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CT Colonography Screening in Patients with a Positive Family History of Colorectal Cancer: Comparison with average-risk adults and implications for guidelines

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Abstract

Objective—The purposes of this study were to compare rates of lesion detection at CT colonographic (CTC) screening of adults without symptoms who had and did not have a family history of colorectal cancer according to American Cancer Society (ACS) guidelines and to consider the clinical implications.

Materials and Methods—Over 134 months, consecutively registered CTC cohorts of adults without symptoms who had ($n=156$; 88 [56.4%] women; 68 [43.6%] men; mean age, 56.3 years) and who did not have ($n=8857$; 4757 [53.7%] women; 4100 [46.3%] men; mean age, 56.6 years) an American Cancer Society-defined family history of colorectal cancer (first-degree relative with diagnosis before age 60 years or two first-degree relatives with diagnosis at any age) were compared for relevant colorectal findings.

Results—For the family history versus no family history cohorts, the frequency of all nondiminutive polyps (≥ 6 mm) reported at CTC was 23.7 % versus 15.5% ($p = 0.007$); small polyps (6-9 mm), 13.5% versus 9.1% ($p = 0.068$); and large polyps (≥ 10 mm), 10.2% versus 6.5% ($p = 0.068$). The rate of referral for colonoscopy was greater for the family history cohort (16.0% vs 10.5%; $p=0.035$). However, the frequencies of proven advanced adenoma (4.5% vs 3.2%; $p=0.357$), nonadvanced adenoma (5.1% vs 2.6%; $p=0.070$), and cancer (0.0% vs 0.4%; $p=0.999$) were not significantly increased. The difference in positive rates between the two cohorts (11.5% vs 4.3%; $p<0.001$) was primarily due to nonneoplastic findings of no colorectal cancer relevance, such as small hyperplastic polyps, diverticular disease, and false-positive CTC findings.

Conclusion—Although the overall CTC-positive and colonoscopy referral rates were higher in the family history cohort, the clinically relevant frequencies of advanced neoplasia and cancer

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were not significantly increased to preclude CTC screening. These findings support the use of CTC as a front-line screening option in adults with a positive family history of colorectal cancer.

Introduction

In 2008, a joint guideline for colorectal cancer (CRC) screening was issued from the American Cancer Society (ACS), the US Multi-Society Task Force (representing the three major United States-based gastrointestinal societies), and the American College of Radiology (ACR), referred to as the ACS guidelines.¹ Perhaps the most important change from past CRC screening guidelines within this landmark work is the following: “it is the strong opinion of these 3 organizations that colon cancer prevention should be the primary goal of screening”.¹ As such, preventive tests such as optical colonoscopy (OC) and CT colonography (CTC) were favored over the stool-based tests (fecal occult blood test, fecal immunochemical test, and stool DNA testing) which are primarily used for detection.^{2,3} This revised guideline actually referred only to adults at average and low-risk, because no new consideration or changes were made with regard to recommendations for patients at high risk. Rather, tables were provided for patients at high risk that were simply carryovers of older guidelines from 2001 to 2003, before quality data existed on CTC screening. For patients with a family history of CRC, defined by the ACS as cancer in a first-degree relative (FDR) diagnosed before age 60 years or in two or more FDRs at any age. OC was listed as the only recommended option, to be performed every 5 years. Similar recommendations for the exclusive use of colonoscopy appear in the most recent guidelines of the National Comprehensive Cancer Network and individual GI societies.⁴

In 2016, the United States Preventive Services Task Force updated its recommendation for CRC screening of adults at average risk.⁵ Although CTC was included as a grade A screening option for adults 50-75 years old, the task force did not consider cohorts at higher risk, including those with a family history of CRC. As such, screening options for the family history cohort have not been updated in over a decade.

Given that CTC was in its infancy at the time that the ACS recommendations were issued, its potential role in screening patients with a family history was not considered. However, because CTC has since been found to be comparable to OC for the screening detection of both advanced adenoma and cancer,⁶⁻¹⁰ we hypothesize that CTC should be an acceptable screening option in individuals without symptoms but with a family history. To date, only limited CTC screening data exist in this setting,¹¹ and they were acquired without a comparison group of control subjects who did not have a family history of CRC. The purposes of this study were to compare the rates of colorectal lesion detection at CTC screening of adults without symptoms with and without a family history of CRC and to consider the clinical implications.

