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A B S T R A C T

Purpose

Colonoscopic surveillance is recommended for individuals with familial colorectal cancer (CRC). However, the appropriate screening interval has not yet been determined. The aim of this randomized trial was to compare a 3-year with a 6-year screening interval.

Patients and Methods

Individuals between ages 45 and 65 years with one first-degree relative with CRC age < 50 years or two first-degree relatives with CRC were selected. Patients with zero to two adenomas at baseline were randomly assigned to one of two groups: group A (colonoscopy at 6 years) or group B (colonoscopy at 3 and 6 years). The primary outcome measure was advanced adenomatous polyps (AAPs). Risk factors studied included sex, age, type of family history, and baseline endoscopic findings.

Results

A total of 528 patients were randomly assigned (group A, $n = 262$; group B, $n = 266$). Intention-to-treat analysis showed no significant difference in the proportion of patients with AAPs at the first follow-up examination at 6 years in group A (6.9%) versus 3 years in group B (3.5%). Also, the proportion of patients with AAPs at the final follow-up examination at 6 years in group A (6.9%) versus 6 years in group B (3.4%) was not significantly different. Only AAPs at baseline was a significant predictor for the presence of AAPs at first follow-up. After correction for the difference in AAPs at baseline, differences between the groups in the rate of AAPs at first follow-up and at the final examination were statistically significant.

Conclusion

In view of the relatively low rate of AAPs at 6 years and the absence of CRC in group A, we consider a 6-year surveillance interval appropriate. A surveillance interval of 3 years might be considered in patients with AAPs and patients with \geq three adenomas.

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INTRODUCTION

Colorectal carcinoma (CRC) is the third most common cancer and fourth leading cause of overall cancer mortality worldwide.¹ Various population screening programs, including fecal occult blood testing, sigmoidoscopy, and colonoscopy, have been implemented worldwide to detect CRC at an early stage or to prevent the development of CRC by removal of adenomatous polyps.²⁻⁸ Screening by fecal occult blood testing has been shown to reduce CRC mortality by approximately 15% and screening by sigmoidoscopy by approximately 50%.⁹⁻¹²

A substantial proportion (10% to 15%) of patients with CRC have a positive family history for

CRC without evidence of an inherited CRC syndrome, such as Lynch syndrome or familial adenomatous polyposis. These individuals have a moderately increased relative risk (RR) of developing CRC, varying from 2 to 6, compared with the general population. Risk depends on the age of onset of CRC in a first-degree relative (FDR) and on the number of family members affected with CRC. An individual with one FDR with CRC diagnosed at age < 50 years has a reported RR of 3 to 4, whereas an individual with two FDRs with CRC diagnosed at any age has an RR of developing CRC of 4 to 6.¹³⁻¹⁶

Surveillance of individuals with an elevated risk for familial CRC is attractive for two reasons, first because the reported compliance rate with early

detection programs is higher than that for average-risk individuals, and second because the yield of surveillance is higher.¹⁷⁻²⁵ Although all experts in the field recommend surveillance by colonoscopy, the optimal surveillance interval between colonoscopic examinations has not yet been clearly defined. Current guidelines recommend surveillance at intervals varying from 3 to 5 to 6 years, starting from the age of 45 years.²⁶⁻²⁸

We therefore initiated a multicenter randomized clinical trial—the FACTS (Familial Colorectal Cancer Surveillance) study—in the Netherlands. The objective of this study was to establish the optimal surveillance interval in familial CRC by comparing occurrence of advanced adenomatous polyps (AAPs) in patients under surveillance every 3 years with occurrence in those at an interval of 6 years.

