


## Gastric cancer in FAP: a concerning rise in incidence

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**Abstract** The highest cancer risks in familial adenomatous polyposis (FAP) include colorectal, duodenal, and thyroid for which surveillance is recommended. Nearly all patients with FAP have gastric fundic gland polypsis (FGP), but gastric cancers are rarely reported with a similar incidence as the general population. We describe a recent, sudden increase in the incidence of gastric cancer in FAP. Seven of the ten cases were diagnosed in the last 20 months. Comparing our population to the SEER database for gastric cancer, the standardized incidence ratio is 140. All cases arose in patients with a carpeting of FGP and associated with large mounds of proximal gastric polyps. Nearly all patients were under upper endoscopic surveillance. This is a concerning observation and reflects a change in the phenotypic presentation of FAP in Western patients.

**Keywords** Familial adenomatous polyposis · Gastric cancer · Endoscopic surveillance · Screening

### Introduction

The hereditary colorectal cancer syndrome familial adenomatous polyposis (FAP) is caused by a germline mutation in the adenomatous polyposis coli (*APC*) gene. The leading causes of cancer in FAP patients are colorectal, duodenal, and thyroid [1, 2]. Numerous guidelines have established surveillance recommendations for prevention of these FAP related cancers [3–5].

Gastric cancer is not cited as a health risk in Western FAP patients with a reported lifetime risk of 0.6%, similar to the general population risk [6]. Gastric polyps are commonly noted on surveillance upper endoscopy recommended for duodenal polyposis. The most commonly observed lesions are fundic gland polyps (FGP). Bianchi et al. demonstrated FGP in 88% of FAP patients with low grade foveolar dysplasia seen in 38% and high grade foveolar dysplasia in 3%. Factors associated with the finding of foveolar dysplasia include FGP size, duodenal polyposis stage, antral gastritis, and lack of acid-suppressive therapy [7].

We report the sudden rise in the incidence of gastric cancer in FAP patients enrolled in a hereditary colon cancer registry and the associated demographic, endoscopic and histologic features in these patients.

### Methods

767 patients with the clinical diagnosis or genotype of familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (aFAP) who have had at least one esophagogastroduodenoscopy were accessed through the IRB approved Cologene™ database of the David G. Jagelman Inherited Colorectal Cancer Registries in the

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Sanford R. Weiss, M.D., Center for Hereditary Colorectal Neoplasia. Patients with gastric cancer were identified through the investigator and query of the Cologene™ database. From time of registration to time of diagnosis, all endoscopic surveillance procedures including EGD, endoscopic ultrasound, endoscopic mucosal resection, and endoscopic submucosal dissection were reviewed. Information extracted included polyp morphology, location, sizes, and histology. The follow-up period extended from either time of diagnosis to death or time of diagnosis to November, 2016.

For statistics, continuous data were described as mean with and range as appropriate. Categorical data were described as raw numbers and percentages or proportions. The standardized incidence ratio (SIR) was calculated as the ratio of observed gastric cancer cases to the expected number of cases estimated using the SEER database of gastric cancer.

## Results

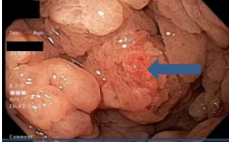

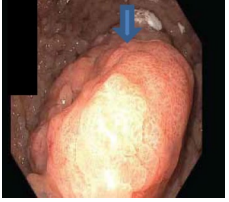
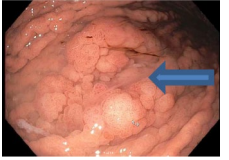
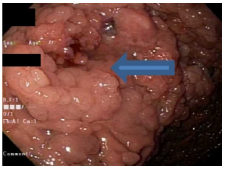
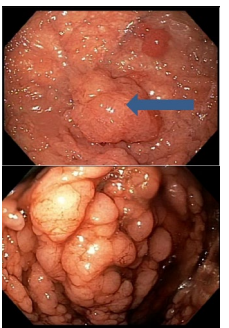
Medical records of 767 FAP patients who underwent one or more upper endoscopies between January 2001 and November 2016 were reviewed. Since the inception of the registry in 1979, no case of gastric adenocarcinoma was seen until 2006. Nine more cases were diagnosed between 2012 and 2016 for a total of 10/767 (1.3%) cases resulting in a standardized incidence ratio of 140. All cases arose in patients with a carpeting of fundic gland polyposis and polypoid masses of gastric polyps in the proximal stomach including the fundus and body. The mean age at cancer diagnosis was 57 years (range 35–75) and six were female.

