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Circulating Fibroblast Growth Factor-21 and Risk of Metachronous Colorectal Adenoma

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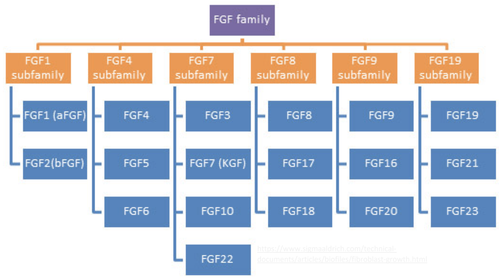
Introduction

- In the United States (US), colorectal cancer (CRC) is the third most common cancer diagnosed in men and women combined → 147,950 new cases expected to occur
- CRC remains the second most common cause of cancer deaths → 51,020 deaths to have occurred
- Hallmarks of cancer
  - Inflammation – CRC is one of the cancers in which tumors are associated with chronic inflammation
  - Metabolic alteration, along with metabolic reprogramming → identifying the inflammatory and metabolic markers that are associated with developing CRC could be beneficial
- Fibroblast growth factor 21 (FGF-21)
  - Qian et al. found that higher circulating concentrations of FGF-21 are associated with an increased likelihood of developing colorectal cancer
  - Characteristics of FGF-21
    - An endocrine FGF
    - Secreted by the liver
    - Acts as a circulating hormone to regulate simple sugar intake
    - Also associated with inflammation, and whole-body and immune homeostases
- CRC is affected by inflammatory pathways, therefore FGF-21 could also play a role in colorectal carcinogenesis



Methods

Participants (n=1,192) in the Ursodeoxycholic Acid (UDCA) Trial at the University of Arizona Cancer Center

- A phase III, randomized, double-blind, placebo-controlled clinical trial; investigated the effect of UDCA on metachronous colorectal neoplasia
- Participants had to have an adenomatous polyp, detected via colonoscopy, resected 6 months prior to randomization into the trial

Current study

- 94 participants with data for baseline and follow-up colorectal adenomas
- Adenoma recurrence (metachronous) was defined as any colonoscopy-detected adenoma or cancer at least six months after randomization to the UDCA trial
- Enzyme-linked immunosorbent assay (ELISA) was used to measure plasma FGF-21 concentrations

Statistical analyses

- Chi-square tests used to assess differences in categorical baseline characteristics across FGF-21 tertiles and colorectal adenoma recurrence; ANOVA for continuous variables
- Logistic regression modeling To determine an association between FGF-21 tertiles and odds of colorectal adenoma recurrence
- The final adjusted model included BMI category, history of polyps, and family history of CRC as well as age and sex.

Objective

- Build upon the findings of these previous reports by using a prospective study design in order to assess the relationship between circulating FGF-21 and odds of developing early neoplastic lesions in the colorectum

Results

Table 1. Baseline characteristics of participants with baseline colorectal adenomas by tertiles of fibroblast growth factor 21 (FGF-21) level (n=94)

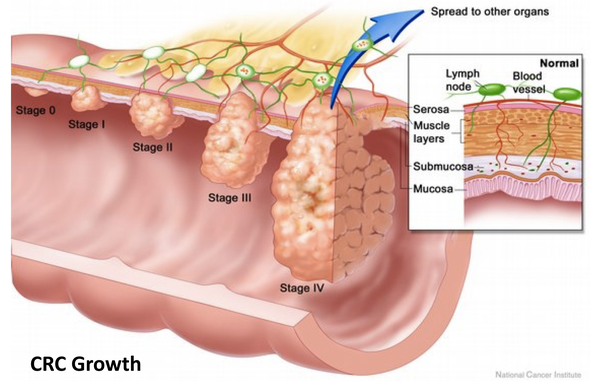
Characteristics[a]	1st Tertile (n=31)	2nd Tertile (n=32)	3rd Tertile (n=31)	p-val
	Number (%) or mean ± std			
Age, years	65.5 ± 8.37	68.0 ± 6.73	66.5 ± 8.88	0.461
Sex				0.825
Male	17 (54.8)	20 (62.5)	18 (58.1)	
Female	14 (45.2)	12 (37.5)	13 (41.9)	
Race[b,c]				0.376[d]
White	26 (83.9)	30 (93.8)	25 (83.3)	
Other	5 (16.1)	2 (6.2)	5 (16.7)	
Married				0.345[d]
Yes	24 (77.4)	28 (87.5)	22 (73.3)	
No[e]	7 (22.6)	4 (12.5)	8 (26.7)	
Education				0.859
Above High School	18 (58.1)	19 (59.4)	20 (64.5)	
High School or Less	13 (41.9)	13 (40.6)	11 (35.5)	
Ever Smoker				0.147
Yes	24 (77.4)	19 (59.4)	17 (54.8)	
No	7 (22.6)	13 (40.6)	14 (45.2)	
Aspirin Use				0.502
Yes	8 (25.8)	9 (28.1)	12 (38.7)	
No	23 (74.2)	23 (71.9)	19 (61.3)	
BMI				0.124
Normal Weight (=<25)	9 (29.0)	7 (21.9)	12 (38.7)	
Overweight (>25 & <30)	18 (58.1)	17 (53.1)	9 (29.0)	
Obese (>=30)	4 (12.9)	8 (25.0)	10 (32.3)	
History of Polyps[c]				0.049
Yes	8 (26.7)	17 (56.7)	14 (50.0)	
No	22 (73.3)	13 (43.3)	14 (50.0)	
Family History of Colon Cancer				0.506
Yes	10 (32.3)	8 (25.0)	12 (38.7)	
No	21 (67.7)	24 (75.0)	19 (61.3)	

Table 2. Odds of metachronous colorectal adenoma classified by tertile of FGF-21

FGF-21 Tertile			Crude OR (95% CI)	Adjusted OR[a] (95% CI)
(pg/ml)	(pg/mL; n)	(pg/mL; mean ± std)		
1	31	123.3 ± 40.7	1.00	1.00
2	32	285.2 ± 71.3	3.49 (1.24, 9.89)	4.72 (1.42, 15.72)
3	31	741.1 ± 424.6	2.91 (1.03, 8.20)	3.82 (1.15, 12.68)
		P-trend	0.034	0.028

Discussion

- Prior reports have established an association between higher concentrations of FGF-21 and increased risk of early and late stages of CRC
- In the current study, in a predominantly older, male and white population, preliminary results indicated that higher concentrations of FGF-21 may increase the risk of metachronous colorectal adenomas
- The highest risk was exhibited in the second tertile, a trend paralleled in the Qian et al. study
- One significant finding from the current study was related to having a personal history of polyps, a risk factor for CRC
- In those with a history of polyps, due to the stress and injury caused on the body by those polyps, it is possible this to have caused the FGF-21 levels to elevate



CRC Growth

- The results exhibited here are similar to those of other studies that have investigated the relationship between FGF-21 and other cancers such as renal and breast
- Though the results are promising, hard to discern if the high levels of FGF-21 led to the colorectal metachronous adenoma, or they increased as a result of the carcinogenesis or the stress caused on the body by the disease
- The current study aimed to contribute to the small, but growing field surrounding and examining the relationship between circulating FGF-21 and odds of developing early neoplastic lesions in the colorectum
- Overall, higher concentrations of FGF-21 were associated with increased odds of metachronous adenoma development
- More in-depth studies with larger sample sizes focusing specifically on FGF-21 will be needed to establish a clearer connection

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- References available upon request.