutamine substitution at codon 732, a cysteine to threonine substitution at codon 1901, a cysteine to threonine substitution at codon 1003, and a mutation in the start codon from “ATG” to “ATA”. The splice site mutation was a change from G to A at the +1 position of intron 1. This genetic alteration affects the canonical donor splice site of intron 1 and is predicted to eliminate the normal donor splice site. The frameshift mutation was an insertion of an adenine insertion at codon 1682.

All patients in our series had an upper endoscopy before the prophylactic operation. Only

1 patient was found to have a focus of intramucosal diffuse gastric cancer. Three patients had evidence of either reflux esophagitis or gastritis on endoscopy. Preoperative computed tomography was unremarkable in 5 patients.

All patients underwent prophylactic total gastrectomy by a single surgeon. The median time from genetic testing to operative intervention was 3 months (Table II). The mean operative time was 213 minutes (range, 187–308). No patient required a blood transfusion. Contrast study of the esophagojejunal anastomosis performed 5 days after surgery revealed no anastomotic leaks. The length of stay was 7 or 8 days for all patients. There was 1 complication within 30 days of surgery. One patient had a pulmonary embolism 2 days after discharge (postoperative day 9) and required readmission for anticoagulation. Three patients suffered late complications (>30 days postoperatively). Two years after prophylactic total gastrectomy, patient 1 presented to the emergency department with significant abdominal pain and bilious emesis. Imaging was suspicious for small bowel intussusception at the jejunojunction. Exploratory laparotomy confirmed a jejunojunctional

**Table I.** CDH1 mutation status and family history

Patient	Age	CDH1 mutation	Gender	Family history	
				Gastric cancer	Breast cancer
1	42	R732Q*	F	Grandfather, mother, aunt	Positive
2	44	1682 ins A†	M	Brother, sister, cousin	Negative
3	46	A634V‡	M	Grandmother, brother	Positive
4	45	IVS1 +1 G→A	M	Grandfather, great aunt, uncle Brother, cousin	Negative
5	41	IVS1+1 G→A	F	Same as patient 4	Negative
6	43	IVS1+1 G→A	M	Grandfather, father	Positive
7	52	1003C→TT§	F	Mother, brother	Negative
8	50	1003C→T	M	Mother, brother	Negative
9	27	1003C→T	M	Grandmother, father	Negative
10	27	3G→A¶	F	Grandmother, mother, great aunt	Positive

\*Missense mutation at amino acid 732 causing arginine to glutamine.

†Frameshift mutation at base pair 1682 with insertion of A.

‡Missense mutation at amino acid 634 causing alanine to valine.

||Splice site mutation from at +1 position of intron 1 with G substituting A.

§Nonsense mutation at base pair 1003 resulting in stop codon.

¶Missense mutation at bp 3 with A substituting G.

**Table II.** Prophylactic total gastrectomy

Patient	Interval from CDH1 testing to surgery (mo)	Operative time (min)	LOS (d)	Morbidity	
				≤30 days	>30 days
1	3	257	8		Intussusception
2	1	213	8		
3	3	308	7		
4	2	200	7		SBO
5	2	187	7		
6	2	245	7	PE	
7	4	199	8		
8	7	204	7		
9	5	263	7		Anastamotic stricture
10	6	263	7		

