Original Article

Invitation to Screening Colonoscopy in the Population at Familial Risk for Colorectal Cancer

A Cluster-randomized Study Aimed at Increasing Participation Rates

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Summary

Background: Screening colonoscopy can lower the incidence of colorectal cancer (CRC), yet participation rates are low even in groups at high risk. The goal of this study was to double the rate of participation in screening colonoscopy among persons at familial risk and then to determine the frequency of neoplasia in this risk group.

Methods: In a nationwide, cluster-randomized, multicenter study, first-degree relatives (FDR) of patients with CRC across Germany received written informational materials concerning the familial risk of CRC, along with an invitation to undergo colonoscopy. Participants in the intervention group were additionally counseled by nurses over the telephone. The primary endpoint of the study was colonoscopy uptake within 30 days.

Results: The participants' mean age was 50.8 years. The colonoscopy uptake rates were 99/125 (79%) in the intervention group and 97/136 (71%) in the control group (RR = 1.11; 95% confidence interval [0.97; 1.28]). A polypectomy was performed in 72 of 196 asymptomatic persons (37%). In 13 cases (7%), an advanced neoplasia was detected; two of these persons had colon cancer (stages T0 and T1). 42% of the participants expressed barriers against colonoscopy. 22 reported mild side effects; there were no serious side effects.

Conclusion: Additional counseling by nurses over the telephone does not increase the participation rate. Approaching patients who have CRC is an opportunity to increase the participation of their first-degree relatives in screening colonoscopy. The frequency of neoplasia that was found in this study underscores the need to screen relatives even before they reach the usual age threshold for screening.

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Colorectal cancer (CRC) is the third most frequently occurring malignant disease in the world, with more than 1.2 million new cases annually (1), and it also ranks third in cancer deaths worldwide, at over 600 000 per year. First-degree relatives (FDR) of persons with CRC are 2 to 4 times more likely to develop CRC themselves (2, 3). The need for a more intense screening of this population is thus supported by empirical data (4, 5).

Colonoscopy is considered the gold standard for early detection of CRC. It enables highly sensitive identification and simultaneous excision of precursor lesions (6, 7). A German case-control study showed that colonoscopy lowers the risk of CRC by 90% (8). Since 2002, residents of Germany aged 55 or over have the right to screening colonoscopy. However, no invitations are issued; the participation is opportunistic. The 10-year colonoscopy uptake rate in Germany is currently only 20 to 25% (9). A German study showed that participation was higher (29%) among those with a known family history of CRC (10).

In other countries too, the colonoscopy rates among those with a familial risk of CRC are less than ideal, at 14 to 69 % (11–13). The reasons for the low uptake are the invasive nature of the procedure, with severe complications in around two of every 1000 colonoscopies (14, 15), and the need for extensive bowel preparation in advance of the examination. Other factors repeatedly shown to hold patients back from making an appointment for screening colonoscopy include lack of awareness of the options for screening (16), unawareness of the familial risk (17–19), incorrect assumptions regarding the procedure (20, 21), inadequate communication within the family (22), and socioeconomic factors (23, 24).

The explicit recommendation by a physician (25, 26) and individual counseling with regard to existing barriers and concerns (17, 27, 28) have been shown to increase the rate of uptake of colonoscopy, by 33% and 27% respectively. We therefore set out to lay the groundwork for active invitation and individual counseling of persons at familial risk of CRC within the framework of a nationwide screening colonoscopy program and in accordance with current data protection laws. The study on transdisciplinary promotion of participation in screening among persons with familial increased risk of CRC (FAMKOL) was carried out to establish whether active invitation and individual counseling by non-physicians raises the uptake rate of screening colonoscopy appreciably in comparison with purely written invitation. Moreover, we also sought to determine the incidence of malignancies in this population, describe the barriers to colonoscopy, and ascertain the complication rates.

