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Polyp Characteristics of Nonsyndromic and Potentially Syndromic Juvenile Polyps: A Retrospective Cohort Analysis

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ABSTRACT

Background: Juvenile polyps (JPs) are the most common gastrointestinal polyps diagnosed in children. There is paucity of evidence differentiating polyp burden groups and the presence and significance of neoplastic changes.

Methods: A retrospective chart review of patients, ages birth through 18 years with nonsyndromic JPs was performed from 2003 to 2017. Abstracted data included basic demographics, age, clinical presentation, colonoscopy findings, and pathology report. Slides of polyps with neoplasia were reviewed by a pathologist.

Results: A total of 213 subjects underwent 326 procedures and 435 polypectomies. Subjects with positive family history, positive gene mutations, or numerous (>10) polyps were excluded. Groups were defined by polyp number (1, 2–4, 5–10). Polyp recurrence on repeat colonoscopy was significantly related to polyp burden (1 polyp: 1.5%/2–4 polyps 19.2%/5–10 polyps 82.6%: $P < 0.001$). Polyp distribution was significantly different amongst different groups with isolated polyps favoring a distal distribution. JPs harboring adenomatous foci were reported in 26 (12%) patients. JPs harboring adenomatous foci were significantly more likely to be proximally distributed but the presence of adenomatous transformation within the polyps did not correlate with polyp number or the likelihood of polyp recurrence on repeat colonoscopy.

Conclusions: JP recurrence is positively and significantly related to polyp burden. JP harbored adenomatous changes independent of polyp number, underscoring a possible malignant potential in JPs. In the absence of a consistent genotype or pedigree, the presence of adenomatous transformation within JPs cannot be construed as a biomarker for syndromic juvenile polyposis.

Key Words: adenomatous polyp, dysplasia, juvenile polyp, juvenile polyposis syndrome, pediatric, polyp volume, polypectomy, sporadic juvenile polyp

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What Is Known

- Juvenile polyps are the most common intestinal polyps seen in children.
- Sporadic juvenile polyps are thought to be low risk and less likely to have recurrence.
- Sporadic juvenile polyps are thought to not harbor any malignant potential.

What Is New

- There is possible malignant potential, even in non-syndromic juvenile polyps, including solitary polyps.
- Right sided juvenile polyps are more likely to have neoplastic changes, further highlighting the need of pancolonoscopy when suspecting polyps.

Juvenile polyps (JPs) are the most common histologic subtype of polyps in the pediatric age. The vast majority of JPs arise as isolated, sometimes multiple synchronous or metachronous colonic lesions in children with no clear hereditary predisposition. A patient with any JPs proximal to the colon, any polyp in the context of a family history of juvenile polyposis syndrome (JPS), or 5 or more JPs in the colon is defined as harboring JPS (1–3). JPS entails a risk of polyp recurrence, intestinal malignancy, and potential hereditary transmission in relation to several well described genetic mutations.

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We confirm that this work is original and has neither been published elsewhere, nor is it currently under consideration for publication elsewhere. We did present some of the data in the article as poster presentations at the NASPGHAN conference in 2017. Below are the titles of the 2 posters we presented:

Focal adenomatous transformation in the pediatric nonsyndromic juvenile polyps: An under recognized entity.

Nonsyndromic juvenile polyp size: Volumetric analysis and retrospective comparison of intraoperative estimate and pathology-histology size determination. NASPGHAN poster presentation, October 2017.

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Colorectal adenocarcinoma (CRC) which is a rare pediatric tumor and current consensus is that sporadic JPs entail minimal to no risk of malignant transformation (5). There are, however, isolated case reports of malignant transformation in young children and several case reports in older individuals (6,7). There is also, a suggestion that neoplastic transformation in JPs may be more common than appreciated by virtue of occasional observation of adenomatous transformation, and the presence of immunohistochemical markers associated with progression through the adenoma-carcinoma sequence (8).