PATIENTS AND METHODS

Study Design

This nationwide randomized controlled trial was coordinated by the Netherlands Foundation for the Detection of Hereditary Tumors at Leiden

University Medical Center in Leiden. Colonoscopies were performed by trained gastroenterologists. On the basis of the results of the baseline colonoscopy, patients were assigned to different study groups (groups A and B). Patients who had ≥ three adenomatous polyps at baseline were excluded and scheduled for a follow-up colonoscopy at 3 years. Patients with zero, one, or two adenomatous polyps at baseline were randomly assigned to one of two groups: Group A underwent colonoscopy at 6 years, whereas group B underwent follow-up colonoscopies at 3 and 6 years (Fig 1). The study protocol was approved by the medical ethics committee at Leiden University Medical Center and by the local medical ethics committees at collaborating hospitals. The study complies with the CONSORT checklist published in 2010.

Participants

As described previously,²⁹ all gastroenterologists and general practitioners (GPs) in the Netherlands were informed about the study. Individuals interested in participating provided both written informed consent and completed a questionnaire regarding their personal medical and family histories. The family history was verified with medical and pathology reports. In suspected cases of hereditary CRC syndrome (patients with CRC age < 50 years), tumors were analyzed for microsatellite instability (MSI), and patients with MSI-high tumors were referred to clinical genetic centers.