Materials and Methods

This retrospective study was HIPAA compliant and approved by our institutional review board. The requirement for signed informed consent was waived.

Patient Population

Individuals eligible for routine CTC screening at our center include adults age 50-75 years old at average risk. Screening of persons older than 75 years is individualized by specific health status. Individuals with a family history of CRC are also considered eligible for CTC screening, but those with a personal history of CRC, a defined familial condition (genetic syndrome), or inflammatory bowel disease are generally referred for primary colonoscopic evaluation.

For all individuals evaluated in our CTC screening program, we prospectively obtain an abbreviated medical history, including any personal history of cancer and family history of CRC or predisposing cancer syndrome. For the purpose of this study, a family history of CRC was defined according to the ACS criteria of an FDR (parent, sibling, or child) with CRC diagnosed before 60 years of age or two or more FDR's with a CRC diagnosis at any age. For all patients with any history of CRC in the family, the specific relationship and age at diagnosis were recorded, but only those meeting the aforementioned ACS criteria were considered for inclusion in the family history cohort. Patients with a personal history of CRC, inflammatory bowel disease, Lynch syndrome (hereditary non-polyposis colorectal cancer, [HNPCC]), or polyposis syndrome were excluded from this study. Over a 134-month period (April 2004 to May 2015), a total of 156 consecutively registered adults without symptoms who had a family history of CRC underwent CTC screening at our medical center. From the same screening program and in the same time frame, a consecutively registered CTC cohort without a family history (according to the ACS definition) consisting of 8857 adults without symptoms were compared with the family history study group. The basic demographic composition of these two cohorts was similar in terms of age and sex (Table 1).

Table 2 details the specifics of FDRs in the family history cohort: 75.6% (118/156) patients had a single FDR with CRC before 60 years of age, and 24.4% (38/156) had two or more FDRs with CRC. Of note, within the no family history cohort, 6% reported having a family history of CRC, but the details they provided (e.g., second-degree relative with CRC) did not meet the ACS criteria. Given the heterogeneity and likely inconsistent reporting in these cases, these participants were not considered separately from the others in the no family history cohort.

CTC Technique & Interpretation

The CTC technique used at our institution has changed only slightly over time and has been described in detail elsewhere.^{7,12} In summary, patients undertook a low-volume bowel preparation the day before CTC using a cathartic cleansing agent. More than 95% of participants used magnesium citrate or sodium phosphate (discontinued after 2008 because of renal toxicity concerns), and most of the others used polyethylene glycol.¹³ Oral contrast material tagging of residual fecal material was achieved with 2.1% weight/volume barium sulfate; fluid tagging was achieved with either diatrizoate or iohexol iodinated contrast medium.¹⁴ During the CTC examination, colonic insufflation was maintained using room air or automated continuous low-pressure carbon dioxide delivered through a small flexible rectal catheter.¹⁵ Patients were routinely scanned in both supine and prone positions, with

additional decubitus positioning as needed.¹⁶ Images were acquired with 16- to 64-MDCT scanners at 1.25-mm collimation, 1-mm reconstruction interval, 120 kVp, and 50-75 mAs or tube-current modulation (range, 30-300 mA).

Images from all CTC examinations were prospectively interpreted by 1 of 12 experienced board-certified radiologists practicing within our abdominal imaging section (mean, 14 years in practice). The interpreting radiologists were not blinded to the CRC family history data. Radiologist performed CTC interpretation using 3D endoluminal fly-through for initial polyp detection and 2D cross-sectional images for secondary detection and polyp confirmation.^{12,17} All studies were interpreted by use of a dedicated CTC software system (V3D Colon, Viatronix). For all CTC studies showing non-diminutive lesions (≥ 6 mm), lesion size, segmental location, morphologic characteristic (sessile, pedunculated, flat, mass), and diagnostic confidence (3, most; 1, least)¹⁸ were prospectively recorded. Flat lesions were defined as less than 3 mm in height and morphologically plaque-like if smaller than 3 cm.¹⁹ Morphologically flat lesions 3 cm or larger, referred to as carpet lesions, often exceed this 3-mm threshold and are considered a separate category.²⁰ Patient-level CT Colonography Reporting and Data System (C-RADS) categorization of colorectal findings was also recorded.²¹