Herein, we present our analysis of the children with colonoscopy findings of nonsyndromic JPs at our institution, including their polyp burden, relationship with adenomatous transformation within the polyp, risk of symptomatic recurrence, subsequent repeat colonoscopy findings and a comparison between the endoscopist estimates of polyp size with the pathologist measured size.

PATIENTS AND METHODS

This study was submitted and approved by the Children's Mercy Hospital Institutional Ethical Review Board. Children ages birth to 18 years, who underwent colonoscopy with polypectomy at Children's Mercy Hospital were identified through the corresponding billing codes queried from Children's Mercy Medical Information Technology Department from January 1, 2003 to March 01, 2017. Retrospective chart review was performed. Abstracted data included basic demographics; age at first colonoscopy; clinical presentation; extent of colonoscopy; endoscopic findings including number, size, and location of polyps; and histological findings including size, pathologic characteristics, dysplastic, or adenomatous changes noted. Recurrence of polyps was also noted on repeat scopes. Repeat scopes were performed at the discretion of the physician for recurrence of symptoms or concern with initial polyps' number, size, or histology.

Children with sporadic JPs or nonsyndromic polyps, defined as polyp burden ≤ 5, no family history of JPS, and no JPs proximal from the colon were included.

Children with incomplete medical records, other types of polyps, Peutz-Jeghers polyps, adenomatous polyps, or inflammatory polyps were excluded. Patients with inflammatory bowel disease were also excluded.

We examined the relationship between select clinical factors and the number of polyps identified, which were assigned to 3 categories (1 polyp, 2–4 polyps, and 5 or more polyps). We first determined whether the number of polyps was differentially distributed across patient-level factors, including sex, race (Hispanic, Black/African American, Asian, White, Alaskan Native/Native American, other/unknown), age (in months) at first scope, and clinical presentation. We then compared polyp location (rectosigmoid, left, transverse, and right colon), polyp volume, and the presence of adenomatous transformation with the number of polyps. We used the ellipsoid volume equation to calculate the volume in cm^3 for each polyp:

$$(4/3)\pi r_1 r_2 r_3$$

We had the slides of polyps reportedly harboring adenomatous transformation independently reviewed by a pathologist to confirm the presence of neoplasia.

We used Fisher exact test for comparing categorical covariates. We report nonparametric summary statistics for polyp volume and patient age, with the Mann-Whitney U test used for determining statistical significance. Lastly, we report Spearman rho to show the correlation between polyp volume determined by the endoscopist and the pathologist. We assumed a P value <0.05 indicated statistical significance. All analyses were completed using Stata software (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

RESULTS

During the study period, 213 patients (54% boys, mean age = 7.03 ± 3.96 years) with nonsyndromic polyps were identified. A total of 326 colonoscopy procedures and 435 polypectomies were performed. Patients were divided into 3 groups: patients with single JP (n = 138), patients with 2 to 4 JPs (n = 52), and patients with 5 to 10 JPs (n = 23). The demographic characteristics and clinical presentation of participants is summarized in Table 1.

There were no observed significant relationships between sex, race, and age at first colonoscopy with cumulative JP burden. The most frequent presenting complaints included painless hematochezia (61%), hematochezia with pain (11.7%), and abdominal pain (10%); clinical presentation was not related to polyp burden.

TABLE 1. Patient characteristics and clinical presentation

	1 Polyp (n = 138)		2–4 Polyps (n = 52)		≥5 Polyps (n = 23)		
Factor	Frequency	%	Frequency	%	Frequency	%	Fisher exact P value
Sex							0.542
Male	76	55.1	25	48.1	14	60.9	
Female	62	44.9	27	51.9	9	39.1	
Race							0.168
Hispanic	6	4.4	7	13.7	0	0.0	
Black	11	8.0	0	0.0	2	8.7	
Asian	3	2.2	0	0.0	0	0.0	
White	107	78.1	42	82.4	20	87.0	
American Indian	2	1.5	0	0.0	0	0.0	
Other/unknown	8	5.8	2	3.9	1	4.4	
Clinical presentation							0.817
Abdominal pain	18	13.0	3	5.8	1	4.4	
Combination	13	9.4	7	13.5	1	4.4	
Other	6	4.4	4	7.7	1	4.4	
Painful hematochezia	17	12.3	5	9.6	3	13.0	
Painless hematochezia	81	58.7	32	61.5	17	73.9	
Prolapse	3	2.2	1	1.9	0	0.0	