Methods

Patients with a first diagnosis of CRC (index patients, IP) were recruited at 61 certified German colorectal cancer centers and three independent gastroenterologi-

FIGURE 1

Flow chart: screening

FDR, first-degree relatives; IP, index patients; n, number

cal practices between December 2012 and August 2015. Based on a written training manual, all nursing staff at the respective sites attended a 2-day training course. No incentives were offered to the IP, FDR, and gastroenterologists to encourage them to participate in the study. The inclusion criteria for IP were a histologically confirmed diagnosis of CRC and the existence of one or more FDR in the age range 40 to 75 years. IP with FDR under 40 were also included if the age of the FDR was no more than 10 years less than that of the IP at first diagnosis. IP were excluded if they had not given written consent for their FDR to be contacted or if they had insufficient command of the German language.

Randomization was carried out at the Institute of Medical Epidemiology, Biometry, and Informatics (IMEBI) at the University of Halle, an external and independent facility, by means of computer-generated block lists with random block sizes. Individual

TABLE 1

Baseline characteristics of the first-degree relatives

	Intervention	Control	p
n	125	136	
Age (n = 261), mean (SD)	51.2 (8.4)	50.6 (7.7)	0.51
Sex (n = 261), n (%)			
– Female	74 (59.2)	94 (69.1)	0.09
– Male	51 (40.8)	42 (30.9)	
Education (n = 260), n (%)			
– Grade school/middle school or grade 8 POS	19 (15.2)	17 (12.6)	0.45
– High school or grade 10 POS	67 (53.6)	71 (52.6)	
– University entrance level	39 (31.2)	47 (34.8)	
Occupational qualification (n = 254), n (%)			
– None	2 (1.6)	4 (2.9)	0.90
– Ongoing training	1 (0.8)	2 (1.5)	
– Completed apprenticeship/training	59 (47.2)	61 (44.9)	
– Vocational school qualification or master craftsman	29 (23.2)	24 (17.6)	
– University degree	29 (23.2)	39 (28.7)	
– Other	3 (2.4)	1 (0.7)	
Occupational status (n = 258), n (%)			
– Unemployed	2 (1.6)	4 (2.9)	0.59
– Employed	95 (76.0)	104 (76.5)	
– Self-employed	9 (7.2)	9 (6.6)	
– Ongoing apprenticeship/studies	0	1 (0.7)	
– Housewife/househusband	7 (5.6)	4 (2.9)	
– Pensioner	12 (9.6)	11 (8.1)	
Number of eligible FDR per IP (n = 261), mean (SD)	2.6 (1.4)	3.0 (1.8)	0.05
Distance from FDR residence to IP colorectal cancer center in km (n = 261), mean (SD)	88.0 (144.3)	63.7 (108.4)	0.12
Age of IP (n = 261), mean (SD)	70.1 (10.7)	67.4 (10.7)	0.04
Sex of IP (n = 258), n (%)			
– Female	55 (44.0)	70 (51.5)	0.17
– Male	70 (56.0)	63 (46.3)	
Tumor stage (UICC) of IP (n = 170), n (%)			
I	23 (18.4)	23 (16.9)	0.28
II	19 (15.2)	15 (11.0)	
III	36 (28.8)	31 (22.8)	
IV	6 (4.8)	17 (12.5)	

FDR, First-degree relatives; IP, index patients; n., number; POS, *polytechnische Oberschule* (high school in the old German Democratic Republic); SD, standard deviation; UICC, Union internationale contre le cancer

randomization to the intervention group or the control group took place at index patient level. The IP formed the cluster criterion for the group allocation of the FDR. A cluster-randomized design was selected to avoid contamination of the study intervention by FDR in different study arms.

FDR with colonoscopy or CT colonography (CT, computed tomography) within the previous 5 years, diagnosed bowel cancer, familial adenomatous polyposis, or chronic inflammatory bowel disease were excluded. Assessment of the exclusion criteria was carried out by telephone interview after the FDR had received the study materials from the IP and given their written consent.

The IP were blinded as to their group allocation. They passed all written information to their FDR in opaque sealed envelopes. The independent gastroenterological practices were blinded as to the group allocation of the IP. However, blinding of the FDR was not possible owing to the counseling.

