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Colonoscopic screening shows increased early incidence and progression of adenomas in cystic fibrosis

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Abstract

Background—Colorectal cancer is an emerging problem in cystic fibrosis (CF). The goal of this study was to evaluate adenoma detection by systematic colonoscopic screening and surveillance.

Methods—We analyzed prospectively collected results of colonoscopies initiated at age 40 years from 88 CF patients at a single Cystic Fibrosis Center. We also reviewed results of diagnostic colonoscopies from 27 patients aged 30–39 years performed during the same time period at the Center.

Results—The incidence of polyp detection increased markedly after age 40 in CF patients. Greater than 50% were found to have adenomatous polyps; approximately 25% had advanced adenomas as defined by size and/or histopathology; 3% were found to have colon cancer. Multivariate analysis demonstrated specific risk factors for adenoma formation and progression.

Conclusions—Early screening and more frequent surveillance should be considered in patients with CF due to early incidence and progression of adenomas in this patient population.

Keywords

Cystic fibrosis; Adenoma; Colon cancer; Colorectal cancer screening

1. Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive genetic disease affecting Caucasians. Individuals with CF suffer from complications in multiple organ systems, including respiratory, gastrointestinal, and reproductive tracts. Pulmonary complications continue to be the leading cause of morbidity and mortality. Fortunately, early detection, improvements in nutrition, bronchial clearance therapy, and organ transplantation

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have led to a marked increase in life expectancy over the past 30 years [1]. With increasing survival, new complications, especially those involving the gastrointestinal tract are being identified. Adult gastroenterologists are increasingly involved in the care of multiple gastrointestinal complications associated with CF [2].

One of the emerging problems in CF patients is gastrointestinal malignancies, and colon cancer in particular [3]. Early detection of colorectal cancers and removal of adenomatous polyps reduce colon cancer mortality [4–6]. There is now broad consensus endorsing population-wide colon screening, generally starting at age 50 for average risk individuals and significantly earlier in the presence of genetic risk factors [7–10]. Currently, there are no specific recommendations from any of the medical societies on the appropriate age for initiation of screening and intervals for re-screening and surveillance in CF patients. Systematic outcome data are critically needed for development of such guidelines. In addition, specific clinical circumstances need to be considered in CF individuals, including their overall medical condition, evaluation for organ transplantation, and use of immunosuppressive medications when developing these guidelines.

The Minnesota Cystic Fibrosis has maintained a systematic colorectal screening program for CF patients starting at age 40, and we have previously published results from 45 patients [11]. We now report updated results on screening, re-screening, and surveillance colonoscopy results from the same program. In addition, we report results of diagnostic colonoscopic examinations in patients aged 30–39.

2. Methods

2.1. Study design

Results of colonoscopies in CF patients were prospectively collected at the Minnesota Cystic Fibrosis Center between 2008 and 2015, although the formal colorectal cancer screening program was started at the Center in January 2010 at which time all patients followed at the Center began receiving uniform recommendations for screening. Screening colonoscopies performed prior to 2010 were requested by individual physicians concerned about increased prevalence of colon cancer in the CF population. The majority of examinations completed at the Minnesota Cystic Fibrosis Center were performed following administration of a CF-specific colonoscopy preparation [11], but results of colonoscopies performed at outside institutions were also included. The qualifying criteria for recommendation of a screening colonoscopy were age ≥40 years, FEV1 ≥ 40% predicted, and absence of other contraindications to endoscopic procedures. Individuals with FEV1 b 40% could still be considered for colonoscopic examinations depending on the individual case assessment in coordination with their primary pulmonologist. Re-screening after negative examinations was recommended after three years. Surveillance examination intervals were determined by the colonoscopist based on the number and histopathology of the polyps. Adenomatous polyps were classified to have advanced pathology if they were N1cm in size, had villous features, or noted to have high-grade dysplasia or carcinoma [10]. In addition, we reviewed adenoma detection rates in colonoscopies performed for various diagnostic indications in patients aged 30 years and above. All patients in this study consented to have their data

collected and used for research. The study was approved by the Institutional Review Board at the University of Minnesota.

2.2. Statistical analysis

Statistical analysis was performed using R statistical software version 3.1.2. Subject age at time of initial colonoscopy versus age of subjects not receiving colonoscopy was compared as a continuous variable by T-testing. For comparison of subjects with and without polyps, chi-square analysis was performed using the categorical variables of sex, history of pancreatic insufficiency, history of cystic fibrosis related diabetes (CFRD), history of distal intestinal obstruction syndrome (DIOS), and history of lung transplant. Age was also compared as a categorical variable for subjects b 50 or age ≥ 50. CF genotype was compared as a categorical variable with ΔF508 homozygotes versus all other genotypes. For multivariate analysis logistic regression analysis was used on the above categorical variables. A p-value of b 0.05 was considered to be a significant association.