Optical Colonoscopy and Histopathology Analysis

When indicated for polypectomy, OC was performed by board-certified gastroenterologists, usually on the same day as CTC. In general, patients are referred for polypectomy for all large (≥ 10 mm) CTC-detected lesions and for three or more small (6-9 mm) lesions (C-RADS category C3). Patients with one or two small polyps (C-RADS category C2) are given the alternative of CTC surveillance if they prefer to avoid OC.²² All resected polyps were sent to the surgical pathology laboratory, and with histologic evaluation is performed by a specialized gastrointestinal pathologist. Advanced neoplasia is defined by the presence of any of the following: adenoma or serrated lesion 10 mm or larger, prominent villous component, high-grade dysplasia, or invasive cancer. Invasive cancer is defined as submucosal spread of malignant-appearing cells (beyond the muscularis mucosae). Given that the study period began in 2004, the histopathologic results on all older right-sided and large polyps initially labeled hyperplastic were reviewed and reclassified as serrated if appropriate. Both sessile and traditional serrated lesions were considered neoplastic, whereas classic hyperplastic polyps were considered nonneoplastic.²³

Statistical Analysis

The relevant colorectal polyp findings at CTC screening for the family history study cohort and no family history control group were compared against each other. The Fisher exact test was used to test for differences in categorical variables. The *t*-test was used to test for differences in continuous variables. Two-tailed $p < 0.05$ was used as the criterion for statistical significance.

Results

The overall rate of positive findings of nondiminutive lesions (≥ 6 mm) at CTC was significantly higher for the family history cohort (23.7%, [37/156]) than for the no family history cohort (15.5%, [1373/8857]) ($p=0.007$) (Table 3). There were a total of 72 prospectively detected colorectal lesions in the family history cohort and 2145 lesions in the no family history cohort. When positive cases were classified into small polyps (6-9 mm) and large polyps (≥ 10 mm) according to the largest detected lesion, the difference in detection rates was no longer statistically significant between the two cohorts. Small (6-9 mm) polyps (without larger lesions) were reported at screening CTC in 13.5% (21/156) of the family history cohort, compared with 9.1% (805/8857) of the no family history cohort ($p=0.068$). Similarly, 10.2% (16/156) of family history patients had at least one large (≥ 10 mm) lesion, compared with 6.4% (568/8857) of the no family history cohort ($p=0.068$). The overall rate of colonoscopy referral was significantly higher for the family history cohort (16.0% [25/156]), than for the no family history cohort (10.5% [931/8857]) ($p=0.035$). The percentage of patients with positive results in the family history group who underwent OC (67.5% [25/37]) was similar to that in the no family history cohort (67.8% [931/1373]) ($p=0.999$). These findings are summarized in Table 3.

Despite the significant differences in overall nondiminutive lesion detection and OC referral between the two groups, the rates of proven advanced adenoma (4.5% [7/156] vs 3.2%, [286/8857]; $p=0.357$), nonadvanced adenoma (5.1% [8/156] vs 2.6% [231/8857]; $p=0.070$), and cancer (0.0% [0/156] vs 0.4% [31/8857]; $p=0.999$) were not significantly increased. There was, however, a significant difference in nonneoplastic findings of no CRC potential (e.g. hyperplastic polyps, diverticular disease, false-positive CTC finding) between the two cohorts (11.5% [18/156] vs 4.3% [383/8857]; $p<0.001$), which largely accounts for the overall difference in positive findings.

In 25 family history patients who underwent OC, 31 lesions were identified and resected, including two tubulovillous adenomas, 11 tubular adenomas, four serrated polyps, six hyperplastic polyps, two mucosal lesions (normal mucosa), one lymphoid lesion, and four other benign findings, including two diverticular strictures, one benign submucosal mass, and one hamartoma. In addition, three polyps were resected but not retrieved. Compared with the results among 751 patients without a family history who underwent OC, in whom 1416 lesions were identified and resected, there was no statistically significant difference in the histologic composition of polyps resected (Table 4).

