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Cancer Risks in Familial Adenomatous Polyposis

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This article reviews Beck SH, et al. Cancer risks in attenuated and classical familial adenomatous polyposis: A nationwide cohort with matched, nonexposed individuals. Am J Gastroenterol. 2025;120(6):1345-1352.

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STRUCTURED ABSTRACT

Question: What are the cancers risks among familial adenomatous polyposis (FAP) patients?

Design: Retrospective matched multiple cohort study.

Setting: National Danish polyposis registry.

Patients/Exposure: Classic (>100 colorectal adenomas before age 25) or attenuated (<100 colorectal adenomas) familial adenomatous polyposis (FAP) with a pathogenic/likely pathogenic variant in the APC gene. These patients were matched 1:4 to patients without FAP on year of birth, sex, and postal code at birth.

Outcomes: Cancer diagnoses (split by organ and overall), colorectal adenomas, and duodenal adenomas.

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Data Analysis: Observation began in 1997 or the patient's date of FAP diagnosis, and ended at each cancer diagnosis, death, loss to follow-up, or end of study in 2022. To estimate relative risk of cancer with age, the authors performed Cox hazards regression adjusted for year of birth, sex, and education level. They only included patients without missing data.

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Results: Of 311 patients with classic FAP (cFAP) and 134 patients with attenuated FAP (aFAP), 11.5% developed at least 1 cancer in any organ with an adjusted HR of 4.83 (cFAP) and 3.24 (aFAP) compared to 16,000 matched non-FAP patients. Overall cancer incidence decreased equally over time in all cohorts; 7.7% died during observation, 53% underwent major gastrointestinal surgery, and the incidence of newly diagnosed aFAP increased over time (and exceeded that of cFAP). In all, 9-11% of FAP patients developed colorectal cancer more often than non-FAP patients (HR 2.16-2.72 for colon cancer, HR 9.12-12.66 for rectal cancer) with no significant difference between cFAP and aFAP patients. Ninety percent of FAP patients had rectal cancer preceding colectomy. The risk for colorectal adenomas with HGD (HR 2.72) and any duodenal adenomas (HR 4.02) was higher in cFAP than aFAP. Pancreatic cancer was more common in cFAP compared to non-FAP patients (HR 7.66). See Table for details. The study was inadequately powered for duodenal cancers.

	aHR (95% CI) for cFAP*	aHR (95% CI) for aFAP*	aHR (95% CI) for cFAP vs aFAP
Any cancer	**4.83 (3.63-6.41)**	**3.24 (2.17-4.85)**	1.49 (0.98-2.27)
Colon cancer	2.16 (0.99-4.72)	**2.72 (1.19-6.22)**	0.80 (0.32-2.00)
Rectal cancer	**12.66 (7.04-22.76)**	**9.12 (4.35-19.12)**	1.39 (0.72-2.69)
Pancreatic cancer	**7.66 (1.67-35.26)**	3.19 (0.61-16.42)	2.41 (0.44-13.07)

Table 1. Cancer diagnoses
*Compared to non-FAP patients
Bold indicates $P < 0.05$
aHR: adjusted Hazard ratio; CI: Confidence Interval; cFAP: classic familial adenomatous polyposis; aFAP: attenuated familial adenomatous polyposis

COMMENTARY

Why Is This Important?

FAP is a difficult population to study because it is relatively rare, although it's clinical presentation is quite dramatic due to the burden of colorectal polyps. Many studies on FAP harken back to historical studies before the advent of routine high-definition colonoscopies for screening, as reflected in the increasing incidence of aFAP over time.[1] It is thus helpful to have a more contemporary description of cancer risks and outcomes in both cFAP and aFAP.

Key Study Findings

With presumed standard-of-care prophylactic colectomies and surveillance colonoscopies (in the United States), most FAP patients will fortunately not develop cancer, although the risk overall is still markedly higher than the average-risk patient without FAP.