3. Results

3.1. Patient characteristics

At the time of analysis 111 patients over age 40 were enrolled at the Minnesota Cystic Fibrosis Center Database (Table 1). Of these, 82 had undergone at least one colonoscopy and 32 patients had at least one subsequent colonoscopy. A total of 88 patients have undergone colonoscopies since 2008, including 6 patients who were no longer in the database of active patients because of death or relocation. One subject had a history of familial polyposis and was excluded from factor analysis. There were no observed differences in the clinical characteristics of age, gender, CF genotype, history of diabetes or pancreatic insufficiency, DIOS, or history of lung transplantation between those who did or did not receive colonoscopic examination.

3.2. Adenoma detection on screening and re-screening colonoscopies

Adenomatous polyps were detected on initial screening colonoscopies in 43/88 patients (49%). In addition, 15 patients with negative initial examinations had undergone follow-up re-screening within a mean period of 49 months. Seven (47%) re-screening examinations revealed adenomas, and three of these examinations showed advanced adenomas. Overall, advanced adenomas were found in 20/88 patients (23%). Three or more adenomas and/or advanced histopathology were found in 28/88 patients (32%). Carcinomas were found in 3/88 patients; two of these neoplasms were in situ carcinomas within large polyps that were successfully removed endoscopically. One patient, a ΔF508 homozygote was found to have invasive rectal carcinoma within the first year following lung transplantation during her first colonoscopy. She ultimately died of complications related to treatments of the cancer.

3.3. Patient factors associated with polyp formation

In order to explore specific patient factors that may be associated with polyp formation in our cohort we examined age, gender, homozygous Δ F508 mutation, pancreatic insufficiency, CFRD, DIOS, and history of lung transplantation using univariate analysis (Supplemental Table 1). We found CFRD and homozygous Δ F508 mutation to be

statistically significant risk factors, and a trend toward significance with lung transplantation. It is important to note that the average time from transplantation to first colonoscopy in this cohort was 4.16 years. CFRD continued to be an independent risk factor on multivariate analysis (Table 2).

3.4. Patient factors associated with multiple or high risk polyp formation

Previously, we found male sex to be associated with greater risk of adenomatous polyp formation in cystic fibrosis [11]. This continued to be a trend in our analyses in this larger cohort. Male sex remained a statistically significant risk factor for the presence of either advanced or multiple adenomas (Table 3). Lung transplantation was also statistically associated with the development of multiple or advanced adenomatous polyps. All three cases of colon cancer were found in patients who were Δ F508 homozygotes with history of CFRD. Their ages ranged between 47 and 51 at the time of diagnosis. One of these patients was female and a lung transplant recipient, as noted above.

3.5. Surveillance colonoscopy adenoma detection

Patients found to have adenomatous polyps on their initial colonoscopies were generally recommended to have repeat examinations within one to two years if they remained medically stable. The majority 13/16 (81%) of these surveillance colonoscopies continued to be positive for adenomatous polyps with 6/16 (38%) having advanced histopathology on subsequent colonoscopies (Table 4).

3.6. Diagnostic colonoscopy adenoma detection (age 30–39)

We found 27 patients with CF in our database, age 30–39, who underwent diagnostic colonoscopies. The most common indications for these colonoscopies were hematochezia (n = 7) and abdominal pain (n = 7). Other indications included screening during transplant evaluation (n = 3), iron deficiency anemia (n = 2), persistent diarrhea (n = 2), colitis (n = 1), early family history of colon cancer (n = 1), pseudomembranous colitis (n = 1), and abnormal radiologic imaging with suspected polyp (n = 1). Indications were not stated in 2 colonoscopies. Four of these patients (15%) had adenomatous polyps noted and an advanced adenoma was documented in one of these examinations (4%).

4. Discussion

Improved life expectancy of CF patients over the past several decades has been accompanied by emergence of new challenges associated with older age. These include digestive tract malignancies, which are present at higher prevalence in CF patients [3]. Of these, colon cancer is the most common, and it is arguably the most preventable with an efficient screening and surveillance program. Most colon cancers arise from adenomatous polyps, which progress into carcinomas as they become larger and accumulate mutations permissive to malignant transformation. Early detection of premalignant adenomas and localized carcinoma can prevent cancer and cancer-related deaths. This is the underlying principle behind colon cancer screening in the general population, which is typically initiated at age 50. There are currently no specific guidelines for colon cancer screening that consider increased risk associated with CF, although these are being considered by the National

Cystic Fibrosis Foundation in collaboration with the American Gastroenterological Association. Paucity of data specific to CF patients continues to be a major challenge for these efforts.