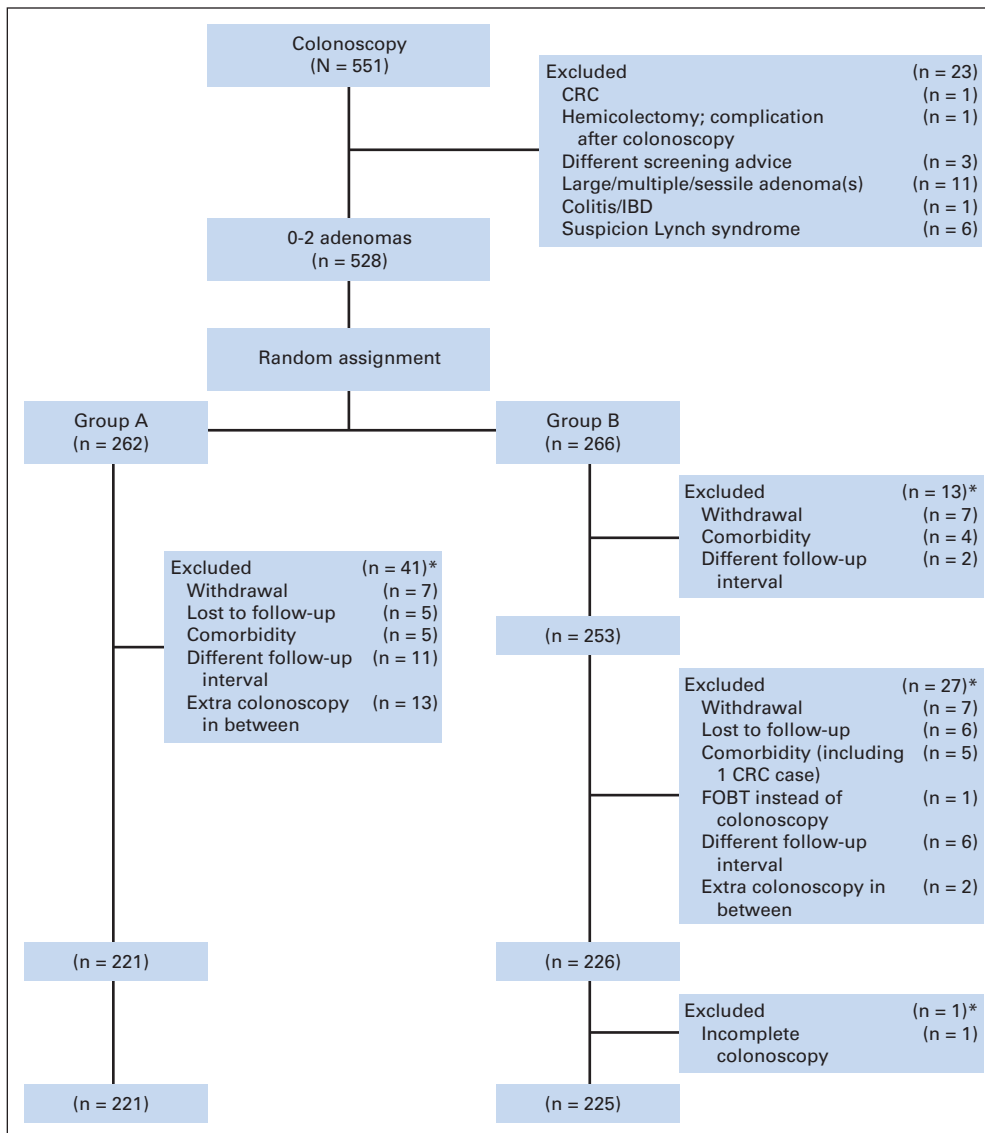


Fig 1. CONSORT diagram/flowchart. CRC, colorectal cancer; FOBT, fecal occult blood test; IBD, inflammatory bowel disease. (*) Included in intention-to-treat analysis.

The inclusion period was 2002 to 2007. Individuals were considered eligible for inclusion if they met the following criteria: age between 45 and 65 years with a positive family history of CRC (ie, one FDR diagnosed with CRC at age < 50 years or two FDRs diagnosed with CRC at any age). Ineligibility was determined on the basis of additional FDRs or second-degree relatives with CRC, a personal history of inflammatory bowel disease, previous colorectal surgery, an FDR with CRC with known MSI, or strong suspicion of Lynch syndrome (eg, combination of CRC and endometrial cancer).

The collaborating centers selected participants using the abovementioned criteria. The informed consent of individuals meeting these criteria was sent to the coordinating center. At the coordinating center, the selected patients from participating centers were alternately allocated, determined by the inclusion order, to the two groups (A and B) by the study coordinator. Participants were not stratified according to sex or participating center. After completion of the randomization process, participants and their gastroenterologists and GPs were informed about their allocated group and the time of the next scheduled colonoscopy.

Colonoscopic Surveillance and Pathologic Review

The outcomes of all colonoscopic examinations were collected at the study center. Information was also gathered on the completeness of colonoscopic examination (visualization of appendiceal opening, cecal valve, and/or insertion of terminal ileum). If the colon was severely contaminated, the examination was repeated.

All pathology reports and adenomas were reviewed by one pathologist in Leiden (H.M.). The primary outcome measure was the presence of an adenoma with advanced pathology (AAP), defined as an adenoma with either high-grade dysplasia, tubulovillous or villous architecture, or a size ≥ 1 cm in diameter. The secondary outcome measure was the presence of adenomas.

Statistical Analysis

Sample-size calculations were based on the detection of a difference in percentage of patients with AAPs at 3 years of 3.75% (in group B) and at 6 years of 10% (in group A), with a power of 80% and one-sided level of significance of .05, requiring 468 and 624 patients, respectively, taking into account a predicted 25% dropout rate resulting from noncompliance (10%), incidence of multiple polyps (10%), and sessile polyps > 3 cm and malignant adenomas (5%). During recruitment, we found that the dropout rate was much lower than expected (approximately 10% instead of 25%), and as a consequence, fewer patients were required.

According to the principles of intention-to-treat analysis, patients with follow-up examinations that deviated from the scheduled protocol were analyzed in their original randomization group. Logistic regression analysis calculating odds ratios (ORs) was used for comparison of the proportions of patients developing AAPs (primary outcome) and adenomas (secondary outcome) at the first follow-up (6 years in group A compared with 3 years in group B) and final follow-up examinations (6 years in group A compared with 6 years in group B).

Logistic regression models were also used for the risk factor analysis. The following risk factors were analyzed as predictors for developing AAPs by the first follow-up examination (intention-to-treat analysis): sex, age at enrollment, age group (\leq and $>$ 55 years), type of family history, and findings at baseline (presence of adenoma, adenoma in proximal colon, and AAPs). All reported *P* values are two sided, and values $<$.05 were considered significant. All analyses were performed using SPSS software (version 22; SPSS, Chicago, IL).