Compared with the no family history group, the family history cohort had significantly fewer polyps within the sigmoid colon relative to other segments (16.7% [12/72] vs 30.1%, [656/2145]; $p=0.013$). However, no other significant differences were seen between the two groups with regard to segmental distribution of polyps (Table 5). Furthermore, although more lesions were detected in the right colon (cecum, ascending, transverse) than in the left colon (descending, sigmoid, rectum) in the family history group (54.1% [39/72] right vs 45.8% [33/72] left) compared with the no family history group (46.2% [992/2145] right vs 53.8% [1153/2145] left), the difference was not statistically significant ($p=0.189$). No

statistically significant differences were seen between the two groups with regard to polyp morphologic characteristic or reader diagnostic confidence (Table 5).

Discussion

Regardless of family history, CRC screening of adults without symptoms by use of preventive tests that can reveal both cancers and nondiminutive benign neoplastic polyps is clearly of benefit to the general population. Accordingly, the 2008 landmark ACS guidelines for CRC screening of adults at average risk strongly emphasized the use of preventive modalities, such as OC and CTC, over stool-based tests.¹ The 2016 U.S. Preventive Services Task Force recommendations for CRC screening include CTC as a grade A screening option.⁵ However, this statement did not consider the 3-10% of individuals with an FDR with CRC.²⁴ Although most new CRC cases arise in patients without any family history of CRC, as many as 15-25% of cases occur in individuals who have an FDR with a history of CRC – in the absence of any defined genetic syndrome (so-called familial CRC).^{25,26} Another 5-10% of diagnoses of CRC are a consequence of recognized hereditary conditions, most commonly HNPCC (Lynch syndrome) and familial adenomatous polyposis.^{24,25}

The actual increased risk of CRC reported for individuals with an FDR history varies somewhat according to the source, but most studies have reported modestly increased relative risk of approximately 1.5-2.25.²⁷⁻³⁰ These figures have been confirmed in two separate meta-analyses.^{29,30} In one study, investigators estimated that the lifetime risk of CRC in these patients increases to 7%, a modest increase from the 5% lifetime risk in the general population.³¹ The exact reasons of the increased risk are not entirely clear but are related to the specific inherited gene profile, shared environmental factors, or some combination of the two. A similar increased risk of nonadvanced and advanced adenomas has also been reported, although some studies have not shown a significant increase.^{28,32-35}

Given the higher likelihood of development of cancer among individuals with an FDR with cancer, the exclusive recommendation for colonoscopic screening every 5 years was perhaps reasonable at its time of issuance. However, because these guidelines were issued before the validation of CTC for asymptomatic screening, inclusion of this modality is now worth considering. In addition to its primary efficacy, with a sensitivity for advanced adenomas and cancer that rivals that of OC,⁶⁻¹⁰ CTC has a number of other advantages for screening. The reduced invasiveness makes it safer, more convenient, preferred by patients over colonoscopy,³⁶⁻³⁸ and more cost-effective.^{39,40} When presented with the screening options of OC and CTC, considerably more individuals choose CTC, leading to increased adherence.^{41,42} The cross-sectional nature of CTC also provides opportunities for screening for additional conditions, including aortic aneurysm and osteoporosis.⁴³⁻⁴⁵

Beyond the general advantages of CTC over OC for CRC screening, the specific findings among patients with a family history in this study support its use in this cohort at higher risk. Compared with the findings among individuals without an ACS-defined family history of CRC, the rates of both advanced and nonadvanced adenomas were not significantly increased. Importantly, no cancers were identified in the family history cohort. Interestingly, the difference in the overall positive rate for nondiminutive lesions was primarily due to

findings unrelated to cancer risk, such as small hyperplastic polyps, diverticular disease, and false-positive CTC findings. Perhaps knowledge of the family history on the part of the interpreting radiologists, who were not blinded to pertinent history, led to a heightened awareness and overcalling of some lesions, such as masslike diverticular disease.

Before this study, few data existed on CTC screening of adults without symptoms who had a family history. Although the number of patients with an FDR with CRC was reported in both the U.S. Department of Defense and American College of Radiology Imaging Network CTC screening trials,^{8,10} the diagnostic performance in these specific subcohorts was not reported. Fini et al performed a prospective trial in which individuals with an FDR family history of CRC were invited to undergo noncathartic CTC with confirmatory OC in all cases.¹¹ Although this study did not have a control group, no cancers were found among the 304 participants. Advanced adenoma was detected with CTC in eight of nine cases, corresponding to a similar prevalence in the 3-4% range. Between this and our current study, the lack of invasive cancers provides reassurance that although these patients carry slightly increased lifetime risk, CTC appears to be an acceptable screening option.

