A Multi-Institutional Cohort of Therapy-Associated Polyposis in Childhood and Young Adulthood Cancer Survivors

Leah H. Biller[1,2], Chinedu Ukaegbu[1], Tara G. Dhingra[1], Carol A. Burke[3], Yana Chertock[4], Anuradha Chittenden[1], James M. Church[3], Erika S. Koeppe[5], Brandie H. Leach[3], Elana Levinson[6], Ramona M. Lim[1,2], Megan Lutz[7], Erin Salo-Mullen[8], Rania Sheikh[8], Gregory Idos[9], Fay Kastrinos[6], Elena Stoffel[5], Jennifer M. Weiss[7], Michael J. Hall[4], Matthew F. Kalady[3], Zsofia K. Stadler[8], Sapna Syngal[1,2], and Matthew B. Yurgelun[1,2]

ABSTRACT

Prior small reports have postulated a link between gastrointestinal polyposis and childhood and young adulthood cancer (CYAC) treatment (therapy-associated polyposis; TAP), but this remains a poorly understood phenomenon. The aim of this study was to describe the phenotypic spectrum of TAP in a multi-institutional cohort. TAP cases were identified from eight high-risk cancer centers. Cases were defined as patients with ≥10 gastrointestinal polyps without known causative germline alteration or hereditary colorectal cancer predisposition syndrome who had a history of prior treatment with chemotherapy and/or radiotherapy for CYAC. A total of 34 TAP cases were included (original CYAC: 27 Hodgkin lymphoma, three neuroblastoma, one acute myeloid leukemia, one medulloblastoma, one nephroblastoma, and one non-Hodgkin lymphoma). Gastrointestinal polyposis was first detected at a median of 27 years (interquartile range, 20–33) after CYAC treatment. A total of 12 of 34 (35%) TAP cases had ≥50 colorectal polyps. A total of 32 of 34 (94%) had >1 histologic polyp type. A total of 25 of 34 (74%) had clinical features suggestive of ≥1 colorectal cancer predisposition syndrome [e.g., attenuated familial adenomatous polyposis (FAP), serrated polyposis syndrome, extracolonic manifestations of FAP, mismatch repair–deficient colorectal cancer, or hamartomatous polyposis] including 8 of 34 (24%) with features of multiple such syndromes. TAP is an apparently acquired phenomenon that should be considered in patients who develop significant polyposis without known causative germline alteration but who have had prior treatment for a CYAC. Patients with TAP have features that may mimic various hereditary colorectal cancer syndromes, suggesting multiple concurrent biologic mechanisms, and recognition of this diagnosis may have implications for cancer risk and screening.

Introduction

Survivors of childhood and young adulthood cancers (CYAC) are at increased risk for a variety of neoplastic and nonneoplastic adverse effects years after original cancer treatment (1–3), including colorectal adenomas and colorectal cancer (4–7). Exposure to abdominopelvic radiotherapy and/or alkylating chemotherapy has been associated with an increased risk of developing such gastrointestinal neoplasia, although the biological mechanisms remain poorly understood (4–6, 8, 9). Because of this increased risk, Children's Oncology Group (COG) long-term follow-up guidelines were recently updated to recommend initiation of colonoscopy for CYAC survivors who received abdominopelvic radiotherapy either at age 30 or 5 years after radiotherapy, whichever occurs later, and continue every 5 years, with those without prior abdominopelvic radiotherapy recommended to begin colorectal cancer screening at age 45 and continue at 10 year intervals (10).

We previously described a phenomenon of striking gastrointestinal polyposis developing in five CYAC survivors in the absence of identifiable germline or familial

[1]Dana-Farber Cancer Institute, Boston, Massachusetts. [2]Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts. [3]Cleveland Clinic Foundation, Cleveland, Ohio. [4]Fox Chase Cancer Center, Philadelphia, Pennsylvania. [5]University of Michigan, Ann Arbor, Michigan. [6]New York Presbyterian Hospital, New York, New York. [7]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin. [8]Memorial Sloan Kettering Cancer Center, New York, New York. [9]University of Southern California, Los Angeles, California.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Prior presentation: Presented in abstract form at the Annual Meeting of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC) in October, 2018, and at the 2019 International Society for Gastrointestinal Hereditary Tumours (InSiGHT) biennial meeting in March, 2019.

Corresponding Author: Matthew B. Yurgelun, Dana-Farber/Brigham and Women's Cancer Center, 450 Brookline Avenue, Dana 1126, Boston, MA 02215. Phone: 617-632-6835; Fax: 617-632-5370; E-mail matthew_yurgelun@dfci.harvard.edu

Cancer Prev Res 2020;13:291–8

doi: 10.1158/1940-6207.CAPR-19-0416

susceptibility (11). This apparently acquired phenotype was postulated to have been induced by prior chemotherapy and/or radiation exposure, and was therefore termed therapy-associated polyposis (TAP). More recently, Dutch investigators published an additional series of three apparent TAP cases in CYAC survivors treated with prior radiotherapy (12). Notably, gastrointestinal polyposis is a hallmark feature of rare hereditary colorectal cancer predisposition syndromes [including familial adenomatous polyposis (FAP), attenuated FAP, *MUTYH*-associated polyposis, serrated polyposis syndrome (SPS), hamartomatous polyposis syndromes, and others], and all eight TAP cases in the literature to date lacked an identifiable germline variant in the high-risk polyposis genes *Adenomatous Polyposis Coli* (*APC*) and *MutY Homolog* (*MUTYH*).

