Duodenal Adenomas and Cancer in MUTYH-associated Polyposis: An International Cohort Study

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Although duodenal adenomas and cancer appear to occur significantly less frequently in autosomal recessive MUTYH-associated polyposis (MAP) than in autosomal dominant familial adenomatous polyposis (FAP),[1] current guidelines recommend similar endoscopic surveillance for both disorders.[2–4] This involves gastro-duodenoscopy starting at 25 to 35 years of age and repeated at intervals determined by Spigelman staging based on the number, size, histological type and degree of dysplasia of adenomas, and by ampullary staging (Supplementary Table 1).

Case reports of duodenal cancers in MAP suggest that they may develop in the absence of advanced Spigelman stage benign disease and even without coexisting adenomas.[1] Recent molecular analyses suggest that MAP duodenal adenomas have a higher mutational burden than FAP adenomas and are more likely to harbor oncogenic driver mutations, such as those in *KRAS*.[5] These apparent differences in the biology and natural history of duodenal polyposis in FAP and MAP challenge the assumption that the same surveillance should be applied in both conditions.

Methods

Study Design and Data Collection

This international multicenter prospective cohort study was approved by South East Wales NHS Research Ethics Committee (reference 11-WA/0208). Genotyping and endoscopies were carried out as part of routine clinical care (see Supplementary Methods). Contributing centers exported de-identified data to the study database. Only patients with homozygous or compound heterozygous class 4 or 5 (likely pathogenic/pathogenic) *MUTYH* variants were included. All had been enrolled for prospective follow-up and had undergone at least 1 duodenoscopy. Data collected included the following: *MUTYH* genotype; gender; date of birth; dates of endoscopies; number, size, and histological classification of duodenal and ampullary polyps (for staging of benign duodenal disease see Supplementary Table 1); and cancers at each endoscopy.

Statistical Analysis

Median values and ranges are reported for non-normally distributed data and absolute numbers and percentages for categorical data. Numbers of polyps in patients with different genotypes, ages, or gender were compared using 1-way analysis of variance with Tukey honestly significant difference correction. Kaplan-Meier analysis was performed for duodenal polyposis by genotype with censoring at development of polyps, death or last endoscopy. Statistical analysis was performed using R (version 3.0.2).

Abbreviations used in this paper: **FAP, familial adenomatous polyposis; MAP, MUTYH-associated polyposis.**

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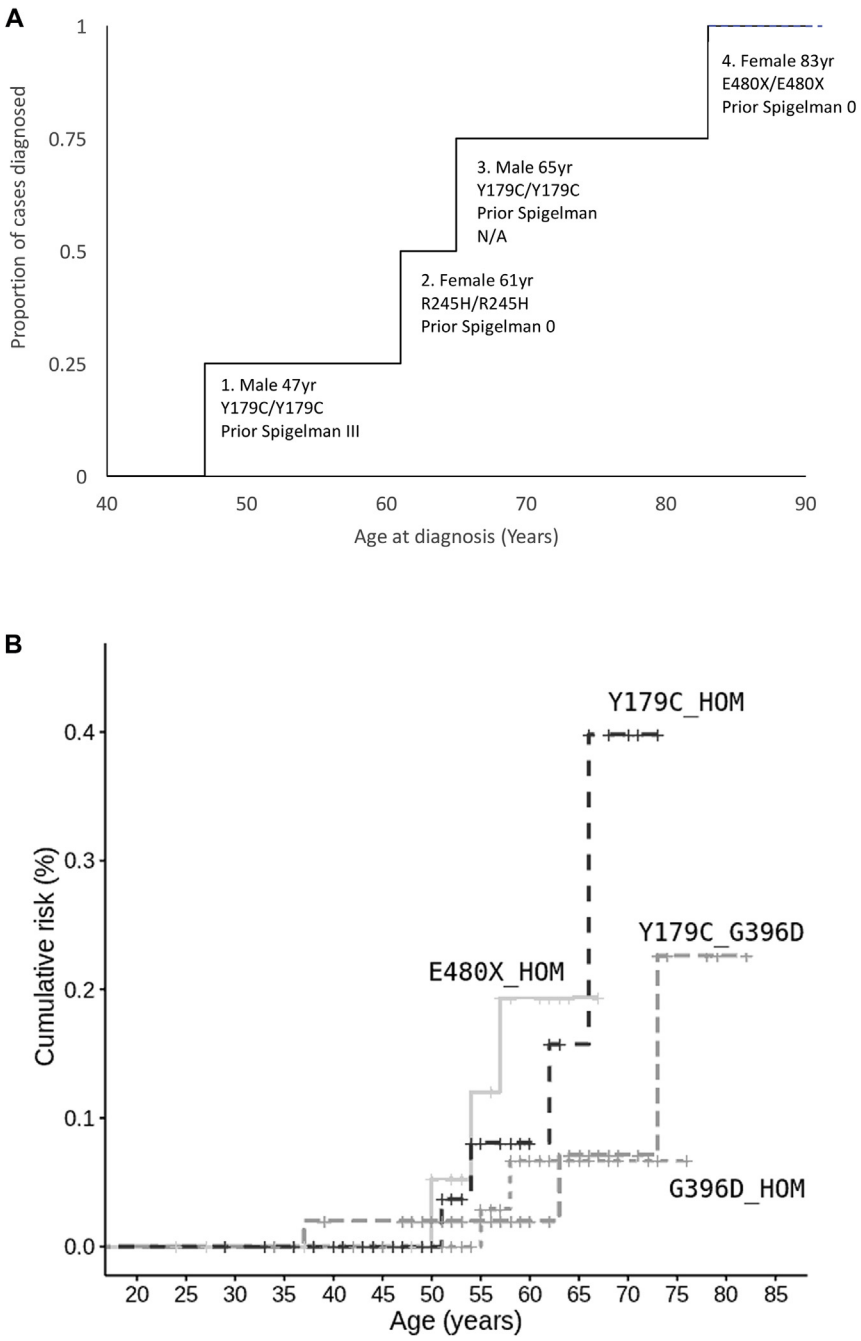