The average interval from initial colectomy to gastric cancer diagnosis was 23.1 years. Eight patients were asymptomatic including four patients diagnosed with stage I gastric adenocarcinoma. Stage IV adenocarcinoma was detected in 6 patients with liver (n=5) and peritoneal (n=1) metastases. Two patients with stage I gastric cancer had previous foregut surgery. One had a pancreaticoduodenectomy for an ampullary adenocarcinoma 15 years prior and the other underwent a prophylactic pancreas preserving duodenectomy for stage IV duodenal polyposis 10 years before the gastric cancer diagnosis. One patient with metastatic adenocarcinoma had a pancreas preserving duodenectomy 15 years prior for stage IV duodenal polyposis. All patients with stage I disease underwent curative gastrectomy. One died of postoperative complications within 3 weeks of surgery and three are alive 6, 8 and 9 months after surgery, respectively. Of the 6 diagnosed with metastatic disease, 4 died within a mean 4.5 months after diagnosis. Two have been receiving palliative chemoradiation for 2 and 19 months, respectively.

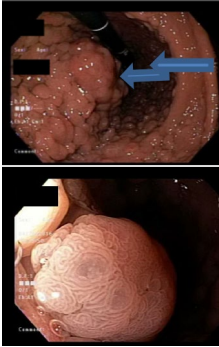
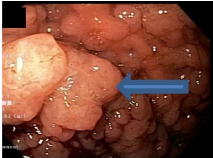
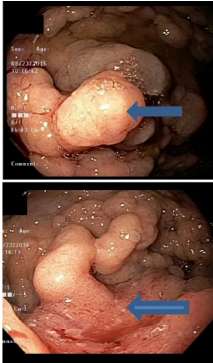
## Endoscopic and histologic findings (Tables 1, 2)

The duration of endoscopic surveillance was 10.9 years (range 4–20). Patients underwent an average of 9.7 EGDs (range 2–17 per patient) with a mean interval between EGDs of 1.78 years (range 0.5–4 years). EGD was performed at intervals based on the duodenal stage of polyposis with random sampling of gastric polyps and targeted resection of polyps >9 mm or of unusual appearance. When the recent diagnosis of gastric cancer occurred, patients with single or mounds of gastric polyps >9 mm or advanced pathology in the stomach underwent a reduced surveillance interval to a mean 6.9 months (range 3–12 months) with the addition of targeted snare resection of polypoid mounds of proximal gastric polyposis. The highest Spigelman stage of duodenal polyposis in the 7 patients with intact duodenum during surveillance was 0 (n=1), I (n=1), II (n=1), III (n=3), and IV (n=1). All but one patient had a carpeting of FGPs on first surveillance endoscopy with the largest polyp <1 cm in size. One patient had 3 polyps greater than 1 cm in size, in addition to numerous FGPs <1 cm in size, on first endoscopy. In all cases, the size of the polyps increased over the surveillance period with the range of size of largest FGPs from 15 mm to a mound of 55 mm. Six patients had cancer diagnosed on pathology from resection specimens of large polyps or densely carpeted mounds of proximal gastric polyposis. Techniques included hot or cold snare polypectomy (n=4) and endoscopic mucosal resection (n=2). Two of these patients had lesions identified from altered pit patterns when examined under both high definition white light and NBI. One patient had invasive cancer detected on random gastric polyp forceps biopsy in massive polyposis. EUS of polypoid mounds of proximal gastric polyposis was performed in 3 patients. Two of the patients had an EUS 4 years prior to cancer diagnosis with demonstration of a thick iso to hypoechoic superficial layer consistent with polyposis. One patient had gastric cancer discovered on EUS-guided fine needle aspiration of a 1.5 cm hypo-echoic mucosal lesion beneath a 4 cm thick layer of FGPs. Biopsies of the overlying mucosa revealed a FGP with low grade dysplasia and no malignancy. Two other patients had cancer incidentally found, one was found to have peritoneal implants on diagnostic laparotomy for small bowel obstruction while another had one foci of adenocarcinoma in a prophylactic gastrectomy specimen done for multifocal tubular adenomas with high grade dysplasia seen on endoscopic biopsies. The gastric cancers were unifocal in all but one patient. FGP with foveolar HGD, PGA with HGD, and TA with HGD were amongst the pathology seen in patients over the surveillance period.