Polyposis is also a known risk factor for the development of gastrointestinal cancers, and patients with inherited polyposis syndromes may warrant earlier and more frequent cancer screening and/or more invasive interventions. While in a large registry study of the general population (unselected for history of childhood and adulthood cancer), adenomatous polyps were seen in 26% of colonoscopies among 50–64 year old and 36% among those 65 and older, and serrated polyps were detected in 9% of colonoscopies for both the 50–64 and 65 and older groups (13), the presence of multiple polyps, however, is much less frequent such that multiple professional societies recommend that patients with polyposis be referred for genetic evaluation and high-risk assessment. The recognition of a nonhereditary polyposis phenomenon (such as TAP) would thus have important implications for management of patients and their families. The primary aim of this study was therefore to further characterize the phenotypic spectrum of TAP in a multi-institutional cohort.

Materials and Methods

For the purposes of this analysis, we defined TAP cases as individuals who developed polyposis without known genetic predisposition, in the setting of prior exposure to chemotherapy and/or radiotherapy for a CYAC. Polyposis was defined as cumulative lifetime incidence of $\geq$10 gastrointestinal polyps of any type, inclusive of the entire gastrointestinal tract. We included individuals with CYAC diagnosed at age $\leq$30 years or individuals diagnosed with CYAC between ages 31–45 years, if their first gastrointestinal polyp were identified $\geq$10 years after initial CYAC treatment. Individuals known to have a personal or family diagnosis of pathogenic or likely pathogenic germline variants in any gene(s) linked to inherited colorectal cancer susceptibility were excluded. Potential TAP cases were ascertained from institutional review board–approved registries at eight cancer genetics programs (Supplementary Table S1). Investigators from individual sites identified cases with suspected TAP on the basis of the above criteria.

Clinical data were obtained from medical record review and querying of cancer genetics registry data, including original CYAC diagnostic and treatment history; endoscopic, surgical, and pathologic findings; genetic testing results; family history of cancer and polyps; and other medical history. Quantification of polyp data was obtained from pathology reports and endoscopic records, when available, and from text descriptions included in provider notes. If number of polyps were documented as a numeric range, the lowest end of this range was used for quantification of lifetime polyp burden. If only qualitative descriptions of polyp burden were provided, "few" was coded as three polyps, "many" as five polyps, and "numerous" as 10 polyps. Tubular, villous, and tubulovillous were all categorized as "adenomas" for this study.

Each TAP case was assessed for clinical features of inherited colorectal cancer predisposition syndromes, even though none of the cases (by definition) had a known personal or familial diagnosis of any genetically defined syndrome. Patients with desmoid tumors, duodenal polyps, epidermoid cysts, hepatoblastoma, osteomas or thyroid cancer were classified as having extracolonic features of FAP. While fundic gland polyps are part of the spectrum of FAP, these polyps typically present in large numbers (>30) in FAP (14), and we elected to consider fundic gland polyps separately given limited data available on the number of fundic gland polyps seen in our cohort. The presence of $\geq$10 colorectal adenomas was considered a feature of attenuated FAP. Individuals whose polyp history fulfilled the World Health Organization (WHO) 2010 SPS criterion 1 ($\geq$5 serrated polyps proximal to the sigmoid colon, $\geq$2 of which were $\geq$1 cm) or criterion 3 (>20 serrated polyps anywhere in the colorectum) were classified as having features of SPS (individuals with $\geq$3 hamartomatous polyps of the gastrointestinal tract were classified as having features of a hamartomatous polyposis syndrome). Cases with mismatch repair–deficient (MMR-D) or microsatellite instability-high (MSI-H) colorectal cancer were also considered to have features of Lynch syndrome.

Results

Thirty-four patients with TAP were identified from eight institutions (**Table 1**; Supplementary Table S1). Twenty-seven had previously been treated for Hodgkin lymphoma, 3 for neuroblastoma, 1 for acute myeloid lymphoma, 1 for medulloblastoma, 1 for nephroblastoma (Wilms' tumor), and 1 for non-Hodgkin lymphoma. Subjects' median age at the time of their original CYAC diagnosis was 18 years [interquartile range (IQR) 14–24 years]. Twenty of 34 TAP cases (59%) received known alkylating chemotherapy for their initial CYAC, 21 (62%) received abdominopelvic radiotherapy, and 12 (35%) received both alkylating chemotherapy and abdominopelvic radiotherapy (**Table 1**; Supplementary Table S2).