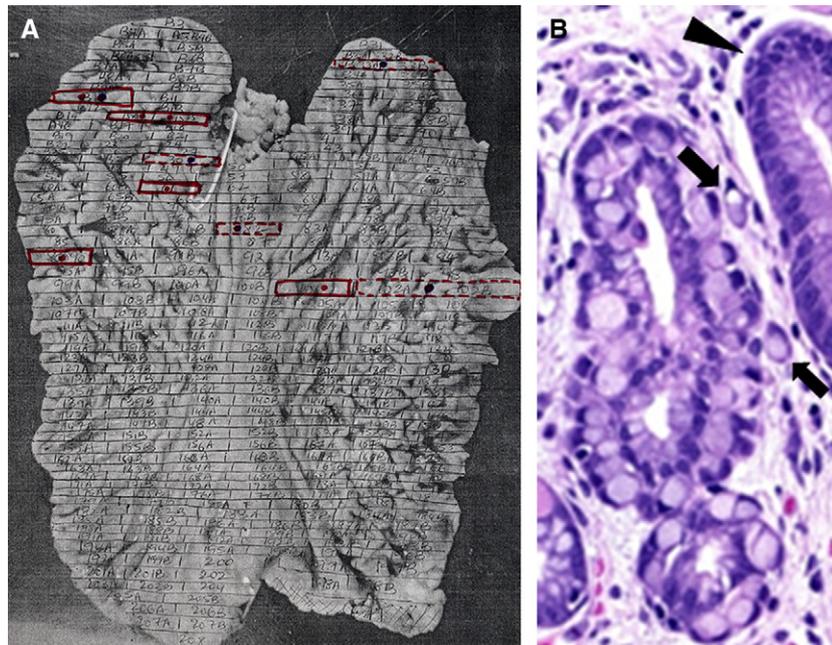
LOS, Length of stay; PE, pulmonary embolism; SBO, small bowel obstruction.

intussusception that required resection. She was subsequently discharged without further complication. Eight months after prophylactic total gastrectomy, patient 4 presented with vague abdominal pain with imaging consistent with a partial small bowel obstruction. He was admitted and managed nonoperatively, improved within 48 hours, and was discharged with no subsequent issues. Five months after prophylactic total gastrectomy, patient 9 had significant dysphagia and barium swallow demonstrated a stricture at the esophagojejunal anastomosis. He underwent upper endoscopy and dilation, and the dysphagia was completely resolved at the time of the last follow-up.

Complete gross and microscopic pathologic evaluation was performed on all gastrectomy specimens. The median number of pathologic sections per specimen was 340 and the highest number of

sections examined in 1 specimen was 470. Up to 77 foci of noninvasive cancer were found in 9 of 10 patients, and 4–12 foci of T1 early invasive cancer were found in 2 patients. Thus, only 1 patient had no evidence of diffuse gastric cancer. Although no formal lymph node dissection was performed, station 1–6 nodes were routinely removed as part of the gastrectomy specimen, and on average 12 lymph nodes were examined per specimen (range, 6–18). There were no lymph nodes with metastatic disease. Figure 2 demonstrates a representative total sectioning of 1 gastrectomy specimen and histologic foci of intramucosal carcinoma.

Patients were followed for ≥1 year after prophylactic total gastrectomy. The median preoperative weight in our cohort was 180 lbs (range, 133–236). At the 6-month follow-up, the median postoperative weight was 146 lbs (range, 116–190),



**Fig 2.** (A) Gross specimen from prophylactic total gastrectomy demonstrating division of entire gastric mucosa into 340 sections. Sections with *solid red outline* indicate areas where intramucosal carcinoma was identified, and sections with *dotted red outline* indicate areas where carcinoma in situ was identified. (B) High-power view of section from prophylactic total gastrectomy specimen demonstrating normal gastric mucosa (*arrowheads*) and foci of intramucosal carcinoma (*arrows*), characterized by signet ring cells that lost their attachment to the gastric unit and invade the surrounding lamina propria. (Color version of figure is available online.)

and the median percentage weight loss was 19% (range, 5–41%). The patient who lost 41% of her baseline weight was obese before surgery, with a preoperative body mass index of 43.2. All patients were started postoperatively on a multivitamin with ferrous sulfate daily and monthly vitamin B<sub>12</sub> injections. No patient developed iron or vitamin B<sub>12</sub> deficiency.

## DISCUSSION

There are few series on prophylactic total gastrectomy for germline *CDH1* mutation given the rarity of this mutation and the magnitude of the surgery. In this article, we have described our results in 10 patients with germline *CDH1* mutation who underwent prophylactic total gastrectomy. All 10 patients had a strong family history of gastric cancer.<sup>8</sup> Preoperative endoscopy identified a focus of diffuse gastric cancer in only 1 patient. Similar to prior series, pathologic analysis of gastrectomy specimens identified up to 77 foci of noninvasive and up to 12 foci of T1 invasive diffuse gastric cancer in 9 of 10 patients. The immediate postoperative course was generally unremarkable with all patients being discharged after 7 or 8 days. Four patients experienced postoperative complications, including 1 pulmonary embolism, 2 small bowel

obstructions, and 1 anastomotic stricture. Six months after total gastrectomy, the median weight loss was 19%.