In addition to CRC, the ACS guidelines also include adenomatous polyps in the definition of family history. We intentionally ignored this factor for the following reasons. First, improvements in OC capabilities and an increased emphasis on adenoma detection rate have vastly increased identification of diminutive tubular adenomas, which are of doubtful clinical relevance.^{46,47} Prevalence rates exceeding 50% at OC screening have now been reported,⁴⁸ for which universal polypectomy will increase both costs and complications with likely relatively little clinical benefit. Inclusion of all adenomas in the ACS family history definition therefore makes little sense, although one could argue for including advanced adenoma. However, it is unrealistic to expect that individuals would have an accurate understanding or even knowledge of such benign findings from a previous OC examination in their FDRs. We do not even inquire about adenomatous findings during the family history intake.

We acknowledge limitations to this study. Most notable was the relatively small size of the family history cohort, despite accrual exceeding a decade. This is likely due in part to the existing guidelines themselves, as CTC is not yet explicitly listed as a recommended screening modality for these patients (unlike adults at average risk). However, by some reports, the expected prevalence of an ACS-defined family history of CRC is approximately 2% in the general population²⁶, similar to our observed 1.7% (156/9013) prevalence at CTC screening in this study. Nonetheless, our study was clearly underpowered for detecting a statistically significant difference in invasive cancers between the two cohorts. Furthermore, the increased detection rate of advanced adenomas in the family history cohort versus control cohort (4.5 vs 2.6%) would become statistically significant if this ratio were to hold up in a larger trial. However, this degree of increase would not preclude the use of CTC as a front-line screening option, especially given its relative advantages over OC. Like most other investigators, we did not specifically consider patients with lesser degrees of a family history, such as second-degree relatives or solitary FDRs with a diagnosis at an advanced age. We also did not consider patients at much higher risk, particularly those with HNPCC,

familial adenomatous polyposis, or ulcerative colitis. We generally consider OC to be the front-line examination for such patients, reserving CTC for limited problem solving.

In summary, although the overall CTC-positive and colonoscopy referral rates were higher in our ACS-defined family history cohort, we found no statistically significant increase in actual rates of neoplasia, including advanced neoplasia and cancer. These findings suggest that CTC can be safely used as a front-line screening strategy for adults with a family history of CRC.

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References

1. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA: A Cancer J Clin*. 2008; 58:130–60.
2. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014; 370:1287–1297. [PubMed: 24645800]
3. Pickhardt PJ. Emerging stool-based and blood-based non-invasive DNA tests for colorectal cancer screening: the importance of cancer prevention in addition to cancer detection. *Abdom Radiol (NY)*. 2016; 41:1441–144. [PubMed: 27259335]
4. Patel SG, Lowery JT, Gatof D, Ahnen DJ. Practical opportunities to improve early detection and prevention of colorectal cancer (CRC) in members of high-risk families. *Dig Dis Sci*. 2015; 60:748–761. [PubMed: 25698379]
5. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016; 315:2564–75. [PubMed: 27304597]
6. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut*. 2009; 58:241–8. [PubMed: 18852257]
7. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med*. 2007; 357:1403–12. [PubMed: 17914041]
8. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003; 349:2191–200. [PubMed: 14657426]
9. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection - systematic review and meta-analysis. *Radiology*. 2011; 259:393–405. [PubMed: 21415247]
10. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *New England Journal of Medicine*. 2008; 359:1207–17. [PubMed: 18799557]
11. Fini L, Laghi L, Hassan C, et al. Noncathartic CT colonography to screen for colorectal neoplasia in subjects with a family history of colorectal cancer. *Radiology*. 2014; 270:784–90. [PubMed: 24475809]
12. Pickhardt PJ. Screening CT colonography: how I do it. *AJR Am J Roentgenol*. 2007; 189:290–8. [PubMed: 17646453]