The Minnesota Cystic Fibrosis Center has maintained a systematic colonoscopic screening program for a number of years for patients age 40 or above. Our results demonstrate that approximately one quarter of these patients have advanced neoplasms in the colon. This is at least 5 times higher than the 2–5% reported in different studies for the general population 40–49 years old [12–14]. Obviously, these numbers alone do not predict the fraction of patients that would progress to incurable cancer prior to another fatal CF-related complication. However, it is notable that three patients (3%) in this study were found to have carcinomas. It is likely that the two individuals who had carcinoma in situ were spared from dealing with a more advanced stage of cancer because of early detection.

In the general population and recognized hereditary colon cancer syndromes the incidence of colon cancer rises steadily with age [14]. This appears to be true also in the CF patients. We found that the rate of colon adenomas and advanced neoplasias was significantly lower in patients 30–39 years of age compared to our screening cohort of patients 40 years of age or older. Remarkably, the rate of advanced neoplasia formation in the CF patients 40–49 years of age is comparable to that of nonagenarians in the general population [15].An accelerated rate of polyp development and growth associated with CF is further suggested by the high detection rate of new adenomas, including advanced polyps, on surveillance and re-screening colonoscopies performed at relatively short intervals in our program despite optimized colon preparations that should have minimized missed polyps [11]. Taken together our data suggest a significant shift in adenoma formation and progression toward the younger age in patients with CF.

The underlying biology that is driving colon carcinogenesis remains speculative. The cystic fibrosis transmembrane conductance regulator (CFTR) was identified as a potential driver of colorectal carcinoma in a forward-based genetic screen [16]. The major recognized function of CFTR is that of an anion channel in the epithelial cells, and its deficiency decreased level of hydration of the mucus layer. Stagnant mucus is associated with bacterial overgrowth in Cftr-deficient mice along with dysregulation in gene expression involved in inflammation and epithelial homeostasis [17,18]. These physical changes in the mucus layer are also associated with compositional changes in microbiota, which can further affect epithelial function [19–22]. Interestingly, the pattern of dysregulated genes associated with CFTR deficiency overlaps with that observed following deletion of Kcnq1, which encodes for a potassium channel that is linked to CFTR function and is another tumor suppressor gene associated with gastrointestinal malignancies [23]. However, it is also important to recognize that CFTR plays important roles in epithelial biology beyond a mere anion channel. It complexes with cytoskeletal elements, associates with protein kinases, participates in maintenance of tight junctions, and may contribute to epithelial cell polarization [24–26]. Disruption of these functions can further contribute to cancer development and progression. In fact, the CFTR gene has been reported to be commonly hypermethylated in different cancer cell lines and tumor samples, suggesting a role for CFTR dysfunction in colon cancer in the general population as well [27–31].

Our attempt at identifying specific clinical variables, although certainly limited by the small size of the study, does not shed significant light on colon cancer pathogenesis in CF patients. Our finding of male sex association with more advanced polyp histopathology is consistent with excess colon cancer risk reported previously in the CF population [3] and recapitulates data obtained in the general population [14,32]. Greater incidence of adenomas in patients with CFRD and Δ F508 homozygocity may be a reflection of a more severe CF phenotype. Our results demonstrating an association between more advanced adenomas and organ transplantation related immunosuppression is consistent with augmentation of colon cancer risk in these patients found in epidemiologic studies. However, all of the subpopulations of CF patients remained at significantly increase drisk of developing advanced adenomas, and by extension colon cancer.

Emergence of colon cancer as a potentially significant clinical problem in the care of CF patients is a consequence of their improved life expectancy under modern medical care. Further increases in survival should be expected with introduction of new treatments entering clinical practice. Therefore, it is increasingly important to recognize that CF is also a colon cancer syndrome, which deserves special considerations for screening and surveillance. Our data support initiation of colorectal cancer screening at age 40 in medically stable patients. The rate of adenoma detection appears to be significantly lower at younger ages, although it should be noted that cases of colon cancer associated with CF have been reported even in teenage years.