Figure 1. Duodenal cancers and adenomas in patients with MAP. (*A*) Age at diagnosis, gender, genotype and prior Spigelman stage in four patients with MAP and duodenal cancer. Patient 1: Initial endoscopy showed 3 adenomas, the largest a 4mm villous adenoma with high grade dysplasia located in the second part of the duodenum. At repeat endoscopy 2 months later further tubulovillous adenomas with low grade dysplasia were noted. A distally located duodenal adenocarcinoma was diagnosed at a third endoscopy 12 months later. Patient 2: was reported to be Spigelman stage 0 at initial endoscopy but a second endoscopy performed 9 months later because of weight loss and anaemia identified a cancer and no background polyps. Patient 3 presented with abdominal pain and vomiting before duodenal endoscopy had been carried out. At laparotomy, a 6cm moderately differentiated adenocarcinoma was identified at the duodenal–jejunal flexure. No background polyps were detected. This patient was reported previously by Nielsen et al[8] to have had upper gastrointestinal endoscopy with normal findings prior to presentation with symptomatic duodenal cancer. However, on reviewing the records this was a gastroscopy only, without inspection of the duodenum. This patient had therefore developed duodenal cancer prior to inclusion in the current study. Patient 4 had an apparently normal initial endoscopy at 82 years of age, but when the procedure was repeated a year later because of persistent iron deficiency anaemia, a 7cm circumferential tumour at the D2/D3 junction was detected. (*B*) Cumulative incidence of duodenal adenomas in MAP by age and genotype. Kaplan-Meier analysis was performed with patients censored at development of polyps, death or last endoscopy. Y179C homozygotes (Y179C HOM) were diagnosed with duodenal polyps at a younger age than G396D homozygotes (G396 HOM) or Y179C/G396D compound heterozygotes, but the differences were not significant.

Results

Clinical Findings

The cohort comprised 394 patients. At first duodenoscopy, at a median age of 51 years (range 19–92 years), 57 (14.5%) patients aged 37–81 years had adenomas, including 31 of 197 men and 26 of 197 women ($P = .45$). The median number of adenomas was 3 (range 1–20). Most were in the second part of the duodenum and smaller than 10 mm in diameter. Seven patients had ampullary adenomas. Spigelman stage was I in 35 patients (61.4%), II in 11 (19.3%), III in 10 (17.5%), and IV in 1 (1.8%).