13. Borden ZS, Pickhardt PJ, Kim DH, Lubner MG, Agriantonis DJ, Hinshaw JL. Bowel Preparation for CT Colonography: Blinded Comparison of Magnesium Citrate and Sodium Phosphate for Catharsis. *Radiology*. 2010; 254:138–44. [PubMed: 20032148]
14. Johnson B, Hinshaw JL, Robbins JB, Pickhardt PJ. Objective and subjective intrapatient comparison of iohexol versus diatrizoate for bowel preparation quality at CT colonography. *American Journal of Roentgenology*. (in press).
15. Shinnors TJ, Pickhardt PJ, Taylor AJ, Jones DA, Olsen CH. Patient-controlled room air insufflation versus automated carbon dioxide delivery for CT colonography. *American Journal of Roentgenology*. 2006; 186:1491–6. [PubMed: 16714635]
16. Buchach CM, Kim DH, Pickhardt PJ. Performing an additional decubitus series at CT colonography. *Abdominal Imaging*. 2011; 36:538–44. [PubMed: 21184064]
17. Pickhardt PJ, Lee AD, Taylor AJ, et al. Primary 2D versus primary 3D polyp detection at screening CT Colonography. *American Journal of Roentgenology*. 2007; 189:1451–6. [PubMed: 18029884]
18. Pickhardt PJ, Choi JR, Nugent PA, Schindler WR. The effect of diagnostic confidence on the probability of optical colonoscopic confirmation of potential polyps detected on CT colonography: Prospective assessment in 1,339 asymptomatic adults. *American Journal of Roentgenology*. 2004; 183:1661–5. [PubMed: 15547207]
19. Pickhardt PJ, Kim DH, Robbins JB. Flat (Nonpolypoid) Colorectal Lesions Identified at CT Colonography in a US Screening Population. *Academic Radiology*. 2010; 17:784–90. [PubMed: 20227304]
20. Pickhardt PJ, Lam VP, Weiss JM, Kennedy GD, Kim DH. Carpet Lesions Detected at CT Colonography: Clinical, Imaging, and Pathologic Features. *Radiology*. 2014; 270:435–43. [PubMed: 24029647]
21. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: A consensus proposal. *Radiology*. 2005; 236:3–9. [PubMed: 15987959]
22. Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. *Lancet Oncol*. 2013; 14:711–20. [PubMed: 23746988]
23. Kim DH, Matkowskyj KA, Lubner MG, et al. Serrated Polyps at CT Colonography: Prevalence and Characteristics of the Serrated Polyp Spectrum. *Radiology*. 2016:151608.
24. Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. *Genet Med*. 2015; 17:702–12. [PubMed: 25590981]
25. Samadder NJ, Jasperson K, Burt RW. Hereditary and Common Familial Colorectal Cancer: Evidence for Colorectal Screening. *Dig Dis Sci*. 2015; 60:734–47. [PubMed: 25501924]
26. Hennink SD, van der Meulen-de Jong AE, Wolterbeek R, et al. Randomized Comparison of Surveillance Intervals in Familial Colorectal Cancer. *Journal of Clinical Oncology*. 2015; 33:4188–+. [PubMed: 26527788]
27. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A Prospective-Study of Family History and the Risk of Colorectal-Cancer. *New England Journal of Medicine*. 1994; 331:1669–74. [PubMed: 7969357]
28. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *New England Journal of Medicine*. 2000; 343:162–8. [PubMed: 10900274]
29. Imperiale TF, Ransohoff DF. Risk for colorectal cancer in persons with a family history of adenomatous polyps: a systematic review. *Ann Intern Med*. 2012; 156:703–709. [PubMed: 22586009]
30. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *American Journal of Gastroenterology*. 2001; 96:2992–3003. [PubMed: 11693338]
31. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. *Eur J Cancer*. 2006; 42:216–27. [PubMed: 16338133]
32. Cottet V, Pariente A, Nalet B, et al. Colonoscopic screening of first-degree relatives of patients with large adenomas: Increased risk of colorectal tumors. *Gastroenterology*. 2007; 133:1086–92. [PubMed: 17919484]