RESULTS

Baseline Findings and Features of Study Groups

A total of 551 patients accepted the invitation to participate in the FACTS study. Family history was confirmed by medical records in 99% of all patient cases, and family history for CRC could be confirmed by pathology reports in 47% of patient cases. All participants

Table 1. Patient Characteristics and Findings at Baseline Colonoscopy

Characteristic	No. of Patients (%)	
	Group A (n = 262)*	Group B (n = 266)†
Age, years		
Median	53.0	53.5
IQR	49-57	49-58
Age group, years		
\leq 55	174 (66)	157 (59)
$>$ 55	88 (34)	109 (41)
Sex		
Male	125 (48)	102 (38)
Female	137 (52)	164 (62)
Family history of CRC		
One FDR age < 50 years	129 (49)	130 (49)
Two FDRs at any age	133 (51)	136 (51)
Two age < 70 years	50 (19)	52 (20)
One age < 70 and one age > 70 years	65 (25)	73 (27)
Two age > 70 years	18 (7)	11 (4)
Adenomas		
No	216 (82)	220 (83)
Yes	46 (18)	46 (17)
Proximal adenomas		
No	246 (94)	249 (94)
Yes	15 (6)	17 (6)
Unknown	1 (0.3)	
AAPs		
No	257 (98.1)	251 (94.4)
Yes	5 (1.9)	15 (5.6)

Abbreviations: AAP, advanced adenomatous polyp; CRC, colorectal cancer; FDR, first-degree relative; IQR, interquartile range.
*One examination (at 6 years).
†Two examinations (at 3 and 6 years).

underwent a baseline colonoscopy in the period from 2002 to 2007. The cecum was visualized in 93%.

For reasons shown in Figure 1 (upper row), 23 patients were excluded from the study. Eight of the 23 patients had \geq three adenomatous polyps. Follow-up colonoscopy at 3 years was thus advised according to national guidelines. Of the remaining 528 patients with zero, one, or two adenomatous polyps at baseline, 262 were randomly assigned to group A for colonoscopy at 6 years and 266 to group B for follow-up colonoscopy at both 3 and 6 years (Table 1). Endoscopic findings at baseline are listed in Table 1. Patients in group B were found to have more AAPs at baseline than those in group A.

First Follow-Up Examination

A total of 245 patients (94%) in group A returned for a follow-up colonoscopy. The cecal intubation rate was 95%. Twenty-four (10%) of the 245 patients had either a follow-up interval that deviated by $>$ 1 year from the planned scheduled colonoscopy interval or an additional colonoscopic examination before the scheduled examination.

In group B, 255 patients (96%) returned for the first follow-up colonoscopy. The cecal intubation rate was also 95%. Two (0.8%) of the 255 patients did not comply with the originally defined follow-up schedule.

The outcomes of colonoscopy at 6 years in group A and 3 years in group B were compared in the intention-to-treat analysis. The proportion of patients with adenomas was 26% after 6 years compared

Table 2. Findings of Follow-Up Colonoscopy

Finding	First Follow-Up Examination		Second Follow-Up Examination
	Group A (n = 245)*	Group B (n = 255)†	Group B (n = 234)*
Adenomas, No. (%)	63 (26)	32 (13)	46 (20)
Crude OR (95% CI)			
6-year A v 3-year B		2.4 (1.5 to 3.9)	
6-year A v 6-year B		1.4 (0.92 to 2.2)	
AAPs, No. (%)	17 (6.9)	9 (3.5)	8 (3.4)
Crude OR (95% CI)			
6-year A v 3-year B		2.0 (0.89 to 4.7)	
6-year A v 6-year B		2.1 (0.89 to 5.0)	
Adjusted OR (95% CI)			
6-year A v 3-year B		2.44 (1.03 to 5.78)	
6-year A v 6-year B		2.61 (1.06 to 6.45)	

Abbreviations: AAP, advanced adenomatous polyp; OR, odds ratio.
*At 6 years.
†At 3 years.

with 13% after 3 years (crude OR, 2.4; 95% CI, 1.5 to 3.9; $P < .001$; Table 2). The proportion of patients with AAPs after 6 years was 6.9% compared with 3.5% after 3 years (crude OR, 2.0; 95% CI, 0.89 to 4.7; $P = .09$). There was one patient case of incident in CRC group B after 3 years, a poorly differentiated tumor in the splenic flexure (stage pT3N0). For the purposes of analysis, this patient case was included with the AAPs.