There is still a subset of FAP patients that can develop rectal cancer after colectomy, thus frequent flexible sigmoidoscopy of the residual rectum (typically every 6-12 months depending on polyp burden) remains important.[2] The burden of duodenal adenomas is still substantial, particularly in the cFAP population, although we still do not fully understand risk factors for duodenal adenocarcinoma otherwise.

Caution

This study does not account for surveillance procedures such as colonoscopy prior to colectomy, as well as surveillance flexible sigmoidoscopy/pouchoscopy (for those with an ileorectal anastomosis or ileo-anal pouch anastomosis) or ileoscopy (for those with an end ileostomy) after colectomy. Prior studies have observed that the risk of ileal adenomas is higher in those with a pouch compared to end ileostomy, which would be an important risk factor to understand given its potential impact on choice of surgery.[3] It is also curious that only about half of patients underwent surgery, which may be from inadequate observation time (i.e. the colectomy has not happened) rather than non-operative colonoscopic management of polyp burden, which is seldomly feasible with substantial resource and colonoscopic burden.[4]

FAP patients are not typically recognized as high risk for pancreatic adenocarcinoma in national guidelines.[5-7] As the authors note, these patients did not undergo genetic re-evaluation to assess for comorbid pathogenic variants. To recognize this as a FAP-associated cancer, future studies must account for differences in other risk factors for pancreatic cancer (alcohol, tobacco, chronic pancreatitis etc.). Finally, the study did not examine desmoid disease, which is a leading cause of

morbidity and mortality in FAP patients despite its non-malignant nature.

My Practice

Upon meeting a newly diagnosed FAP patient, I counsel the patient that although the risk of colorectal cancer is high, the risk can be dramatically reduced with colectomy and subsequent frequent lower endoscopies. Prior to colectomy, I find that the removal of most diminutive/small adenomas and counting the exact number of polyps is practically less useful. Given that the majority of FAP patients require extended or total colectomy, I perform colonoscopy with several diagnostic goals in mind: 1) masses concerning for cancer or advanced polyps; 2) estimating whether the rectal burden of polyps is "endoscopically manageable" over time with repeat procedures; 3) define the anatomic extent of endoscopically "un-manageable" polyposis in collaboration with colorectal surgery to inform whether the patient is a candidate for an ileorectal or even ileosigmoid anastomosis to improve post-operative quality of life. Finally, I do stress to the patient that even after surgery, frequent lower endoscopies are still critical to avoid the risk of rectal cancer.

For Future Research

Larger studies incorporating endoscopic data is still needed to understand how to manage the upper intestinal manifestations of FAP such as duodenal or gastric neoplasia, as well as medication interventions to help manage those with advanced duodenal neoplasia given the morbidity associated with duodenectomy.

Conflict of Interest

The author has no reported conflicts of interest.

REFERENCES

1. Yen T, Stanich PP, Axell L, et al. APC-Associated Polyposis Conditions. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews. Seattle (WA): University of Washington, Seattle, WA.
2. Hodan R, Gupta S, Weiss JM, et al. Genetic/familial high-risk assessment: Colorectal, endometrial, and gastric, version 3.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2024;22:695-711.
3. Aelvoet AS, Roos VH, Bastiaansen BAJ, et al. Development of ileal adenomas after ileal pouch-anal anastomosis versus end ileostomy in patients with familial adenomatous polyposis. Gastrointestinal Endoscopy 2023;97:69-77.e1.
4. Ishikawa H, Yamada M, Sato Y, et al. Intensive endoscopic resection for downstaging of polyp burden in patients with familial adenomatous

polyposis (J-FAPP Study III): a multicenter prospective interventional study. Endoscopy 2023;55:344-352.
5. Sawhney MS, Calderwood AH, Thosani NC, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. Gastrointest Endosc 2022;95:817-826.
6. Daly MB, Pal T, Maxwell KN, et al. NCCN guidelines insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2024. J Natl Compr Canc Netw 2023;21:1000-1010.
7. Aslanian HR, Lee JH, Canto MI. AGA clinical practice update on pancreas cancer screening in high-risk individuals: Expert review. Gastroenterology 2020;159:358-362.