Patients with germline *CDH1* mutation have a lifetime risk of developing HDGC of up to 87%.<sup>7,10</sup> A significant challenge in managing patients with *CDH1* mutations is the inadequacy of current screening or surveillance techniques. Nearly all patients who have undergone prophylactic total gastrectomy in previously reported series have had preoperative endoscopy, and <7% of these were able to identify foci of diffuse gastric cancer, yet >90% of gastrectomy specimens had foci of diffuse gastric cancer.<sup>15</sup> Early foci of diffuse gastric cancer in HDGC patients is characterized by multiple infiltrates of signet ring cell carcinoma that underlie normal-appearing mucosa.<sup>22</sup> In our series, preoperative endoscopy successfully identified a focus of diffuse gastric cancer in 1 patient in our study, and this patient ultimately had 76 foci of intramucosal cancer on analysis of his gastrectomy specimen.

Enhanced endoscopic techniques may increase the detection of early gastric cancer lesions. Chromoendoscopy involves using a combination of 0.05% methylene blue solution and 0.3% Congo red solution that is sprayed over the entire surface

of the gastric mucosa to selectively visualize undifferentiated carcinoma from normal acid-secreting gastric mucosa.<sup>23</sup> Shaw et al<sup>24</sup> performed both routine upper endoscopy and chromoendoscopy using the Congo red/methylene blue technique on 33 members of the original HDGC kindred and demonstrated improved detection of early gastric cancer. All 33 patients underwent a total of 99 surveillance endoscopies. Routine upper endoscopy detected 2 macroscopically visible lesions that were confirmed to be signet ring cancer on pathologic analysis. Chromoendoscopy identified 56 pale lesions, 23 (41%) of which were proven foci of gastric cancer upon biopsy. More recently, Barber et al<sup>25</sup> suggested that endoscopic detection of microscopic foci of signet ring cells is possible when multiple biopsies (>20) are performed. This group also emphasized that, although adjunctive techniques such as chromoendoscopy may increase the detection of small lesions, concerns over embryotoxicity and carcinogenic potential have recently resulted in Congo red and methylene blue being withdrawn from clinical use.

In 2001, 2 surgical series of 5 patients each were the first to describe prophylactic total gastrectomy for individuals with germline E-cadherin mutations.<sup>11,13</sup> All 10 of these patients had foci of diffuse gastric cancer upon analysis of the surgical specimen. Table III summarizes these 2 surgical series and 4 other series published since that time. In total, there have been roughly 93 patients with *CDH1* mutation who have undergone prophylactic total gastrectomy and for whom results have been reported.<sup>15</sup> Although the majority of patients had normal upper endoscopies before surgery, 86 of 93 patients (93%) had intramucosal or superficially invasive carcinoma identified in the gastrectomy specimen and 42 of 52 patients (81%) had multifocal disease. In our series, the pathologic analysis of gastrectomy specimens demonstrated noninvasive foci of cancer in 9 of 10 patients and invasive T1 gastric cancer was found in 2 patients.

Reconstruction after total gastrectomy is generally performed with a Roux-en-Y reconstruction with at least a 50-cm Roux limb to prevent bile reflux.<sup>26</sup> Some authors have advocated the creation of a jejunal pouch. At least 15 randomized trials have investigated this issue, and there may be a small benefit of jejunal pouches in terms of early food intake, which diminishes over time. In the largest prospective trial to date, Fein et al randomized 138 patients to Roux-en-Y reconstruction with or without a 15 cm pouch and followed patients for a median of 3.6 years.<sup>27</sup> There were no differences in short- or long-term weight loss. Quality of life was

equivalent in the first year, but was improved in the pouch group in the third, fourth, and fifth years.