AAPs at baseline were found in five (1.9%) of 262 patients in group A and in 15 (5.6%) of 266 patients in group B. We corrected for this finding in a bivariable logistic regression analysis with study group and AAPs (as dichotomous variable) in the model. After correction for the differences in presence of AAPs at baseline between the two groups, the difference in the presence of AAPs at first follow-up was statistically significant (adjusted OR, 2.44; 95% CI, 1.03 to 5.78; $P = .044$).

Second Follow-Up Examination

A total of 235 (88%) of the original 266 patients in the group requiring two examinations (group B) returned for their second follow-up colonoscopy. The cecal intubation rate was 96%.

Ten (4%) of 235 patients had different follow-up intervals or incomplete or additional unplanned colonoscopies. At the second examination of group B at 6 years, a lower proportion of patients had adenomas and AAPs compared with the single-examination group (group A) at 6 years. However, the differences were not significant in the intention-to-treat analysis (Table 2). After correction for the difference in presence of AAPs at baseline between the two groups, the difference in the presence of AAPs at the final examination was statistically significant (adjusted OR, 2.61; 95% CI, 1.06 to 6.45; $P = .038$; Table 2).

Risk Factors

Sex, age, type of family history, and findings at baseline colonoscopy were analyzed as individual risk factors for the development of AAPs at the first follow-up examination in group A at 6 years and in group B at 3 years. Patients with a different follow-up interval or with additional unplanned colonoscopies were included in the intention-to-treat analysis. Only AAPs were identified as a predictor for the

Table 3. Risk Factor Analyses for Presence of AAPs at First Follow-Up Colonoscopy

Risk Factor at Enrollment	No. With AAPs of No. Examined (%)	Univariable OR (95% CI)	P
Sex			
Male	15 of 217 (6.9)	1.8 (0.83 to 4.1)	.14
Female	11 of 283 (3.9)	1.0	
Age, years			
≤ 55	18 of 313 (5.8)	1.0	
> 55	8 of 187 (4.3)	0.7 (0.31 to 1.7)	.48
		1.006 (0.94 to 1.1)	.88
Age			
Family history of CRC			
One FDR age < 50 years	9 of 241 (3.7)	1.0	
Two FDRs any age	17 of 259 (6.6)	1.8 (0.79 to 4.1)	.160
Two age < 70 years	7 of 95 (7.4)	2.1 (0.74 to 5.7)*	.17
One age < 70 and one age > 70 years	7 of 135 (5.2)	1.4 (0.51 to 3.9)*	.51
Two age > 70 years	3 of 29 (10.3)	3.0 (0.76 to 12)*	.12
Adenomas			
No	19 of 413 (4.6)	1.0	
Yes	7 of 87 (8.0)	1.8 (0.74 to 4.5)	.19
Proximal adenomas			
No	24 of 468 (5.1)	1.0	
Yes	2 of 31 (6.5)	1.3 (0.29 to 5.7)	.75
Unknown	1		
AAPs			
No	22 of 480 (4.6)	1.0	
Yes	4 of 20 (20)	5.2 (1.6 to 16.87)	.006

Abbreviations: AAP, advanced adenomatous polyp; CRC, colorectal cancer; OR, odds ratio.
*One FDR age < 50 years = reference group.

development of AAPs by first follow-up (OR, 5.21; 95% CI, 1.61 to 16.87; $P = .006$; Table 3).