Among the 34 TAP cases, gastrointestinal polyposis was first detected at a median age of 49 years (IQR 37–54) and at a median of 27 years (IQR 20–33) after initial CYAC treatment

Table 1. Clinical characteristics and original cancer history of patients with TAP ($n = 34$).

	N	(%)[a]
Gender		
Male	21	(62)
Female	13	(38)
Type of original cancer		
Hodgkin lymphoma	27	(79)
Neuroblastoma	3	(9)
Acute myeloid leukemia	1	(3)
Medulloblastoma	1	(3)
Nephroblastoma	1	(3)
Non-Hodgkin lymphoma	1	(3)
Median age (years) at original cancer diagnosis (IQR)	18(14–24)	
Treatment received for original cancer[b]		
Chemotherapy (any)	29	(85)
Alkylating chemotherapy	20	(59)
Radiation (any)	28	(82)
Abdominopelvic radiation	21	(62)
Unknown	3	(9)
Family history		
FDR with CRC before age 50	0	(0)
FDR with ≥10 polyps	2	(6)
SDR with CRC before age 50	1[c]	(3)
SDR with ≥10 polyps	0	(0)

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative; SDR, second-degree relative.
[a]Percentages listed are of total cohort ($n = 34$).
[b]Categories not mutually exclusive. Please see Supplementary Table S2 for more details.
[c]Maternal grandmother with rectal cancer at age 42.

Table 2. Gastrointestinal polyposis and other clinical manifestations of TAP ($n = 34$).

	N	(%)[a]
Median time (years) from initial cancer treatment to first colorectal polyp (IQR)	27(20–33)	
Median age (years) at first polyp (IQR)	49(37–54)	
Median number of colonoscopies (IQR)	4(2–6)	
Median number of colorectal polyps (IQR)	32(16–52)	
At least 20 colorectal polyps	23	(68)
At least 50 colorectal polyps	12	(35)
Clinical features suggestive of other inherited GI cancer syndromes	25	(74)
Attenuated adenomatous polyposis (≥10 colorectal adenomas)	18	(53)
Serrated polyposis syndrome (WHO 2010 criteria)	10	(29)
Extracolonic FAP-related neoplasia[b]	6	(18)
Lynch syndrome like (MMR-D/MSI-H colorectal cancer)	3	(9)
Hamartomatous polyposis (≥3 GI hamartomatous polyps)	1	(3)
More than one of the above	8	(24)
Presence of gastroduodenal polyps[c]	7	(30)[d]
Gastric hamartoma	2	(9)[d]
Gastric hyperplastic polyps	2	(9)[d]
Duodenal adenoma	1	(4)[d]
Duodenal hyperplastic/serrated polyp	1	(4)[d]
Duodenal inflammatory polyp	1	(4)[d]
Colorectal cancer diagnosis	10	(29)
Median age (years) at colorectal cancer diagnosis (IQR)	46(33–57)	

Abbreviations: CRC, colorectal cancer; FAP, Familial adenomatous polyposis; GI, gastrointestinal; IQR, interquartile range; MMR-D, mismatch repair deficient; MSI-H, microsatellite instability; WHO, World Health Organization.
[a]Percentages listed are of 34, unless otherwise specified.
[b]Includes: thyroid cancer ($n = 5$, 15%); desmoid tumor ($n = 2$, 6%); duodenal adenoma ($n = 1$, 3%); and osteoma ($n = 1$, 3%).
[c]Does not include fundic gland polyps ($n = 17$, 50%).
[d]Percentage out of 23 with known Esophagogastroduodenoscopy.

(**Table 2**). Patients had gastrointestinal surveillance data available from a median of 4 (IQR 2–6) colonoscopies obtained over 6 (IQR 3–9) years.

Of the 21 patients who received abdominopelvic radiotherapy, 5 (24%) had polyps detected prior to the age they would have been recommended to start colonoscopic screening by COG guidelines. Of the 10 cases who did not receive abdominopelvic radiotherapy, 3 (30%) had a polyp detected <45 age (the age that would be recommended by COG to initiate colonoscopy). Three patients had unknown radiation exposure, but all had first polyp detected after age 45. Similarly, of the 9 patients who developed colorectal cancer and had known radiotherapy exposure, 3 (33%) were diagnosed prior to the COG recommended age to start colonoscopy screening (2 with history of abdominopelvic radiotherapy, 1 without abdominopelvic radiotherapy).

All TAP cases had colorectal polyps, with a median lifetime aggregate of 32 polyps (IQR 16–52). Twenty-three of 34 TAP cases (68%) had a lifetime aggregate of ≥20 colorectal polyps and 12 (35%) had ≥50 colorectal polyps (**Fig. 1**). Thirty-two of 34 TAP cases (94%) had more than one histologic type of colorectal polyps (the remaining two [**Fig. 1**, cases 16 and 31] did not have polyp histology available. Of the 23 patients known to have undergone an esophagogastroduodenoscopy (EGD), 7 (30%) had gastric and/or duodenal polyps with 1 patient having an upper gastrointestinal predominant phenotype (**Fig. 1**, case 34). Including fundic gland polyps, 19 of 23 (74%) patients who underwent EGD had upper gastrointestinal polyp findings.