**Table 1** Gastric findings on EGD and polyp pathology over the surveillance period

Patient	Baseline EGD	Interval surveillance EGDs	Endoscopic findings at diagnosis	EGD image at diagnosis	Adenocarcinoma staging (method)	Survival after Dx
1	Number: carpeting Size: 5–10 mm Location: C, F, B Path: FGP-LGD	Number: carpeting Size: 5–15 mm Location: C, F, B Path: FGP-LGD	Number: carpeting Size: 4 to >50 mm Location: C, F, B Path: FGP-HGD; TA-HGD Cancer: intramucosal		Stage IV (metastatic on ex lap)	Deceased—5 months
2	Number: carpeting Size: 2–10 mm Location: C, F, B Path: FGP-ND, TA-LGD	Number: carpeting Size: 5–25 mm Location: C, F, B Path: PGA, TA-LGD, FGP-LGD	Number: carpeting Size: 2–20 mm Location: C, F, B Path: FGP-HGD Cancer: intramucosal		Stage IV (liver mets on biopsy)	Alive—19 months—on chemotherapy with no evidence of disease on surveillance EGD
3	Number: carpeting Size: 5–10 mm Location: F, B Path: FGP-ND, TA	Number: carpeting Size: 5–10 mm Location: F, B Path: FGP-ND, TVA-LGD	Number: carpeting Size: 3–30 mm Location: C, F, B Path: FGP-HGD Cancer: invasive		Stage IV (liver metastasis on CT)	Deceased—2 months
4	Number: carpeting Size: 5–10 mm Location: C, F, B Path: FGP-LGD	N/A (only two EGDs)	Number: carpeting Size: largest >10 mm Location: C, F, B Path: FGP-LGD Cancer: none found	None available	Stage IV (peritoneal carcinomatosis on laparoscopy)	Decreased—1 month
5	Number: carpeting Size: <5 mm Location: C, F, B Path: FGP-ND	Number: carpeting Size: <5 mm Location: C, F, B Path: FGP-HGD, PGA-HGD	Number: carpeting Size: up to 25 mm Location: C, F, B Path: FGD Cancer: invasive		Stage 1B (T2NoMo on gastrectomy)	Deceased—3 months (within 3 weeks of gastrectomy from postoperative complications)
6	Number: carpeting Size: <5 mm Location: B Path: FGP-ND	Number: carpeting Size: 3–50 mm Location: F, B Path: PGA-HGD, FGP-HGD	Number: carpeting Size: 3–50 mm Location: F, B Path: FGP-HGD, PGA-HGD, TA-HGD Cancer: invasive		Stage IV (liver metastasis on PET)	Deceased—10 months
7	Number: carpeting Size: <5 mm Location: F Path: FGP-LGD	Number: carpeting Size: <5 mm Location: C, F, B Path: FGP-LGD	Number: carpeting Size: 3 to >50 mm Location: C, F, B Path: FGP-LGD, PGA-HGD Cancer: intramucosal		Stage 1A (EGD)	Alive—9 months. Status post curative total gastrectomy

**Table 1** (continued)

Patient	Baseline EGD	Interval surveillance EGDs	Endoscopic findings at diagnosis	EGD image at diagnosis	Adenocarcinoma staging (method)	Survival after Dx
8	Number: carpeting Size: 2–10 mm Location: C, F, B Path: FGP-ND, TA-LGD	Number: carpeting Size: 2–50 mm Location: C, F, B Path: FGP-LGD, TA-LGD	Number: carpeting Size: 2–50 mm Location: C, F, B Path: hyperplastic polyp, FGP-LGD, TA-LGD Cancer: none found		Stage 1A (EUS-FNA positive for adenocarcinoma; gastrectomy specimen)	Alive—8 months. Status post curative total gastrectomy
9	Number: carpeting Size: 3 × > 1 cm Location: C, F, B Path: FGP-LGD	Number: carpeting Size: 2–50 mm Location: C, F, B Path: FGP-HGD, TA-HGD	Number: carpeting Size: 3–50 mm Location: C, F, B Path: FGP-HGD, multifocal TA-HGD		Stage 1a (gastrectomy specimen)	Gastrectomy—6 months
10	Number: carpeting Size: < 8 mm Location: C, F, B Path: FGPLGD	Number: carpeting Size: 2 mm–2 cm Location: C, F, B Path: PGA-LGD, FGP-LGD	Number: carpeting Size: 3–30 mm mounds Location: C, F, B Path: PGA-LGD, FGP-LGD Cancer: invasive		Stage IV (liver metastasis on CT)	Alive—2 months. Started chemotherapy