DISCUSSION

Hereditary factors play a role in a substantial proportion of patient cases of CRC. Although 3% to 5% of all patient cases of CRC result from hereditary cancer syndromes, such as Lynch syndrome and polyposis syndromes, 5% to 10% of all patient cases of CRC are caused by a combination of hereditary and environmental factors; these are collectively referred to as familial CRC. The lifetime risk of developing CRC for individuals with hereditary CRC syndromes varies from approximately 50% in Lynch syndrome to 90% in familial adenomatous polyposis. In familial CRC, the lifetime risk is approximately 10% to 20%, depending on the age of onset of CRC in the FDR and on the number of affected FDRs.^{13,15,16}

The frequency of a significant family history of CRC (ie, one FDR with early-onset CRC or two FDRs with CRC) in the general population age between 45 and 70 years is approximately 2%.³⁰ The expected number of individuals with familial CRC in the United States is 2.7 million.

British investigators have shown that colonoscopic surveillance in high-risk families leads to a reduction in the incidence of CRC and CRC-related mortality by > 80%.³¹ However, the study, which is the only available investigation in this field, did not include a control group, and the > 80% reduction was calculated by comparing the observed incidence of CRC and mortality in the

high-risk cohort under surveillance with those expected in the absence of surveillance.

Although colonoscopic surveillance in familial CRC is currently recommended by all experts, the appropriate surveillance interval has not yet been clearly established. To our knowledge, our multicenter nationwide randomized trial is the first study to compare different surveillance intervals in familial CRC. The participants were primarily selected by GPs and gastroenterologists from all parts of the Netherlands. The study population is therefore representative for all such individuals in the Netherlands. The intention-to-treat analysis showed that there was no statistically significant difference in the presence of AAPs at the first follow-up examination between individuals who had colonoscopy at 6 years compared with those who underwent colonoscopy at 3 years. However, if we corrected for the difference of AAPs at baseline, the difference became statistically significant.

There was also no statistically significant difference in the presence of AAPs at the final examination at 6 years between the individuals who had one follow-up examination 6 years after the baseline colonoscopy and those who had two follow-up examinations after 3 and 6 years. After correction for the difference in presence of AAPs at baseline, the difference became statistically significant.

Several cautionary notes must be made with regard to our findings. First, the fact that more participants in the 6-year group compared with the 3-year group underwent a colonoscopy that deviated from the original protocol may have influenced the outcome.

A clinically important finding was the observation of a relatively low absolute rate (6.9%) of AAPs in group A, in addition to the absence of CRC in this group. Although there was a significant difference in AAPs between the two groups, in view of this relatively low rate of AAPs and the absence of CRC in group A, we consider a 6-year surveillance interval appropriate for individuals with familial CRC. However, a 3-year surveillance interval might be recommended for patients with AAPs. Future studies in larger groups should compare 6- and 10-year surveillance intervals.

A strength of this study is its randomized design. Moreover, family history was verified by medical reports in 99% of all patient cases and by pathology reports in almost 50% of patient cases. All adenomas identified at baseline and follow-up colonoscopies were revised by one pathologist.

A possible weakness of the study is that the colonoscopies were performed in various university and regional hospitals in the Netherlands. However, all colonoscopic examinations were performed by well-trained gastroenterologists, and appropriate cecal intubation

rates were achieved. Moreover, additional imaging was performed if the colonoscopy was incomplete.

A second weakness of the study is that there were a few patient cases of early-onset CRC in which MSI or immunohistochemical analysis of the mismatch-repair proteins was not performed. These patient cases of CRC may have represented Lynch syndrome. However, because the detection rate of a pathogenic mismatch-repair mutation in patients with CRC before the age of 50 years is only 6%,³² and the possible patient cases of Lynch syndrome were randomly distributed among the two arms of the study, we do not expect our findings to be significantly affected by inclusion of patients with incidental Lynch syndrome.

A third limitation of the study is that the statistical power was limited, and AAPs are a surrogate outcome to CRC and CRC-related mortality.

In summary, and taking all the findings of this study into consideration, a 6-year colonoscopic surveillance interval can be recommended in familial CRC. Future studies should address the upper age limit for surveillance and, in particular, determine the cutoff point at which the advantages of surveillance are outweighed by disadvantages of colonoscopic surveillance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

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Randomized Comparison of Surveillance Intervals in Familial Colorectal Cancer

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