Thirty-two of 34 TAP cases (94%) had prior germline genetic testing. Twenty-two of 34 (65%) had multi-gene panel testing (including *APC* and *MUTYH* among other genes); none had pathogenic or likely pathogenic variants in any tested gene (Supplementary Table S2). The remaining, 10 of 34 (29%) had only single-gene testing including *APC* and *MUTYH* although 1 patient had testing performed after allogenic stem cell transplant with thereby uninformative results. Only one TAP case had a first- or second-degree relative with colorectal cancer diagnosed prior to age 50 and two cases (6%) had one first-degree relative with a reported history of ≥10 colorectal polyps.

Twenty-five of 34 (74%) TAP cases had clinical features of an inherited gastrointestinal cancer syndrome (**Table 2**): 18 (53%) had a colorectal adenomatous polyp burden consistent with attenuated FAP; 10 (29%) met WHO 2010 SPS criteria; six (18%) had extracolonic FAP-related neoplasia; three (9%) had an MMR-D/MSI-H colorectal cancer; and one (3%) had hamartomatous polyposis. Eight of 34 (24%) had features of

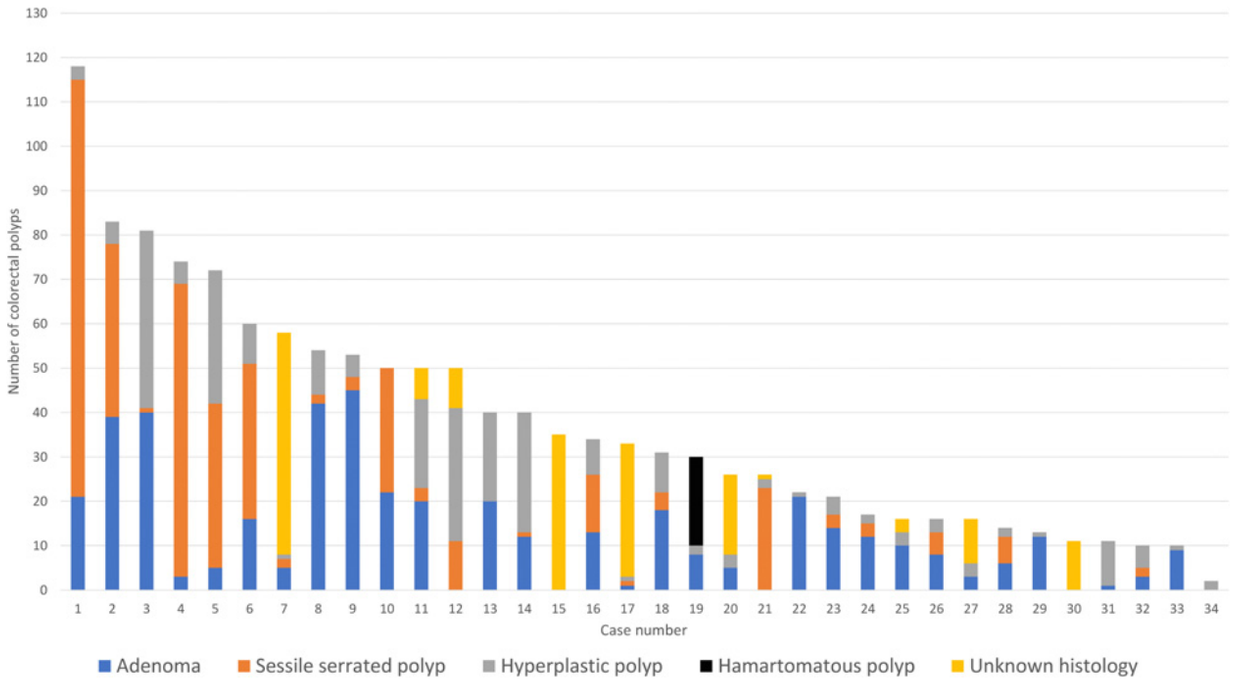

Figure 1.
Colorectal polyps per TAP case, stratified by histologic type of polyp (if known).

≥1 syndrome. If we included the presence of fundic gland polyps as an extracolonic feature of FAP, 31 of 34 (94%) would have met criteria for a hereditary syndrome, and 15 of 34 (44%) met more criteria for ≥1 hereditary colorectal cancer predisposition syndrome.