A total of 220 patients underwent 575 further endoscopies providing 1463 years of prospective follow-up (median 4 years, mean 6.65 years), during which 38 (21.1%) of 183 previously unaffected patients developed adenomas. Fourteen (38%) of 37 with initial Spigelman stage I, II, or III disease who had follow-up progressed to a higher stage (although some were down-staged again later). The number with stage IV disease increased from 1 at first endoscopy to 3 at last endoscopy and 3 more progressed to stage IV during follow-up but were down-staged by endoscopic intervention. In all, 95 (24.1%) of 394 patients had adenomas detected during the study. Prevalence at last endoscopy varied from 8 (18%) of 44 in those aged 40 years or younger to 15 (38%) of 39 in those aged 70 years or older. The incidence of adenomas varied between centers, from 1 (5%) of 20 to 22 (38%) of 57, but duration of follow-up and distribution of genotypes also varied.

Eighteen adenomas with high-grade dysplasia were identified at first or follow-up endoscopy. Their diameters ranged from 3 to 25 mm and 9 (50%) of 18 were smaller than 10 mm. Three patients (1.4%) developed duodenal cancer during follow-up, and another before inclusion (Figure 1*A*).

Genotype-Phenotype Relationships

The most frequent pathogenic *MUTYH* variants were Y179C and G396D (European ancestry) and E480X (Indian subcontinent ancestry). Y179C homozygotes were more likely to have adenomas at initial endoscopy (22/67, 32.8%) than G396D homozygotes (6/62, 9.7%, $P = .002$) or Y179C/G396D compound heterozygotes (5/55, 9.1%, $P = .003$), whereas E480X homozygotes had an intermediate prevalence of adenomas (7/44, 15.9%). Age-related development of adenomas by genotype among patients who were unaffected at initial endoscopy was determined by Kaplan-Meier analysis and suggested the same genotype-phenotype relationships, although small numbers precluded further statistical analysis (Figure 1*B*). Y179C homozygotes were more likely to have adenomas with villous components and/or high-grade dysplasia (8/67, 12%) than were G396D homozygotes (0/62, 0%, $P = .007$) or Y179C/G396D compound heterozygotes (2/55, 4%, $P = .11$).

Discussion

Duodenal polyposis occurs less frequently in MAP than FAP, affecting 21.1% of patients in our cohort compared with 65% to 90% in FAP cohorts.[6] We found that the risk of duodenal polyposis in MAP depends on genotype, with Y179C homozygotes at increased risk, as found previously for colorectal cancer.[7] These genotype-phenotype relationships may reflect differential effects of mutations on glycosylase activity for DNA repair.

Spigelman stage IV disease occurred rarely in MAP, reflecting low adenoma burden. Its incidence was 1.5% at a median age of 55 years, compared with 35% to 50% by 60 years of age in FAP.[6] Although stage IV disease strongly predicts future cancer in FAP,[7] none of the 8 MAP-associated duodenal cancers reported previously[1] or in this study developed in the context of prior stage IV disease and in 4 no other adenomas were detected. These observations suggest that Spigelman staging fails to identify patients with MAP who are at risk of future cancer. We also noted high-grade dysplasia in small adenomas, suggesting more proactive endoscopic intervention should be considered in MAP, because current guidelines recommend resection of adenomas only measuring 10 mm or larger.[4] Two patients developed cancer following apparently normal endoscopies 9 months and 1 year earlier. It is likely that lesions in these cases were missed initially. It is also noteworthy that 3 of the 4 cancers reported here were located in the distal duodenum. Revision of guidelines for duodenal surveillance may be required to better prevent duodenal cancer in MAP.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.10.038.

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CRediT Authorship Contributions

The Collaborative Group on Duodenal Polyposis in MAP, n/a (Conceptualization: Lead; Formal analysis: Equal; Funding acquisition: Lead; Investigation: Lead; Methodology: Equal; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

Conflict of interest

The authors disclose no conflicts.

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Supplementary Methods

Identification of Patients With MAP

Patients with MAP were identified from the records of 11 specialist centers in 7 countries (number of patients identified from each center in parentheses): Milan, Italy (103); Leiden, the Netherlands (57); Lyon, France (51); London, United Kingdom (41); Barcelona, Spain (36); Paris, France (31); Amsterdam, the Netherlands (28); Navarra, Spain (20); Cardiff, United Kingdom (13); Helsinki; Finland (9); and Texas, USA (5). Inclusion criteria were (1) a genetic test result showing homozygosity or compound heterozygosity for clinically actionable (class 4 or 5) variants of *MUTYH* according to variant classification in the Leiden Open Variation Database for *MUTYH* (https://databases.lovd.nl/shared/genes/MUTYH); and (2) enrollment to prospective endoscopic surveillance of the duodenum with at last 1 completed procedure. The criteria may have led to exclusion of very elderly or unwell patients who were not offered duodenoscopy, affecting the reported prevalence of duodenal polyposis.