Key: *FGP* fundic gland polyp, *TA* tubular adenoma; *PGA* pyloric gland adenoma, *LGD* low grade dysplasia, *HGD* high grade dysplasia, *ND* no dysplasia, *C* cardia, *F* fundus, *B* body of stomach, *ND* no dysplasia, *LGD* low grade dysplasia, *HGD* high grade dysplasia

## Discussion

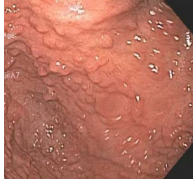

Since the introduction of genetic testing and prophylactic colectomy, the incidence and death from colorectal cancer in FAP has decreased and screening for extra-colonic cancers is recommended [3, 4]. Our data demonstrating the sudden rise in the incidence of gastric adenocarcinoma is alarming. Six developed cancer despite yearly or more frequent surveillance with all but one undergoing at least one intervention with EMR or ESD for resection of the largest collection of FGP. Current EGD surveillance recommendations do not account for gastric polyposis but rather are determined by the duodenal stage of polyposis. We suggest that EGD surveillance intervals need to reflect the newly emerging gastric cancer risk.

While the pathologic precursor of the malignant focus is unclear, we have identified a few endoscopic factors in our

FAP patients who developed gastric adenocarcinoma. All had a carpeting of proximal gastric polyposis on initial surveillance EGD with a progression in the size of individual polyps over the surveillance period and the development of large, thick mounds of polyps within 1–2 years prior to the cancer diagnosis. 8 of 10 (80%) of our cancer patients had FGP with LGD or HGD during the surveillance period; other pathologic findings included PGA (n=4) and TAs (n=3) on surveillance EGD.

Our patients underwent EGD surveillance at intervals based on their duodenal stage of polyposis with random sampling of gastric polyps and removal of polyps >9 mm in size or of unusual color or configuration. The surveillance interval was reduced for patients to a mean 6.9 months for the discovery of high-grade dysplasia, or multiple tubular adenomas or massive proximal gastric polyposis once we were alerted to the cancer risk. The diagnosis of early stage

**Table 2** Clinical and endoscopic features of FAP patients with gastric cancer

Patient	Age/year diagnosis	Mutation	Total surveillance period (years)	# of EGDs	Months between 1st EGD with polyps ≤10 mm and last EGD with polyps <10 mm	Months between last EGD with polyps ≤10 mm and 1st with polyps >10 mm	Months between 1st EGD with polyps >10 mm and Ca Dx	Illustration of baseline EGD with fundic gland polyposis
1	65/2015	3202del4	12.5	7	96	36	18	
2	36/2015	3182del5	10.1	9	98	7	17	
3	64/2014	4350delA	10.6	15	120	8	0	Illustration of size progression in polyposis 
4	43/2006	4733_4734delG	4	2	–	48	0	
5	56/2012	None found	11.25	11	108	17	10	
6	57/2016	Q1328X	20	15	171	14	55	
7	62/2016	1495C>T	10.6	5	59	30	45	
8	60/2016	453delA	9.5	9	65	12	62	
9	55/2016	None found	8.5	6	0	0	0	
10	75/2016	None found	17.8	12	171	38	46	

gastric cancer was reached with more aggressive sampling and polyp debulking with three of the four stage I cancers diagnosed in 2016. Patients diagnosed with stage I cancers were all undergoing surveillance at 3–6 month intervals.