Ten of 34 (29%) TAP cases were diagnosed with colorectal cancer. Seven colorectal cancer cases were diagnosed on the individuals' first ever colonoscopy, with six of seven cases (86%) detected in patients less than age 50. The majority had early stage disease (seven had stage 0/I), with only one each with stage IIa and stage IIIa colorectal cancer (one with stage unknown). MMR-D was identified in three cases of colorectal cancer, all of whom had negative germline testing for the 5 Lynch syndrome genes. Two MMR-D colorectal cancer cases (one with loss of *MSH6* and the other with loss of *MSH2/MSH6*) were ultimately identified to have biallelic somatic MMR gene inactivation identified on paired tumor/germline testing. The third case had loss of *MLH1/PMS2* but did not have available *MLH1* promoter hypermethylation testing or paired somatic testing data.

Fourteen of 34 TAP (41%) cases underwent some degree of colorectal surgical resection (Supplementary Table S3); seven were performed as treatment for a colorectal cancer and seven were performed for management of polyposis alone.

Twenty-five of 34 (74%) TAP cases had other medical history suggestive of treatment-related complications: 17 of 34 (50%) had non-colorectal neoplastic conditions; and 16 of 34 (47%) had nonneoplastic sequelae of prior treatment (**Table 3**).

Discussion

In this multi-institutional study, we present 34 patients with TAP, an apparently acquired gastrointestinal polyposis phenomenon manifesting years after chemotherapy and/or radiotherapy exposure. While there already is robust literature on the development of at least one adenoma or advanced lesion in CYAC survivors (4, 6, 15), the identification of frank polyposis after CYAC treatment has only been described in 8 patients in the literature to date. Importantly, despite the absence of larger studies, we suspect that this is under recognized, and other survivor cohorts may also include potential TAP cases even if not characterized as such. For example, in an analysis of 101 Dutch Hodgkin lymphoma survivors who underwent their first colonoscopy, six (6%) met WHO 2010 criteria for SPS; as they were only assessed for the presence of at least one adenoma (and only had results from the first colonoscopy), it is possible that some of these patients may have met TAP criteria (6). As the default is often to manage patients with polyposis as if there were a familial syndrome present, which would lead to increased screening and/or other invasive interventions for both patients and relatives, it is therefore critical to better identify patients with TAP. In our expanded cohort, nearly all patients with TAP actually had features mimicking specific hereditary colorectal cancer predisposition syndromes in spite of the apparently acquired biology, and almost half of TAP cases demonstrated manifestations of multiple such syndromes.

Hereditary syndromes provide important biologic models for understanding pathways of colorectal carcinogenesis and

Table 3. Other (nonpolyposis) medical comorbidities and sequelae of original anticancer treatment ($n = 34$).

	N	%[a]
Non-colorectal neoplasms (any)[b]	17	(50)
Barrett esophagus	5	(15)
Non-melanomatous skin cancer	5	(15)
Breast cancer	4	(12)
Meningioma	2	(6)
Prostate cancer	2	(6)
Schwannoma	2	(6)
Melanoma	1	(3)
Non–small cell lung cancer	1	(3)
Pancreatic adenocarcinoma	1	(3)
Renal cell carcinoma	1	(3)
Non-neoplastic conditions (any)	16	(47)
Cardiovascular		
Early onset coronary artery disease	3	(9)
Cardiomyopathy	2	(6)
Heart block	2	(6)
Valvular heart disease	1	(3)
Early cardiac disease (unknown type)	1	(3)
Endocrine		
Hypothyroidism	7	(21)
Hypogonadism	4	(12)
Gynecologic		
Endometriosis/polyps	2	(6)
Uterine fibroids	2	(6)
Neurologic		
Cataracts	1	(3)
Cognitive impairment	1	(3)
Pulmonary		
Pulmonary fibrosis	2	(6)
Any of the above (neoplastic and/or non-neoplastic)	25	(74)

[a]Percentages listed are of total cohort ($n = 34$).
[b]Does not include thyroid cancers ($n = 5$) or desmoid tumors ($n = 2$) as these were included in **Table 2** as "extracolonic FAP-related neoplasia."

the role of benign polyp precursors. In FAP, adenomatous polyps undergo malignant transformation via activation of *Wnt* signaling pathway (due to germline *APC* mutations) and the resultant chromosomal instability (16, 17); the majority of sporadic colorectal tumors (due to somatic *APC* mutations) arise from adenomatous polyps via this same adenoma carcinoma sequence (18–20). Early case reports of familial hyperplastic polyposis (now known as serrated polyposis syndrome) suggested the cancerous potential of serrated polyps (21–23); we know now that serrated polyps can be precursors for sporadic MSI-H colorectal cancer via activating *BRAF* mutations and the CpG island hypermethylation phenotype as part of the serrated neoplasia pathway (24, 25). Conversely, Lynch syndrome–associated MSI-H colorectal cancer (by definition in the setting of germline alterations in MMR genes) have classically been thought to arise in adenomatous polyps via the MSI pathway (26–29). While these inherited colorectal cancer predisposition syndromes are typically associated with a single histologic polyp type, the polyps seen in TAP actually varied between and even within cases (**Fig. 1**). For example, case 10 developed both 22 adenomas and 28 serrated polyps, meeting our criteria for attenuated FAP and SPS, respectively, in addition to having an extracolonic manifestation of FAP (thyroid cancer). In fact, all patients with TAP with available polyp histology data had more than one histologic type of polyp identified. We thus speculate that the development of multiple histologic polyp types in TAP may be driven by more than one molecular pathway, and that these appear to be co-occurring within the same individual.