Intervention

The study had two levels. At the level of the IP in the colorectal cancer centers, specifically trained nursing staff informed the patients of both groups about the elevated familial risk for their FDR and about the goals of the study. IP of both groups were advised to talk to their relatives specifically about bowel cancer and to encourage eligible FDR to join the study. All IP were asked to pass on, in person or by post, a study leaflet with information about the elevated familial risk and the availability of CRC screening to their FDR.

FDR of the intervention group received telephone counseling from specifically trained nursing staff at the study coordination center. The aim of these conversations was to identify barriers to screening colonoscopy and then to overcome them by counseling. Furthermore, information was provided about the sensitivity, specificity, and complications of colonoscopy and other screening methods. If required, help was given in arranging appointments with an office-based gastroenterological practice. By contrast, the FDR in the control group received only the study documents and an information leaflet.

Both groups were sent written questionnaires 3 and 6 months after the beginning of the study. Neither group had any restriction on their choice of gastroenterologist for colonoscopy.

Primary endpoint

The primary endpoint of the study was the physician-confirmed colonoscopy uptake rate within 30 days of enrollment. This period was kept short to ensure that only colonoscopies connected with the study were recorded. We also included physician-confirmed cases where an appointment for colonoscopy had been made but the examination had not yet been conducted. In these cases the colonoscopy findings were recorded later. All macroscopic and histologic findings were

TABLE 2

Barriers to screening colonoscopy

Number of barriers mentioned during telephone counseling* (%)	Participation in screening colonoscopy		
	Yes n = 99	No n = 26	p
No barriers	59 (60)	12 (46)	0.22
Knowledge-related barriers			
– Lack of knowledge of colonoscopy and other screening methods	6 (6)	8 (31)	<0.01
Colonoscopy-related barriers			
– Anxiety regarding bowel cleansing	11 (11)	3 (12)	0.95
– Fear of complications	0 (0)	2 (8)	<0.01
– Fear of pain	2 (2)	0 (0)	<0.01
– Misconceptions about the examination	2 (2)	0 (0)	<0.01
– Embarrassment	2 (2)	0 (0)	<0.01
Organizational barriers			
– Not knowing whether the examination is covered by health insurance	5 (5)	0 (0)	<0.01
– Time constraints	3 (3)	2 (8)	0.28
– Difficulty in getting an appointment to see a gastroenterologist	3 (3)	1 (4)	0.83
False assessment of colorectal cancer risk			
– Ignorance of familial risk	4 (4)	1 (3)	0.96
Physician-related barriers			
– Physician advised against colonoscopy	3 (3)	1 (3)	0.83
– Lack of trust in doctors	2 (2)	1 (3)	0.59
Emotional barriers			
– Fear of cancer diagnosis	4 (4)	0 (0)	<0.01

n, Number

* Multiple answers possible; restricted to the intervention group, as the probands in the control group received no telephone counseling

communicated by fax to the study coordination center. The advice given by telephone was documented and categorized on standardized forms. At the 6-month follow-up we asked the FDR for whom no colonoscopy was documented why they had not participated.

Secondary endpoint

The secondary endpoints were the carcinoma/adenoma detection rate, barriers to uptake of screening colonoscopy, and the spectrum of complications up to 30 days after colonoscopy.

Sample

It was calculated that 77 FDR per group would be needed to detect an absolute and clinically meaningful difference of 25% in the primary endpoint between the intervention group and the control group (17, 27, 28) with an α error of 0.05 and power (1- β) of 0.90. To take

account of possible intracluster effects, we used a conservative intracluster correlation coefficient (ICC) of 0.10 (29) and an estimate of three FDR per IP. With a design effect for cluster randomization of 1.2 (30), the effective sample size rose to 93 FDR per group. On the assumption of a 50% drop-out rate, the required sample size was 186 per group.