The underlying lesion progressing to gastric adenocarcinomas in FAP is not known. It may arise from fundic gland polyposis or stem from other gastrointestinal lesions hidden by the massive proximal gastric polyposis including gastric adenomas and/or pyloric gland adenomas. 5/10 patients had PGAs discovered during surveillance or at time of diagnosis, much higher than the expected 6% prevalence from previous published work [8]. Sporadic and FAP-associated PGAs have a high prevalence of KRAS and GNAS mutations. With an underlying APC mutation, these may serve as “second hits” as per the Knudson hypothesis. Interestingly, sporadic PGAs were also shown to have a high prevalence of APC mutations and result from similar DNA alterations with B-catenin accumulation in the absence of an APC mutation [9]. Individuals with gastric adenocarcinoma and proximal polyposis of the stomach, or GAPPS, demonstrate an autosomal dominant phenotype of FGPs

and have an increased gastric cancer risk. Li et al. demonstrated germline point mutations in the APC promoter 1B in 6 GAPPS families not picked up by whole genome sequencing, in addition to second-hit mutations in the FGPs [10]. Though none of our patients have an APC promoter 1B mutation, proximal gastric adenocarcinoma development may share a similar pathway. The second hit could be due to a number of mechanisms, including the accumulation of mutations with aberrant protein function, wild-type allele loss, and DNA hypermethylation [11]. FGPs arise from second hit alterations in the APC gene or B-catenin oncogene in FAP-related and sporadic FGPs, respectively [12, 13]. Similarly, it is plausible that other gastric lesions, including fundic gland polyps and tubular adenomas, are intimately associated with PGAs with an accumulation of mutations and eventual transformation into a cancer.

We suggest endoscopic surveillance of the upper gastrointestinal tract include evaluation of both the duodenum and stomach and be done at the shorter interval based upon the organ with most severe disease expression, the duodenum or stomach (Table 3). As suggested by Bianchi, we suggest



**Table 3** Recommended surveillance for proximal gastric polyposis

Polyp number size of solitary polyp, presence of polypoid mounds	Histology	Surveillance strategy
Numerous, <10 mm	FGP with or without foveolar LGD	EGD according to SS duodenal polyposis or 3 years
Numerous or carpeted, <10 mm	PGA or TA	1 year
Numerous or carpeted, >10 mm	FGP with or without foveolar LGD, TA, PGA	6–12 months
Numerous, any size, no polypoid mounds	FGP-HGD, PGA-HGD or TA-HGD	3–6 months or offer gastrectomy
Any proximal polypoid mounds	FGP with or without foveolar LGD, PGA, TA	3–6 months, baseline EUS, consider CT or MRI abdomen
Any, proximal polypoid mounds	FGP-HGD, PGA-HGD, TA-HGD	Prophylactic gastrectomy
Any size or number	Intramucosal or invasive Adenocarcinoma	Gastrectomy

*FGP* fundic gland polyp, *PGA* pyloric gland adenoma, *TA* tubular adenoma, *LGD* low grade dysplasia, *HGD* high grade dysplasia, *SS* Spigelman stage

gastric surveillance include random biopsy of numerous polyps, targeted biopsy of unusual appearing proximal polyps and snare resection of individual polyps >10 mm or lesions in the antrum. The severity of gastric polyposis should be based upon the size, number and pathology of gastric polyps. An interval of 3 years is recommended for patients with few to numerous small FGPs or FGPs with foveolar LGD. Individuals with a carpeting of proximal gastric polyposis should undergo an EGD at a 1 year interval and more frequently pending the size of solitary polyps, presence of polypoid mounds and histology of polyps. Patients with polypoid mounds of proximal gastric polyposis should have a baseline EUS with FNA of suspicious lesions and endoscopic debulking of the polypoid mounds with follow up every 3–6 months and based upon pathology. A baseline MRI or CT scan of the abdomen to survey for metastatic disease is encouraged at the time when polypoid masses are found due to the frequent finding of metastatic disease. If any pathology specimens demonstrate HGD, gastrectomy should be recommended. Patients with numerous or carpeted, proximal polyposis without polypoid mounds and with FGP-HGD, PGA-HGD or TA-HGD should be surveyed every 3 months or offered a prophylactic gastrectomy. Any patient with intramucosal or invasive cancer should be offered gastrectomy.

Further research is required to identify the causes and determine the optimal approach to screening and early detection of gastric cancer in FAP. Investigation into the genetic and environmental associations of gastric cancer arising in FAP will lend progress in the prevention of this deadly cancer.

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