The varying polyp histologies occurred in patients both with and without abdominopelvic radiation exposure, suggesting that any biological mechanism is not exclusive to radiation injury. It is well established that prior exposure to radiation and/or chemotherapy in CYAC survivors is associated with a broad range of late organ effects (1, 2). We found that almost 75% of TAP cases also developed other nonpolyposis medical conditions (e.g., secondary cancers, endocrinologic disorders, and early-onset cardiac disease) and we therefore speculate that patients with TAP might possess a systemic susceptibility to treatment-related toxicities, rather than a specific susceptibility to polyposis alone.

Clinical concern for an inherited polyposis syndrome, however, may be how patients with TAP are first identified, especially given that distinctive features of inherited colorectal cancer syndromes are frequently present. The diagnosis of TAP may also therefore have significant implications for the screening and colorectal cancer risk of family members. In fact, whereas multiple professional society guidelines recommend early initiation of colonoscopy for relatives in suspected high-risk polyposis families (as early as age 10 for first-degree relatives of individuals with suspected FAP; refs. 30–32), we suspect that a diagnosis of TAP may not be associated with risks of gastrointestinal neoplasia for relatives, given its presumed acquired nature. In fact, we did not find any early-onset colorectal cancer in first-degree relatives of patients with TAP, although this result must be qualified by the limitations of a descriptive study. Thus, it remains unclear whether relatives of TAP cases require any early or enhanced screening for gastrointestinal neoplasia.

For CYAC survivors overall, however, colorectal cancer screening guidelines by the COG were revised in 2018 to recommend earlier and more frequent colonoscopy screening, especially among those treated with abdominopelvic radiotherapy. In our cohort, almost 20% had polyps first detected at an age prior to the COG recommended start time for colonoscopy screening, as were 33% of colon cancers; both patients with and without prior abdominopelvic fell outside of the COG screening guidelines. We emphasize that our data are insufficient to develop definitive screening recommendations, but we would propose that COG guidelines be expanded to include individuals who received chemotherapy (without abdominopelvic radiation), and that initiation of screening begin at age 35 or 10 years after age of chemotherapy, whichever occurs first. With these guidelines, none of the patients in this cohort would have been missed. In addition, COG guidelines do not currently

address upper gastrointestinal tract screening among CYAC survivors. Given that almost a third of TAP cases who underwent EGD screening had polyps in the stomach or duodenum, we would propose consideration of at least a baseline EGD at the age when colorectal polyposis is first identified.

We recognize that there are other limitations to our study. First, there is an inherent ascertainment bias and the specific age and polyp cutoffs used to define TAP cases were somewhat arbitrary. Cases were identified from high risk or cancer genetics clinics by individual providers rather than systematically from a CYAC survivor registry and we are also therefore unable to infer the prevalence of TAP. Because of the descriptive nature of this study and size of the cohort, we were unable to assess predictive factors that might suggest a CYAC survivor is at risk for TAP or would benefit from earlier colonoscopic screening.

Medical records were also incomplete regarding specific CYAC treatments and pathology reports, as many patients with TAP were treated at least a decade prior to our study and/or underwent colonoscopies at outside centers. We relied on historical reports and documentation in clinic notes as available. Accordingly, we were unable to determine the anatomic location of colorectal polyps or determine whether polyposis was present within radiation fields (although polyposis clearly did occur in patients without any prior abdominopelvic radiation exposure). There also was no centralized pathologic review of polyps so it is possible that histology types may have been misclassified, particularly with regard to differentiating between hyperplastic polyps and sessile serrated polyps given the known intraobserver variability (33) and changes in WHO classification in 2010 (34). We also did not specifically have data on the frequency of advanced adenomas or other high-risk features within our cohort.

Importantly, because of limited records, we did not have reliable data on the indications for colonoscopies (whether obtained for COG-based screening or diagnostic and related to patients' symptoms), so we cannot directly assess effectiveness of these guidelines. We also could not control for unknown lifestyle factors (e.g., cigarette smoking, alcohol use, obesity, and/or aspirin) that may also impact the risk of polyp formation.

A key limitation is that the majority of cases did not have genetic testing for all genes with known possible associations to polyposis nor did we have full germline panels for all patients. We recognize that it is therefore possible that we may have inadvertently included cases with an inherited polyposis or cancer predisposition syndrome. In addition, while a known history of genetic predisposition was an exclusion criterion, we did include 2 patients without documented negative *APC* and *MUTYH* testing, as they otherwise appeared similar to patients with TAP and did not have any concerning family history. The presence of somatic *APC* mosaicism, which has been identified in small series of patients with unexplained polyposis (35), could not be excluded as a potential cause of adenomatous polyposis in this cohort, although this would not account for the mixed histologic types we saw in 94% of patients. We were also limited by the lack of molecular-based polyp or colorectal cancer tissue testing, so we are currently only able to speculate about the biology of TAP, although we plan to investigate this in future studies.