TABLE 2. Recurrence rate in the different groups

	1 Polyp (n = 138)		2–4 Polyps (n = 53)		≥5 Polyps (n = 24)		Fisher exact
Factor	Frequency	%	Frequency	%	Frequency	%	*P* value
Recurrence							<0.001
No	138	100.0	42	80.8	4	17.4	
Yes	0	0	10	19.2	19	82.6	

TABLE 3. Juvenile polyp distribution by number

	1 Polyp		2–4 Polyps		≥5 Polyps		
Factor	Frequency	%	Frequency	%	Frequency	%	Pearson *P* value
Location (n = 399)							<0.001
Rectosigmoid	97	73.5	63	52.5	65	44.5	
Left colon	15	11.4	17	14.2	16	11	
Transverse colon	6	4.6	11	9.2	11	7.5	
Right colon	14	10.6	29	24.2	54	37	

Polyp recurrence on repeat colonoscopy was significantly related to cumulative polyp burden (1 polyp = 0% vs 2–4 polyps = 19.2% vs ≥5 polyps = 82.6%; $P < 0.001$; Table 2). Polyp distribution and size were significantly different amongst individuals harboring 1 or more polyps; specifically, isolated polyps favored a distal distribution and larger size (Table 3). Paired, endoscopist and pathologist, values for individual polyp size were available in 123 polyps and showed a good correlation between the 2 with a tendency toward overestimation of size by the endoscopist in comparison to the pathologist. We had 123 polyps that were measured by both an endoscopist and a pathologist. Mean endoscopist volume was 2.27 cm^3, whereas mean pathologist volume was 1.01 cm^3 (Spearman correlation = 0.7514, $P < 0.001$).

Twenty-six patients (12%) had JPs harboring adenomatous foci (aJP). Slides from all 26 cases were independently reviewed by a pathologist and the presence of neoplasia was confirmed. In this subgroup of patients, 65% had adenomatous transformation in the context of an isolated, that is, single JP. Adenomatous foci were noted in only 3 patients, that is, 12% with 5 to 10 polyps, whereas 6 patients (23%) with aJP had 2 to 4 polyps (Table 4). The median age of patients with aJP was 4.8 years (interquartile range: 3.8, 9.3 years). There was no association with sex, age at initial presentation, or racial background. Adenomatous transforming JPs were significantly more likely to be proximally distributed than nonadenoma harboring polyps (Fig. 1), tended to be slightly larger (pathologist reported volume [cm^3]: $M_{\text{non-aJP}} = 0.2$ vs $M_{\text{aJP}} = 0.26$; $P = 0.21$, NS), and were as likely to be solitary lesions during colonoscopy for painless hematochezia as was the observation with nonadenoma harboring JP ($P = 0.98$, NS). Patients with aJP were significantly more likely to undergo repeat colonoscopy than non-aJP (53.9% vs 27.3%; $P = 0.011$), but polyp recurrence if undergoing and at the time of endoscopy was not significantly different in the 2 groups (non-aJP = 13.90% vs aJP = 19.23%; $P = 0.55$, NS).

DISCUSSION

JPs are predominantly isolated hamartomatous lesions with a low risk of recurrence. They are the most frequent explanation for painless hematochezia in children (8–10) and can give rise to abdominal pain and anemia. JPs are thought to harbor very low risk of progression to colorectal cancer unless syndromic, but there is ambiguity on the precise number of polyps in the defining syndromic JPs. The incidence of JPS in children has been estimated at 1:100,000 to 1:160,000 (1). The polyps associated with JPS are frequently multiple and tend to a more distal colonic distribution (11).