Operative morbidity and mortality is likely to be significantly lower for prophylactic total gastrectomy than for gastrectomy performed for invasive cancer. The *CDH1* mutation patient population is generally younger and healthier, and the operation does not require any formal lymphadenectomy, which can increase complications.<sup>18</sup> Mortality after gastrectomy performed for gastric cancer ranges from <1% at specialized, high-volume centers to 7% in small, nontertiary care facilities.<sup>28,29</sup> Previously reported series have shown that prophylactic total gastrectomy in *CDH1* mutation carriers can be performed without mortality, but significant morbidity still exists. The largest surgical series comes from Newfoundland, Canada, where 23 patients underwent prophylactic total gastrectomy (Table III). Operative complications in this series included 3 patients with venous thromboembolism, 2 anastomotic leaks, and 1 intraabdominal abscess.<sup>30</sup> One patient was hospitalized for 107 days. Thus, even at a center with significant experience, there can be significant complications from this type of prophylactic surgery. In our series, only 1 patient had a complication within 30 days of surgery (pulmonary embolism), but there were 3 late complications (2 small bowel obstructions and 1 anastomotic stricture).

There are clear nutritional consequences after total gastrectomy. Nearly all patients lose weight, which nadirs after 3–6 months and averages about 25% of preoperative weight.<sup>31</sup> Postoperative issues such as early dumping syndrome (secondary to hyperosmotic carbohydrate loads) and diarrhea (secondary to rapid transit or malnutrition) occur in 20–30% of patients, and can be severe immediately after surgery but tend to improve over time.<sup>32,33</sup> Patients can also experience lactose intolerance; bacterial overgrowth resulting in malabsorption and bloating can also occur. All patients generally report some dumping and diarrhea, which seem to resolve by 6 months with appropriate nutritional counseling and diet modification. Patients are initially instructed to eat small amounts continuously over the course of the day, and after several months can reach a point of eating 3 small to moderate meals per day with snacks in between. Total gastrectomy results in loss of intrinsic factor secretion, significantly impairing vitamin B<sub>12</sub> absorption, and predisposes to iron malabsorption and deficiency. Additionally, vitamin D and calcium absorption are also diminished. Decreased intestinal transit time is thought to cause some degree

**Table III.** Surgical series of prophylactic gastrectomy for *CDHI* mutations

Author	No. of families/ patients	Age (yrs)	Preoperative endoscopy	Pathology	Complications	LOS
Huntsman et al <sup>11</sup>	2/5	22–40	4/5 negative within 15 mos	Superficial carcinoma ( <i>n</i> = 5); multifocal ( <i>n</i> = 3)	NR	NR
Chun et al <sup>13</sup>	1/5	37–47	5 negative within 3 yrs	Intramucosal carcinoma ( <i>n</i> = 5); multifocal ( <i>n</i> = 3)	None	POD 6–9
Lewis et al <sup>12</sup>	2/6	22–40	NR	Superficial carcinoma ( <i>n</i> = 5); multifocal ( <i>n</i> = 4)	Septic phlebitis ( <i>n</i> = 1); anastomotic stricture ( <i>n</i> = 1)	Mean POD 7
Suriano et al <sup>37</sup>	1/6	NR	5 negative within 6 mos	Carcinoma (depth NR; <i>n</i> = 5); multifocal ( <i>n</i> = 5)	NR	NR
Hebbard et al <sup>30</sup>	3/23	26–43	21/23 negative	Intramucosal carcinoma ( <i>n</i> = 22)	Venous thromboembolism ( <i>n</i> = 3); anastomotic leaks ( <i>n</i> = 2); abscess ( <i>n</i> = 1)	POD 9–107 (median <i>n</i> , 11)
Present series	6/10	26–51	9/10 negative within 6 mos	Noninvasive carcinoma ( <i>n</i> = 9); early invasive carcinoma ( <i>n</i> = 2); multifocal ( <i>n</i> = 8)	Pulmonary embolism ( <i>n</i> = 1); SBO ( <i>n</i> = 2); anastomotic stricture ( <i>n</i> = 1)	POD 7–8

NR, Not reported; POD, postoperative day; SBO, small bowel obstruction.

of fat malabsorption, contributing to vitamin A, D, E, and K deficiencies. Patients should receive an intramuscular injection of vitamin B<sub>12</sub> monthly along with an oral multivitamin with ferrous sulfate daily. There is a minority of patients who have significant difficulty in maintaining an adequate nutritional status after total gastrectomy, and thus regular follow-up visits with the surgeon and nutritionist are essential.<sup>34</sup>