Several collaborating centers had previously reported upper gastrointestinal endoscopic findings in some of their patients,[1–3] but none had analyzed findings by genotype. To optimize power in the present study, patients who had been included in previous reports were included in the current study, with updating of data from subsequent follow-up where available.

Endoscopic and Histopathological Data and Staging of Benign Disease

Endoscopies were undertaken between December 12, 1986, and December 18, 2017, with most, 893 (92.2%) of 969, being undertaken after January 1, 2000. All were performed as part of routine clinical care following the local protocols operational at each center. The protocols varied between centers and over time; for example, in the use of forward vs side-viewing endoscopes, manufacturer and model of endoscope, and use of dye-spray (chromoendoscopy). Adenoma size was estimated by comparison of the maximum diameter with the known dimensions of aligned open biopsy forceps. These variables are expected to influence polyp detection and staging.[4]

Histology of adenomas from patients at UK centers was reviewed by a single experienced gastrointestinal pathologist. Adenomas that had been classified previously as showing "moderate dysplasia" where, in each case, reclassified to "low grade." Dysplasia was reported by centers in other countries as "low grade" or "high grade" and was not reviewed.

Methods used for staging of duodenal and ampullary disease are detailed in Supplementary Table 1.

Other Variables, Sources of Bias, and Limitations

We did not collect data on lifestyle factors (such as smoking and alcohol consumption) or pharmacological treatments (such as aspirin/nonsteroidal anti-inflammatory drugs), which could have affected duodenal polyp burden in this study. As patients were recruited from specialist hospital centers, the cohort is likely to have been subject to referral bias. The study did not include a control group and therefore we could not determine the efficacy of endoscopic surveillance for prevention of duodenal cancer.

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Supplementary Table 2. Genotypes, Endoscopic Findings, and Cancers in 394 Patients With MAP

	Number of patients	Number of patients with duodenal polyps at initial EGD		Number of patients with duodenal polyps or cancer during the study		Number of patients with colorectal cancer[a]		Number with other cancers[a]	
		n	%	n	%	n	%	n	%
Y179C_Y179C	67	22	33	28	42	34	51	8	12
G396D_G396D	62	6	10	8	13	29	47	6	10
Y179C_G396D	55	5	9	8	15	31	56	7	13
E480X_E480X	44	7	16	11	25	20	45	3	7
E410GfsX43_E410GfsX43	14	3	21	5	36	13	93	2	14
E480del_E480del	9	0	0	1	11	6	67	2	22
G396D_E410GfsX43	9	0	0	0	0	5	56	0	0
Y179C_E480del	8	0	0	1	13	2	25	1	13
G396D_P405L	7	2	29	2	29	6	86	0	0
Y179C_P405L	6	0	0	5	83	3	50	1	17
Y179C_G264WfsX7	6	1	17	3	50	4	67	2	33
Y179C_A385PfsX23	6	1	17	2	33	2	33	0	0
Y104X_Y104X	6	0	0	0	0	3	50	1	17
G396D_G264WfsX7	5	1	20	1	20	3	60	1	20
Y179C_Q338X	5	0	0	0	0	3	60	0	0
G396D_R245H	5	0	0	1	20	4	80	4	80
G396D_E480del	5	0	0	0	0	1	20	0	0
G396D_A385PfsX23	4	0	0	0	0	2	50	0	0
Y179C_R247X	3	0	0	1	33	1	33	0	0
Y179C_R245H	3	2	67	2	67	2	67	0	0
Y104X_E480del	3	0	0	0	0	2	67	1	33
Y179C_Y104X	3	0	0	0	0	1	33	0	0
Q338X_Q338X	2	0	0	1	50	1	50	1	50
M15V_A385PfsX23	2	0	0	0	0	2	100	1	50
R241W_R241W	2	0	0	0	0	1	50	1	50
Y179C_E410GfsX43	2	0	0	0	0	0	0	0	0
Q391X_Q391X	2	0	0	1	50	1	50	0	0
G189E_G189E	2	0	0	2	100	0	0	0	0
W174X_W174X	2	0	0	0	0	1	50	0	0
R245H_A385PfsX23	2	0	0	1	50	2	100	1	50
Y104X_G264WfsX7	2	0	0	0	0	1	50	1	50
G396D_933+1delAG	2	1	50	1	50	1	50	1	50
G396D_Q314X	1	0	0	0	0	1	100	0	0
E410GfsX43_E480del	1	1	100	1	100	1	100	0	0