Isolated larger distal lesions are the most common phenotype of nonsyndromic JP (12). Patients with small polyp burden have historically been considered low risk for polyp recurrence and there have been no evidence-based pediatric guidelines for surveillance colonoscopy in these patients. Previous reports suggest that recurrent polyp formation is common in JPs, and can occur even with solitary polyps (13,14). In our cohort, recurrence of polyps was related to initial polyp burden even in the subgroup of patients traditionally thought of as not harboring a syndromic pattern of disease (2–4 polyps; Table 2). Older age does not relate to increased polyp burden, arguing against a cumulative burden effect over time.

The accepted paradigm for the development of colorectal cancer CRC—adenocarcinoma in pediatric and most adult patients is a dysplastic evolution from adenoma to adenocarcinoma. CRC

TABLE 4. Adenomatous changes in different polyp burden groups

	1 Polyp (n = 138)		2–4 Polyps (n = 52)		≥5 Polyps (n = 23)		Fisher exact
Factor	Frequency	%	Frequency	%	Frequency	%	*P* value
Adenomatous transformation							<0.981
No	121	64.7	46	24.6	20	10.7	
Yes	17	65.4	6	23.1	3	11.5	
Adenomatous transformation present	12.3		11.5		13.0		

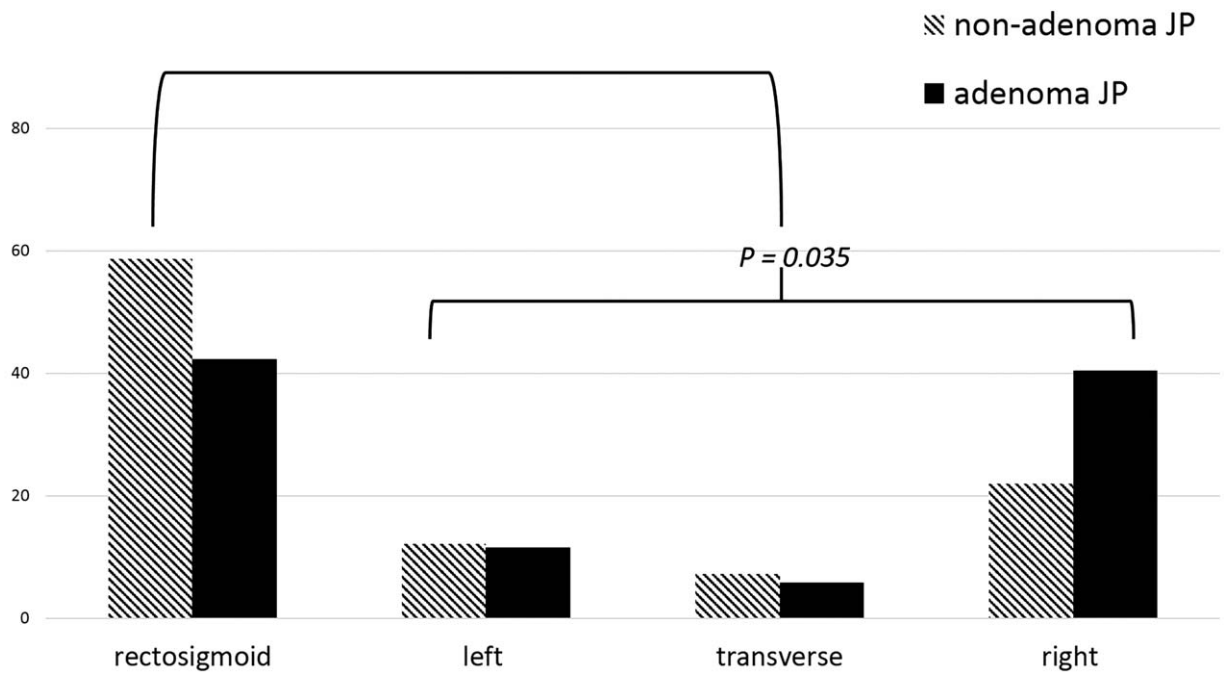

FIGURE 1. Percentage comparative localization of adenoma harboring juvenile polyps by anatomic localization within the colon. JP = juvenile polyp.