In conclusion, this series demonstrates that TAP should be considered in patients with significant polyposis, no known pathologic germline variant and/or family history of gastrointestinal neoplasia, and a history of prior CYAC treatment. TAP appears to be an acquired phenomenon that may mimic biologically distinct forms of inherited colorectal cancer predisposition syndromes; this raises the potential for misdiagnosis, with concomitant implications for both patient- and family-specific cancer screening recommendations. The heterogeneous phenotypes and varied histologic polyp types may also suggest that multiple diverse biologic pathways are involved in TAP. Further work is needed to better understand the underlying mechanisms for polyposis development, as this may in turn inform management of TAP- and other treatment-related sequelae.

Disclosure of Potential Conflicts of Interest

B.H. Leach reports personal fees from Invitae and personal fees from Myriad Genetics Lab outside the submitted work. G. Idos reports other funding from Myriad Genetics and Laboratories outside the submitted work. J.M. Weiss reports grants from American Cancer Society during the conduct of the study; personal fees from American College of Physicians outside the submitted work; and National Comprehensive Cancer Network - Vice Chair of the Genetics/Familial High-Risk Assessment: Colorectal Guidelines Committee. M.J. Hall reports a patent to 9157124B2 issued; and performed a collaborative research (no research funding received, no financial support received) with several commercial entities who perform genetic testing for cancer. These research activities are unrelated to the current publication but are broadly related to hereditary colorectal and GI cancers, the subject of this paper. Z.K. Stadler reports personal fees from Roche, personal fees from RegenexBio, personal fees from Spark Therapeutics, personal fees from Genentech, personal fees from BioMarin Pharma, personal fees from Optos, personal fees from Regeneron Pharma, personal fees from Allergan, and personal fees from Adverum outside the submitted work. S. Syngal reports grants from NCI during the conduct of the study; personal fees from Myriad Genetic Labs and personal fees from Digital China Health outside the submitted work; and in addition, she has a patent to PREMM5 licensed and with royalties paid. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: L.H. Biller, M. Lutz, J.M. Weiss, M.F. Kalady, Z.K. Stadler, S. Syngal, M.B. Yurgelun

Development of methodology: L.H. Biller, M.B. Yurgelun

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Ukaegbu, C.A. Burke, A. Chittenden, E.S. Koeppe, B.H. Leach, E. Levinson, R.M. Lim, M. Lutz, E. Salo-Mullen, R. Sheikh, G. Idos, F. Kastrinos, E. Stoffel, J.M. Weiss, M.J. Hall, M.F. Kalady, Z.K. Stadler, S. Syngal, M.B. Yurgelun

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.H. Biller, J.M. Church, F. Kastrinos, E. Stoffel, M.F. Kalady, Z.K. Stadler, M.B. Yurgelun

Writing, review, and/or revision of the manuscript: L.H. Biller, C. Ukaegbu, C.A. Burke, J.M. Church, B.H. Leach, E. Levinson,

R.M. Lim, E. Salo-Mullen, F. Kastrinos, E. Stoffel, J.M. Weiss, M.J. Hall, M.F. Kalady, Z.K. Stadler, S. Syngal, M.B. Yurgelun
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Ukaegbu, T.G. Dhingra, Y. Chertock, R. Sheikh, M.B. Yurgelun
Study supervision: C. Ukaegbu, M.B. Yurgelun

Acknowledgments

This work was supported by the NIH (NCI) K24CA113433 (to S. Syngal), R01CA132829 (to S. Syngal), K07CA151769 (to F. Kastrinos), The Pussycat Foundation Helen Gurley Brown Presidential Initiative (to C. Ukaegbu), and American Cancer Society Mentored Research Scholar Grant MRSG-13-144-01-CPHPS (to J.M. Weiss).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 4, 2019; revised December 10, 2019; accepted January 9, 2020; published first February 12, 2020.