Statistical analysis

The analysis took the form of a logistic regression model with group allocation as random effect according to the intention-to-treat principle. Because FDR of the same IP represented correlated observations, the final model was adjusted for the number of family members. We adjusted for the distance between the residence of the FDR and the recruitment site of the IP to minimize intrafamily distortions through personal contact. Chi-square tests were used for the secondary endpoints to compare the number of events in each treatment group. All hypothesis tests were two-sided with the level of significance set at 0.05. Analyses were carried out using SAS (version 9.4) and SPSS (version 23.0).

Results

Overall, 2360 IP were screened. Of these, 1251 were excluded because they did not meet the inclusion criteria. Thus 1109 IP aged 31 to 91 years (mean 68.4, SD 10.8) were included (*Figure 1*). A total of 556 FDR submitted their signed agreement to participate in the study. Of these, 261 FDR aged 28 to 75 years (mean 50.8, SD 8.1) fulfilled the inclusion criteria and gave information regarding the primary endpoint. The characteristics of the FDR in the two groups were comparable at the beginning of the study, except that the control group had a significantly higher number of FDR and the age of the FDR was significantly higher in the intervention group (*Table 1*). The FDR in the intervention group received one episode of telephone counseling with a mean duration of 26.6 min (range 5 to 50, SD 9.7).

Colonoscopy uptake

Altogether, 196 of the 261 FDR (75%) underwent a screening colonoscopy. The uptake rates were 99 out of 125 (79%, including 57 women) in the intervention group and 97 out of 136 (71%, including 66 women) in the control group (relative risk [RR] = 1.11; 95% confidence interval [0.97; 1.28]; $p = 0.16$). The RR decreased to 1.09 ([0.95; 1.25]; $p = 0.22$) after adjustment for cluster size and the distance between recruitment center and residence of FDR. In neither case were there any significant differences between the intervention group and the control group.

CRC and advanced adenoma

Polypectomy was carried out in 72 of 196 asymptomatic persons (37%), with no significant difference between the intervention group and the control group (RR = 1.05 [0.59; 1.88]). A total of 75 adenomas were detected in 45 persons. Twelve adenomas in 11 patients

TABLE 3

Reasons for not having had a colonoscopy after 6 months

	Intervention (n = 26)	Control (n = 36)	p
	n* (%)	n* (%)	
No symptoms	15 (58)	20 (56)	0.73
Time constraints	10 (38)	9 (25)	0.21
Physician advised against colonoscopy or no medical advice given	6 (23)	13 (36)	0.32
Occurrence of another disease	4 (15)	6 (17)	0.95
Anxiety regarding bowel cleansing	6 (23)	2 (6)	0.04
Fear of complications	3 (12)	5 (14)	0.83
Fear of pain during examination	5 (19)	1 (3)	0.03
Fear of cancer diagnosis	2 (8)	2 (6)	0.70
Embarrassment	2 (8)	1 (3)	0.35
Unwilling to get involved with cancer screening	3 (12)	1 (3)	0.15
Excessive waiting time for a colonoscopy appointment	1 (4)	1 (3)	0.79
Uncertain how the examination helps	1 (4)	0 (0)	0.23

* Multiple answers possible

TABLE 4

Complications in the first 30 days after colonoscopy

	Intervention		Control	
	Without polypectomy n = 58	With polypectomy n = 31	Without polypectomy n = 57	With polypectomy n = 30
	n*3 (%)	n*3 (%)	n*3 (%)	n*3 (%)
Bleeding	0 (0)	0 (0)	0 (0)	0 (0)
Circulatory problems	1 (1.7)	3 (9.7)	0 (0)	1 (3.3)
Injury to bowel wall	0 (0)	0 (0)	0 (0)	0 (0)
Pain	5 (8.6)	2 (6.5)	3 (5.3)	2 (6.6)
Fever	0 (0)	1 (3.2)	0 (0)	0 (0)
Flatulence or cramp	3 (5.2)	4 (12.9)	2 (3.5)	2 (6.6)
Other	1 (1.7)*1	0 (0)	0 (0)	1 (3.3)*2

*1 Increased need for sedation; *2 constipation until 48 h after intervention; *3 multiple answers possible

were classified advanced (size >1 cm, villous components, or high-grade dysplasia). Two cases of CRC stage T0 and T1 in patients aged 55 and 67 years were reported to the cancer registry. The detection rate of advanced neoplasia of the colon was therefore 6.6% (13 of 196 FDR; RR = 2.21 [0.70; 6.92]).