accounts for 1% of all childhood malignancies and has an incidence of approximately 1 per million (4,15,16). The pathogenesis of development of pediatric CRC is still not well understood. Pediatric CRC may arise in the setting of predisposing conditions, such as polyposis syndromes and inflammatory bowel disease, but it more frequently develops in children without known predisposing factors (4).

Adenomatous transformation within JP has traditionally been considered a characteristic of syndromic JP and separately, is suspected to be an intermediary in the progression toward CRC; however, adenomatous foci have been reported in sporadic JP and adenocarcinoma of the colon has been reported in both children and adults with nonsyndromic JP (6,7,16). The significance of adenomatous transformation in nonsyndromic JP is unknown. In the largest cohort of pediatric patients with CRC available to date, Hill et al (16) reported that 17 out of the 77 patients with CRC had 1 or more polyps identified at the time of operation. Nine patients had single polyps, 6 of which were JPs. Other studies have shown the presence of immunohistochemical markers associated with progression through the adenoma-carcinoma sequence in subjects with syndromic JPs, and solitary JPs (6,8).

In our cohort, we found 26 (12%) patients with JPs harboring adenomatous foci (aJP). Most of these patients (65%) had a solitary polyp and aJP were significantly more likely to be proximally distributed than nonadenoma harboring polyps (Fig. 1.), reiterating the need for pancolonoscopy if suspecting polyps.

Accurate estimation of polyp size by the endoscopist is a necessary skill, both toward accurate assessment of polyp burden and therefore management and surveillance interval and an outcome measure in chemopreventive trials. The reliability of pediatric endoscopist polyp size estimation is, however, unknown. In our comparison of polyp size estimates by pediatric endoscopist and size recorded by the pathologist, we had 123 polyps with paired volumes and found reasonably good correlation between pediatric gastroenterologist-endoscopist estimate and actual pathologist measurement (Spearman correlation = 0.75), albeit there being a tendency for endoscopists to overestimate size.

Our results are consistent with several other studies performed in adults showing a tendency for endoscopists to overestimate polyp size (17,18). The difference in size may be partially secondary to formalin fixation and postpolypectomy sheering causing polyp shrinkage; however, previous studies have demonstrated no significant difference in polyp size ($\leq$2 mm) between pre- and postfixation (19,20).

Based on these findings, we caution that neoplastic transformation in nonsyndromic JPs may be more common than appreciated and a significant observation. Dysplasia warrants closer scrutiny and lower threshold for repeat colonoscopy. We do not have enough data to recommend routine re-endoscopy of adenomatous transforming JPs but cautiously suggest that it be discussed with the family in the context of the existing literature so that an individualized decision is made.

Our study had several limitations, including its retrospective nature over a long period of time, variability in endoscopic and pathologic reporting, and multiple endoscopists with a spectrum of expertise, and presumably accuracy in assessing polyp size. Furthermore, outcomes could only be determined through chart review, so we had potential attrition through the family moving or transferring to another facility.

Further investigations, including large, prospective, multicenter studies are warranted to provide more complete information regarding recurrence rate, neoplastic transformation, and long-term outcomes in patients with nonsyndromic JPs.

This study highlights the importance of pancolonoscopy when polyps are suspected, especially given our observation of adenomatous changes in JPs being more proximally located. The significance of the high incidence of adenomatous changes in nonsyndromic JPs remains unclear; it does not predict syndromic polyp burden although increased numbers of polyps at presentation predict further polyp development.

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