Supplementary Table 2. Continued

	Number of patients	Number of patients with duodenal polyps at initial EGD		Number of patients with duodenal polyps or cancer during the study		Number of patients with colorectal cancer[a]		Number with other cancers[a]	
		n	%	n	%	n	%	n	%
G396D_L388AfsX143	1	0	0	0	0	1	100	0	0
E479X_E479X	1	0	0	0	0	0	0	0	0
G396D_E479X	1	0	0	0	0	1	100	0	0
Y179C_E196X	1	0	0	0	0	1	100	0	0
G396D_Q338X	1	0	0	0	0	0	0	0	0
Q414X_Q414X	1	0	0	0	0	0	0	0	0
Y104X_Q338X	1	0	0	0	0	1	100	0	0
G396D_M15V	1	0	0	0	0	0	0	0	0
G396D_R368QfsX164	1	0	0	0	0	1	100	0	0
Q414X_Y104C	1	0	0	1	100	0	0	0	0
Y104X_Q414X	1	0	0	1	100	0	0	1	100
G396D_R217H	1	0	0	0	0	0	0	0	0
R247X_P405L	1	0	0	0	0	1	100	0	0
A385PfsX23_P405L	1	0	0	1	100	0	0	0	0
Y179C_V130EfsX98	1	0	0	0	0	0	0	0	0
G396D_R247G	1	0	0	1	100	1	100	0	0
Y179C_V493F	1	1	100	1	100	1	100	0	0
Y179C_E490del	1	1	100	1	100	1	100	0	0
L393fsX_L393fsX	1	0	0	0	0	1	100	0	0
P405L_P405L	1	1	100	1	100	1	100	0	0
Y179C_P430L	1	0	0	0	0	1	100	0	0
V132N_c.924+3A>C	1	0	0	0	0	1	100	1	100
Q338X_A385PfsX23	1	0	0	0	0	0	0	0	0
c.577–2A>G_c.577–2A>G	1	0	0	0	0	1	100	0	0
R245H_R245H	1	0	0	1	100	0	0	1	100
A385PfsX23_E410GfsX43	1	1	100	1	100	1	100	0	0
G264WfsX7_G264WfsX7	1	0	0	0	0	1	100	0	0
G396D_R182C	1	0	0	0	0	1	100	0	0
G264WfsX7_A385PfsX23	1	0	0	0	0	0	0	0	0
G396D_Y104X	1	0	0	0	0	0	0	0	0
G396D_F432del	1	0	0	1	100	1	100	0	0
G396D_R182L	1	0	0	0	0	0	0	0	0
G396D_A333S346del	1	0	0	0	0	0	0	0	0
933+1delAG_E480X	1	1	100	1	100	1	100	0	0

Supplementary Table 2. Continued

	Number of patients	Number of patients with duodenal polyps at initial EGD		Number of patients with duodenal polyps or cancer during the study		Number of patients with colorectal cancer[a]		Number with other cancers[a]	
		n	%	n	%	n	%	n	%
R182H_R182H	1	0	0	1	100	1	100	0	0
R245H_c.349–2A>G	1	0	0	0	0	1	100	1	100
K155E168del_K155E168del	1	0	0	0	0	1	100	0	0
Total	**394**	**57**		**98**		**211**		**49**	

NOTE. Forty-two different pathogenic *MUTYH* variants, occurring in 71 different homozygous or compound heterozygous combinations were reported among the 394 patients. The most commonly identified pathogenic variants were the Y179C and G396D founder mutations that are frequent in northern Europeans. There were 67 Y179C homozygotes, 61 G396D homozygotes, and 55 Y179C/G396D compound heterozygotes. Forty-four patients were homozygous for the E480X variant that is commonly found in MAP patients with ancestry from the Indian subcontinent. Other genotypes occurred infrequently, and 29 patients had genotypes that were seen only once.

[a]Colorectal cancers were diagnosed in 211 (54.4%) of 394 patients and other cancers in 49 (12.4%) of 394. These included 9 endometrial cancers and 2 stomach cancers. Fundic gland polyps (FGPs) were not reported in either patient with stomach cancer, but small numbers of FGPs were reported in some patients. Four patients had 2 or more non-colorectal primary cancers. Patients who developed non-duodenal cancers were not significantly more likely to have duodenal polyps (58/227, 25.5% vs 37/167, 22.2%) ($P > .5$).