33. Tsai FC, Strum WB. Impact of a Family History of Colorectal Cancer on the Prevalence of Advanced Neoplasia at Colonoscopy in 4,967 Asymptomatic Patients. *Digestive Diseases and Sciences*. 2012; 57:3234–9. [PubMed: 22183823]
34. Armelao F, Paternolli C, Franceschini G, et al. Colonoscopic findings in first-degree relatives of patients with colorectal cancer: a population-based screening program. *Gastrointest Endosc*. 2011; 73:527–34. [PubMed: 21353850]
35. Ng SC, Lau JYW, Chan FKL, et al. Increased Risk of Advanced Neoplasms Among Asymptomatic Siblings of Patients With Colorectal Cancer. *Gastroenterology*. 2013; 144:544–50. [PubMed: 23159367]
36. Moawad FJ, Maydonovitch CL, Cullen PA, Barlow DS, Jenson DW, Cash BD. CT colonography may improve colorectal cancer screening compliance. *American Journal of Roentgenology*. 2010; 195:1118–23. [PubMed: 20966316]
37. Pickhardt PJ. Incidence of colonic perforation at CT colonography: Review of existing data and implications for screening of asymptomatic adults. *Radiology*. 2006; 239:313–6. [PubMed: 16641348]
38. Pooler BD, Baumel MJ, Cash BD, et al. Screening CT colonography: multicenter survey of patient experience, preference, and potential impact on adherence. *American Journal of Roentgenology*. 2012; 198:1361–6. [PubMed: 22623549]
39. Pickhardt PJ, Hassan C, Laghi A, Zullo A, Kim DH, Morini S. Cost-effectiveness of colorectal cancer screening with computed tomography colonography: the impact of not reporting diminutive lesions. *Cancer*. 2007; 109:2213–21. [PubMed: 17455218]
40. Pyenson B, Pickhardt PJ, Sawhney TG, Berrios M. Medicare cost of colorectal cancer screening: CT colonography vs. optical colonoscopy. *Abdom Imaging*. 2015; 40:2966–76. [PubMed: 26350285]
41. Sali L, Mascacchi M, Falchini M, et al. Reduced and Full-Preparation CT Colonography, Fecal Immunochemical Test, and Colonoscopy for Population Screening of Colorectal Cancer: A Randomized Trial. *J Natl Cancer Inst*. 2016; 108
42. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncology*. 2012; 13:55–64. [PubMed: 22088831]
43. Pickhardt PJ, Lee LJ, del Rio AM, et al. Simultaneous Screening for Osteoporosis at CT Colonography: Bone Mineral Density Assessment Using MDCT Attenuation Techniques Compared With the DXA Reference Standard. *J Bone Miner Res*. 2011; 26:2194–203. [PubMed: 21590738]
44. Hassan C, Pickhardt P, Laghi A, et al. Computed tomographic colonography to screen for colorectal cancer, extracolonic cancer, and aortic aneurysm. *Arch Intern Med*. 2008; 168:696–705. [PubMed: 18413551]
45. Pickhardt PJ, Hassan C, Laghi A, Kim DH. CT colonography to screen for colorectal cancer and aortic aneurysm in the Medicare population: cost-effectiveness analysis. *AJR Am J Roentgenol*. 2009; 192:1332–40. [PubMed: 19380558]
46. Bond JH. Clinical relevance of the small colorectal polyp. *Endoscopy*. 2001; 33:454–7. [PubMed: 11396767]
47. Pickhardt PJ, Kim DH. Colorectal cancer screening with CT colonography: key concepts regarding polyp prevalence, size, histology, morphology, and natural history. *American Journal of Roentgenology*. 2009; 193:40–6. [PubMed: 19542393]
48. Austin GL, Fennimore B, Ahnen DJ. Can Colonoscopy Remain Cost-Effective for Colorectal Cancer Screening? The Impact of Practice Patterns and the Will Rogers Phenomenon on Costs. *American Journal of Gastroenterology*. 2013; 108:296–301. [PubMed: 23208273]

Table 1
Demographic Data on the Two Screening cohorts

Variable	CRC FH(+)	CRC FH(-)
Patients (N)	156	8857
Mean age (years)	56.3	56.6
Age range (years)	23-93	44-97
Male:Female	68:88	4100:4757
% Female	56.4%	53.7%

Table 2
Specifics of Family History in the Family History Cohort (N=156)