Currently, we recommend our patients have a re-screening or surveillance colonoscopy in three years if their examination showed less than three polyps without advanced histopathology. This recommendation is based on the high rate of colon neoplasms during such examinations at relatively short intervals. We recommend surveillance colonoscopy after one year in patients found to have three or more polyps or polyps with advanced histopathology. Colonoscopic method of screening is preferred because of high likelihood of polyp detection and associated polypectomy. However, it may be reasonable to consider at least a fecal immunochemical test (FIT) for patients with poor lung function undergoing a work-up for transplantation. Premature colon cancer related death in an organ transplant recipient is tragic for the patient who may have underwent a difficult surgical procedure only to face another major crisis. In addition, detection of colon cancer in a transplant candidate is an important consideration in terms of organ allocation given limited organ availability. If the FIT test is positive, a colonoscopy can still be usually done despite a somewhat increased risk. If negative, colonoscopic screening can be postponed until after transplantation.

In summary, our study confirms the concern for earlier development of colon cancer in CF patients arising via the classic adenoma growth and progression. Increasing life expectancy of CF patients necessitates focused attention on this emerging problem and development of dedicated recommendations. Limitations of this study include its small size and a single center experience. Further research is clearly needed, and can be aided by careful and detailed entry of neoplasm detection in regional and national CF registries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CF	cystic fibrosis
CFRD	cystic fibrosis related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
DIOS	distal intestinal obstruction syndrome

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Table 1

Characteristics of 88 CF patients over the age of 40 that underwent screening colonoscopy.

Patient factor	Number of patients (percentage)
Age at First Colonoscopy	46.22 years (average)
Male sex	45 (51%)
Delta F508 homozygote	38 (43%)
Pancreatic insufficiency	70 (80%)
CFRD	50 (57%)
DIOS	18 (20%)
Lung transplant	24 (27%)
Polyp (any colonoscopy)	49 (56%)
Polyp on 1st colonoscopy	43 (49%)
Advanced pathology (any colonoscopy)	20 (23%)
3 or more polyps (any colonoscopy)	20 (23%)
Advanced pathology and or 3 or more polyps (any colonoscopy)	28 (32%)
Colon cancer	3 (3%)

Table 2

Multivariable regression analysis of polyp vs. non-polyp formers.

Variable	Polyps presents (48 patients)	Polyps absent (39 patients)	Adjusted OR (95% CI)	P value
Age > 50	19 (40%)	10 (28%)	1.82 (0.64–5.17)	0.2628
Male sex	27 (56%)	17 (44%)	2.18 (0.77–6.17)	0.1411
ΔF508 homozygote	27[a] (57%)	11 (28%)	3.88 (1.23–12.24)	0.0206*[a]
Pancreatic insufficiency	40 (83%)	29 (74%)	0.46 (0.12–1.80)	0.2628
CFRD	35 (73%)	15 (38%)	4.15 (1.29–13.40)	0.0171*
DIOS	9 (19%)	9 (23%)	0.42 (0.12–1.43)	0.1641
Lung transplant	17 (35%)	7 (18%)	2.00 (0.58–6.89)	0.2715

*P < 0.05.

[a]One patient with polyps had no genotype information available and was excluded from the analysis.

Table 3

Multivariate analysis of patient attributes association with ≥3 or high-risk polyp formation.

Variable	Multiple (≥ 3) or advanced polyps (27 patients)	Few (<3) or absent polyps (60 patients)	Adjusted OR (95% CI)	P value
Age > 50	11 (41%)	19 (32%)	1.36 (0.47–4.02)	0.5685
Male sex	19 (70%)	25 (42%)	4.51 (1.37–14.88)	0.0133 *
ΔF508 Homozygote	15[a] (58%)	23 (39%)	1.66 (0.53–5.18)	0.3842
Pancreatic insufficiency	25 (93%)	44 (73%)	2.02 (0.33–12.45)	0.44927
CFRD	20 (74%)	30 (50%)	1.67 (0.49–5.67)	0.41357
DIOS	7 (26%)	11 (18%)	1.25 (0.36–4.38)	0.72154
Lung transplant	12 (44%)	12 (20%)	3.90 (1.10–13.82)	0.03501 *

* $P < 0.05$.

[a] One patient with polyps had no genotype information available and was excluded from the analysis.

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Table 4

Results of surveillance colonoscopies, 16 individual patients.

Patient	Number of polyps on initial colonoscopy	Number of polyps on follow-up examinations						
		1 year	2 years	3 years	4 years	5 years	6 years	7 years
1	**11***	**4***	1					
2	**10***	**6***	9		**7***		1	
3	**8***		**2***					
4	**7***	1		7				
5	**7***	0						
6	**6***	3						
7	5	2		**2***		3		
8	4	4	5	**5***	**6***			
9	4	2						
10	4		1					
11	4			8				
12	3		**3***	0				
13	3	0						
14	**1***		1					
15	1	0	2					
16	1							0

Asterisk (*) and bold text indicate advanced polyp features such as size ≥1 cm or presence of villous histopathology, high grade dysplasia, or carcinoma in situ.