References

1. Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011;305:2311–9.
2. Turcotte LM, Neglia JP, Reulen RC, Ronckers CM, Van Leeuwen FE, Morton LM, et al. Risk, risk factors, and surveillance of subsequent malignant neoplasms in survivors of childhood cancer: a review. J Clin Oncol 2018;36:2145–52.
3. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet 2017;390:2569–82.
4. Teepen JC, Kok JL, van Leeuwen FE, Tissing WJE, Dolsma WV, van der Pal HJ, et al. Colorectal adenomas and cancers after childhood cancer treatment: a DCOG-LATER record linkage study. J Natl Cancer Inst 2018;110:758–67.
5. Henderson TO, Oeffinger KC, Whitton J, Leisenring W, Neglia J, Meadows A, et al. Secondary gastrointestinal cancer in childhood cancer survivors. Ann Intern Med 2012;156:757–66.
6. Rigter LS, Spaander MCW, Aleman BMP, Bisseling TM, Moons LM, Cats A, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 2019;125:990–9.
7. Daly PE, Samiee S, Cino M, Gryfe R, Pollett A, Ng A, et al. High prevalence of adenomatous colorectal polyps in young cancer survivors treated with abdominal radiation therapy: results of a prospective trial. Gut 2017;66:1797–801.
8. Rigter LS, Schaapveld M, Janus CPM, Krol ADG, van der Maazen RWM, Roesink J, et al. Overall and disease-specific survival of Hodgkin lymphoma survivors who subsequently developed gastrointestinal cancer. Cancer Med 2019;8:190–9.
9. Nottage K, McFarlane J, Krasin MJ, Li C, Srivastava D, Robison LL, et al. Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 2012;30:2552–8.
10. Children's Oncology Group. Long-term follow up guidelines for survivors of childhood, adolescent, and young adult cancers. Available from: http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf.
11. Yurgelun MB, Hornick JL, Curry VK, Ukaegbu CI, Brown EK, Hiller E, et al. Therapy-associated polyposis as a late sequela of cancer treatment. Clin Gastroenterol Hepatol 2014;12:1046–50.
12. Rigter LS, Kallenberg FGJ, Bastiaansen B, van Os TAM, van Leeuwen FE, van Leerdam ME, et al. A case series of intestinal adenomatous polyposis of unidentified etiology; a late effect of irradiation? BMC Cancer 2016;16:4–9.
13. Anderson JC, Butterly LF, Goodrich M, Robinson CM, Weiss JE. Differences in detection rates of adenomas and serrated polyps in screening versus surveillance colonoscopies, based on the New Hampshire colonoscopy registry. Clin Gastroenterol Hepatol 2013;11:1308–12.
14. Bianchi LK, Burke CA, Bennett AE, Lopez R, Hasson H, Church JM. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. Clin Gastroenterol Hepatol 2008;6:180–5.
15. Au S, Marquez V, Donnellan F, Salh BS, Nimmo M, Goddard KJ, et al. Colorectal polyps in childhood cancer survivors treated with radiation therapy. Dig Dis Sci 2018;63:2451–5.
16. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
17. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159–70.
18. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis. Nature 1992;359:235–7.
19. Hill MJ, Morson BC, Bussey HJR. Aetiology of adenoma–carcinoma sequence in large bowel. Lancet 1978;1:245–7.
20. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525–32.
21. Jeevaratnam P, Cottier DS, Browett PJ, Van De Water NS, Pokos V, Jass JR. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. J Pathol 1996;179:20–5.
22. Buchanan DD, Roberts A, Walsh MD, Parry S, Young JP. Lessons from Lynch syndrome: a tumor biology-based approach to familial colorectal cancer. Future Oncol 2010;6:539–49.
23. Young J, Jass JR. The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. Cancer Epidemiol Biomarkers Prev 2006;15:1778–84.
24. Guarinos C, Sanchez-Fortun C, Rodriguez-Soler M, Perez-Carbonell L, Egoavil C, Juarez M, et al. Clinical subtypes and molecular characteristics of serrated polyposis syndrome. Clin Gastroenterol Hepatol 2013;11:705–11.
25. Yan HHN, Lai JCW, Ho SL, Leung WK, Law WL, Lee JFY, et al. RNF43 germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. Gut 2017;66:1645–56.
26. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816–9.
27. Kloor M, Huth C, Voigt AY, Benner A, Schirmacher P, von Knebel Doeberitz M, et al. Prevalence of mismatch repair-deficient crypt foci in Lynch syndrome: A pathological study. Lancet Oncol 2012;13:598–606.
28. Aaltonen LA, Peltomaki P, Leach FS, Sistonen P, Pylkkanen L, Mecklin JP, et al. Clues to the pathogenesis of familial colorectal cancer. Science 1993;260:812–6.
29. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal

a new mechanism for colonic carcinogenesis. Nature 1993;363:558–61.
30. NCCN clinical practice guidelines in oncology: genetic/familial high risk assessment: colorectal. Version 2. 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
31. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223–62.
32. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MWY, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice guidelines. J Clin Oncol 2015;33:209–17.
33. Glatz K, Pritt B, Glatz D, Hartmann A, O'Brien MJ, Blaszyk H. A multinational, internet-based assessment of observer variability in the diagnosis of serrated colorectal polyps. Am J Clin Pathol 2007;127:938–45.
34. Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In:Bosman T, Carneiro F, Hruban R, Theise ND. WHO classification of tumours of the digestive system. Lyon, France: IARC; 2010:160–5.
35. Ciavarella M, Miccoli S, Prossomariti A, Pippucci T, Bonora E, Buscherini F, et al. Somatic APC mosaicism and oligogenic inheritance in genetically unsolved colorectal adenomatous polyposis patients. Eur J Hum Genet 2018;26:387–95.