Barriers to colonoscopy

Barriers to colonoscopy were discussed during the telephone counseling, so these data refer only to the 125 FDR of the intervention group. Serious concerns about colonoscopy were found in 54 of these FDR (43%), who were allowed to give multiple answers when asked

about their concerns (Table 2). At 6-month follow-up, 61 FDR across the two groups stated their reasons for not having had a colonoscopy (Table 3).

Complications

Information on complications of colonoscopy was available for 176 of the 196 patients. Altogether, 22 of 176 FDR (13%) experienced minor complications within 30 days (intervention 14/89 versus control 8/87; RR = 1.31 [0.92; 1.86]). The most frequently reported events were flatulence in the first 3 days after the intervention (12/176) and mild pain for up to 7 days (11/176). No major complications occurred (Table 4).

FIGURE 2

Forest plot for the efficacy of interventions to improve the rate of participation in colonoscopy

I^2 , Heterogeneity; CI, confidence interval; N, number of patients; cases, number of patients in whom colonoscopy was performed; OR, odds ratio

Discussion

Our study, carried out in a large number of colorectal cancer centers, showed the efficacy of the invitation of first-degree relatives to undergo screening colonoscopy. The colonoscopy uptake rate of 75% is 2.7 times higher than achieved with the standard opportunistic screening in Germany (9, 10), where all members of public health insurance schemes are eligible for colonoscopy from the age of 55 years. Additional personal counseling increased the uptake nonsignificantly by just under 8%, whereby almost half of the FDR expressed barriers to colonoscopy. The absence of major complications in a 30-day period following the procedure confirms the low risk profile of screening colonoscopy (14, 15, 31). Aversion to the necessary bowel preparation and fear of pain were named significantly more often as reasons for not having a colonoscopy in the group that was counseled by nurses. In contrast, there were no clinically meaningful or statistically significant differences with regard to the adenoma detection rate. Future efforts should therefore be directed towards reducing unfounded anxiety about the bowel cleansing process and pain in connection with colonoscopy.

In line with previous studies, adding counseling improved knowledge about screening colonoscopy but did not increase the uptake rate any further (5, 16).

Advanced malignancies were detected in 7% of our study population with an average age of 50.8 years. The corresponding detection rate in a USA population with a similar average age but no familial risk of CRC was 2.1% (2). This contrast underlines the importance of screening colonoscopy for persons at familial risk—including those under the hitherto applicable age limits (32–35).

The unadjusted odds ratio (OR) of 1.53 [0.97; 2.71] in our study is consistent with the findings of previous investigations in which FDR were approached via IP and the effect of individual counseling was evaluated

(Figure 2). However, the interventions, study populations, and relevant laws are comparable to only a limited extent. Ingrand et al. found that individual counseling increased the colonoscopy uptake rate by 21% (to 56.3%) compared with provision of information material alone (36). In contrast to our study, their intervention also included standardized counseling of the patients by independently practicing gastroenterologists. Studies of other screening procedures (fecal occult blood test, flexible sigmoidoscopy) also found that individual counseling increased the uptake rate by 11 to 12% (17, 37). On the other hand, some studies found no or only slight effects for the provision of individualized information (12, 38). A possible explanation for the wide variation in results emerged from a study on information preferences that showed contrasting effects of sending one or two standardized newsletters by e-mail (39). In comparison with standardized information, individualized information clearly increased colonoscopy uptake among those probands who preferred to weigh up the advantages and disadvantages of various screening options themselves (26% versus 17%; $p < 0.05$). In contrast, the group of probands with a preference for a directive style of communication showed lower colonoscopy uptake when provided with individualized information materials (18% versus 24%; $p > 0.05$).