Women with *CDHI* germline mutations have been shown to have an increased frequency of breast cancer, predominantly of the lobular type.<sup>35</sup> In an analysis of 11 HDGC families, Pharoah et al<sup>36</sup> found 7 cases of breast cancer and estimated that the risk of breast cancer in carrier women was 39% (95% confidence interval, 12–84%) by the age of 80 years. These numbers should be cautiously

interpreted owing to the relatively small number of patients found to have breast cancer in this analysis. Of the 45 HDGC kindred identified, 18 kindreds include a history of ≥1 case of breast cancer (total of 32 cases). Breast cancer histotype has been confirmed in only 9 of these cases, 7 of which have been lobular carcinoma. This represents a much higher proportion than would be expected in the normal population, in which <10% of sporadic breast cancer is the lobular type. Although the association between HDGC and lobular breast cancer is not concrete, it does suggest that there is a role for increased screening in this population. Unfortunately, patient screening in this setting may be limited by the fact that invasive lobular carcinoma frequently is missed by mammographic surveillance. These lesions are more readily seen

with MRI (75). In *CDH1* afflicted pedigrees, prophylactic bilateral mastectomy, risk reduction strategies using tamoxifen, or surveillance every 6 months with MRI alternating with breast ultrasonography, may be reasonable approaches.

Given that we are early in the experience regarding prophylactic total gastrectomy for germline *CDH1* mutation, there remain many unresolved issues. First, the timing of prophylactic operative interventions remains unclear. The earliest reported case of a germline E-cadherin mutation carrier developing gastric cancer is 14 years old, and the median age in developing clinically apparent gastric cancer is around 40 years old.<sup>3</sup> Clinically, GC tends to develop at an earlier age in patients with HDGC.<sup>7,37</sup> Pharoah et al<sup>36</sup> estimated the cumulative risk of diffuse GC by age 80 at 67% in men and 83% in women based on a cohort of 476 individuals carrying the *CDH1* germline mutation. They also estimated a <1% risk of GC in children <20 years old, increasing to 4% by the age of 30, and a 21% risk for men and 46% for women by age 50. Second, given a total gastrectomy is not an insignificant undertaking, a more accurate ability to estimate risk in relation to specific mutations may improve patient selection for prophylactic operative intervention and reduce the morbidity associated with gastrectomy in the individuals who will not ultimately develop gastric cancer. Third, there may be selection bias in the current predictions of risk. It is possible that the families with mutations that are more likely to result in the development of diffuse gastric cancer have been identified earlier and risk calculations are based on these families. Subsequent families with lower risk mutations and thus a less pronounced family history may be identified in the future, but such families will be given risk estimates based on the earlier high-risk families. Fourth, it is unknown whether individuals who fit the clinical criteria for HDGC and do not have a *Cdh1* mutation would benefit from prophylactic total gastrectomy. Currently, prophylactic total gastrectomy is not generally recommended for these individuals. Fourth, laparoscopic or laparoscopy-assisted total gastrectomy has been described for other benign and malignant gastric diseases by a number of groups with reductions in postoperative ileus and recovery time compared with open operations.<sup>38-40</sup> Given that no formal lymph node dissection is required, minimally invasive prophylactic total gastrectomy for patients with germline *CDH1* mutations is likely a reasonable option for those highly experienced with this technique.

In conclusion, prophylactic total gastrectomy is the definitive treatment for patients harboring

germline *CDH1* mutations to eliminate the risk of developing HDGC. Screening endoscopies are currently inadequate in detecting early invasive cancers. Candidates should undergo extensive counseling and evaluation by a multidisciplinary team, including a genetic counselor, gastroenterologist, surgical oncologist, and nutritionist before surgery. Over 90% of gastrectomy specimens in these patients will have  $\geq 1$  foci of diffuse gastric cancer. Prophylactic total gastrectomy entails significant risks of complications, and thus the procedure should be performed by experienced surgeons. Patients lose about 20% of their body weight, but the majority adapt well to life without a stomach over the course of 6–12 months. Further research is needed to stratify risk for specific mutations, determine the optimal timing of the operation, and develop better screening methods.

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