FDR CRC Data	FDR <60 years (N=118)	2 FDR's (N=38)
Father (N, % of sub-cohort)	39 (33.0%)	26 (68.4%)
Mother (N, % of sub-cohort)	30 (25.4%)	23 (60.1%)
Sibling (N, % of sub-cohort)	46 (39.0%)	24 (63.2%)
Child (N, % of sub-cohort)	3 (2.5%)	0 (0.0%)
Age at CRC dx (mean, range)	48.6 (21-59) years	62.3 (20-90) years

Table 3
Comparison of Colorectal Findings Between the Two Screening Cohorts*

Variable	CRC FH(+) (N=156)	CRC FH(-) (N=8857)	P-value
Patients with polyps ≥ 6 mm	23.7% (37/156)	15.5% (1373/8857)	0.007
Patients with polyps ≥ 10 mm	10.3% (16/156)	6.4% (568/8857)	0.068
Patients with polyps 6-9 mm	13.5% (21/156)	9.1% (805/8857)	0.068
Patients evaluated at OC	16.0% (25/156)	10.5% (931/8857)	0.035
Patients with non-advanced adenomas *	5.1% (8/156)	2.6% (231/8857)	0.070
Patients with advanced adenomas	4.5% (7/156)	3.2% (286/8857)	0.357
Patients with other benign histology	11.5% (18/156)	4.3% (383/8857)	<0.001
Patients with adenocarcinoma	0% (0/156)	0.4% (31/8857)	0.999

* By-patient assessment was made according to most significant colorectal lesion

Table 4

Comparison of Histologic Findings on Non-diminutive Polyps

Polyp histology	CRC FH(+) (N=31 polyps in 25 patients)		CRC FH(-) (N=1416 polyps in 751 patients)		p-value
	N	%	N	%	
Tubular adenoma	11	35.5%	654	46.2%	0.277
Tubular adenoma/HGD *	0	--	7	0.5%	0.999
Serrated adenoma	4	12.9%	68	4.8%	0.064
Serrated adenoma/HGD	0	--	1	0.1%	0.999
Tubulovillous adenoma	2	6.5%	126	8.9%	0.999
Tubulovillous adenoma/HGD	0	--	12	0.8%	0.999
Villous adenoma	0	--	6	0.4%	0.999
Villous adenoma/HGD	0	--	2	0.1%	0.999
Adenocarcinoma	0	--	33	2.3%	0.999
Hyperplastic	6	19.4%	325	23.0%	0.829
Inflammatory	1	3.2%	12	0.8%	0.246
Lymphoid	1	3.2%	4	0.3%	0.103
Normal mucosa	2	6.5%	35	2.5%	0.187
Other benign [†]	4	12.9%	131	9.3%	0.525
TOTAL POLYPS	31	100%	1416	100%	--

* HGD = high-grade dysplasia.

[†] Includes submucosal lesions, hamartoma, venous bleb, lipoma, etc.

Table 5
Polyp Location, Morphologic Features, and Diagnostic Confidence at Screening CT Colonography

Variable	CRC FH(+) (N=72 polyps in 156 patients)		CRC FH(-) (N=2145 polyps in 8857 patients)		p-value
	N	%	N	%	
Colonic Segment					
Cecum	7	9.7%	239	11.1%	0.850
Ascending	18	25.0%	429	20.0%	0.297
Transverse	14	19.4%	324	15.1%	0.317
Descending	10	13.9%	178	8.3%	0.126
Sigmoid	12	16.7%	646	30.1%	0.013
Rectum	11	15.3%	329	15.3%	0.999
Polyp Morphology	N	%	N	%	P-value
Sessile	45	62.5%	1338	62.4%	0.999
Pedunculated	13	18.1%	346	16.1%	0.627
Flat *	10	13.9%	379	17.7%	0.528
Mass – Bulky	2	2.8%	40	1.9%	0.399
Mass – Carpet *	1	1.4%	20	0.9%	0.147
Mass – Benign Stricture	1	1.4%	11	0.5%	0.328
Submucosal/Extrinsic	0	0.0%	11	0.5%	0.999
Diagnostic Confidence	N	%	N	%	P-value
3 = most confident	51	70.8%	1678	78.2%	0.462
2 = somewhat confident	18	25.0%	406	18.9%	0.222
1 = least confident	3	4.2%	61	2.8%	0.148

* See Methods for flat lesion definition