Limitations

The inclusion of 64 centers from all over the country ensures that the results are representative for Germany and simultaneously confirms that such a program is practicable. Despite the complex nature of the study, colonoscopy of the FDR who opted for screening took place on average as soon as around 70 days after the initial approach to the IP. The requirement for confirmation of colonoscopy by a physician permits precise assessment of the primary endpoint. Nevertheless, there are limitations with regard to the generalizability

of our findings. Due to data protection regulations, we could not approach the FDR directly. The advice that therefore had to be given to the IP about passing on the information to their relatives very probably acted as an unintended intervention itself and also contributed to the failure to attain the planned number of cases. For this reason, the observed nonsignificant difference between the intervention group and the control group is of only limited generalizability. However, a study arm without any intervention would have been questionable from an ethical perspective.

Moreover, we restricted ourselves to colonoscopy uptake as endpoint, not recording alternative forms of screening. The efficacy of the intervention in increasing the uptake of screening measures may therefore have been underestimated (40). Furthermore, it is probable that intrafamily effects moderate the uptake (22). It is not clear whether adjustment for the number of eligible family members helped to reduce this effect sufficiently.

Conclusions

Active invitation of first-degree relatives resulted in a higher rate of colonoscopy than the conventional opportunistic screening. Judging from the findings of earlier studies (25, 26), additional counseling by physicians might have increased the colonoscopy uptake rate further still. Although the result did not achieve statistical significance, the high rate of barriers to colonoscopy suggests that it may be necessary to offer individual counseling to members of risk groups.

The probands included persons under 50 years of age who would not have been eligible for the existing screening colonoscopy program. The observed rate of advanced neoplasia confirms the need for screening the relatives of CRC patients—including those outside the current age limits. Funding bodies and the health care system should take steps to tailor CRC screening to risk groups, which will involve individualization.

Future research should examine the effect of the FAMKOL intervention on the uptake of other screening methods. Moreover, to optimize the efficacy of the screening program, the follow-up of patients with advanced adenoma should also be included (e1).

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Ethics statement

The study was approved before the beginning of recruitment by the ethics committee of the Faculty of Medicine, University of Halle-Wittenberg (no. 2012-47) and the ethics committees of the medical associations of all 16 federal states of Germany under the title "Transdisziplinäre Förderung der Screeningteilnahme bei Personen mit familiär erhöhtem Risiko für kolorektale Karzinome. Eine prospektive clusterrandomisierte kontrollierte Multi-Center-Studie (FAMKOL)" [Transdisciplinary promotion of participation in screening among persons with familial increased risk of colorectal cancer. A prospective cluster-randomized controlled multicenter study (FAMKOL)].

Key Messages

- Personal invitation for screening colonoscopy increases to 75 % the participation rate among persons at familial risk of colorectal cancer.
- Quality-assured counseling about colorectal cancer screening can be delivered by non-physician staff.
- Transdisciplinary cooperation greatly improves the uptake of colonoscopy compared with opportunistic screening.
- Because of the increased risk of advanced neoplasia, persons at known familial risk of colorectal cancer should be offered screening colonoscopy from the age of 50 years.
- Risk groups have a substantial need for information and face barriers to screening colonoscopy. These problems should be addressed by means of individual counseling.

Study registration

Clinicaltrials.gov registration number: NCT01903395

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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► Supplementary material

For eReferences please refer to:
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Supplementary material to:

Invitation to Screening Colonoscopy in the Population at Familial Risk for Colorectal Cancer

A Cluster-randomized Study Aimed at Increasing Participation Rates

by Alexander Bauer, Jürgen F. Riemann, Thomas Seufferlein, Max Reinshagen, Stephan Hollerbach, Ulrike Haug, Susanne Unverzagt, Stephanie Boese, Madeleine Ritter-Herschbach, Patrick Jahn, Thomas Frese, Michael Harris, and Margarete Landenberger

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