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Adding familial risk assessment to faecal occult blood test can increase the effectiveness of population-based colorectal cancer screening

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ABSTRACT

Background: The Dutch Health Council recently recommended the introduction of a colorectal cancer (CRC) screening programme by faecal occult blood testing (FOBT) for individuals aged 55–75 at population risk of CRC. Individuals at an increased familial CRC risk (⩾2 times population risk) should be identified at a younger age, so they and their relatives can receive earlier, more intensive surveillance instead of FOBT.

Aims: To determine the percentage of participants with a positive FOBT in a CRC screening programme with an increased familial CRC risk.

Methods: In a population-based study, 10,569 individuals aged 50–75 received an FOBT. Individuals with a positive FOBT were invited for colonoscopy and familial risk assessment. Participants with an average familial CRC risk were compared to those with an increased risk. Increased familial CRC risk was defined as a cumulative lifetime risk of CRC of at least 10%.

Results: Of 6001 participants, 430 had a positive FOBT, of whom 324 (63% males; mean age 63 years) completed colonoscopy and familial risk assessment. CRC ($n = 22$) and/or advanced adenomas ($n = 122$) were found in 133 participants. Familial CRC risk was increased in 6% of participants with a positive FOBT. No significant differences were found between participants with an average versus an increased familial CRC risk.

Conclusion: Six percent of participants with a positive FOBT had an increased familial CRC risk. Identifying at-risk participants enables them and their relatives to undergo regular colonoscopies. Adding familial risk assessment to FOBT screening may thus prevent a substantial number of CRCs.

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1. Introduction

In Western society, the lifetime risk of developing colorectal cancer (CRC) is 5–6%.[1–3] In concordance with advice by the European Union, the Health Council of The Netherlands recommended the introduction of a CRC screening programme for individuals aged 55–75, consisting of a biennial faecal occult blood test (FOBT), followed by colonoscopy in case of a positive FOBT.[4,5]

Familial and hereditary CRCs account for 15–20% of all CRCs.[6–8] de Jong et al. found that 2.3% of the Dutch population had multiple relatives with CRC and/or a relative with CRC before the age of 50.[7] Members of these families have an increased familial CRC risk, i.e. a cumulative lifetime risk of developing CRC of at least 10%. According to international guidelines, these individuals should be identified at a younger age than the advised screening age of 55–75 years, to receive increased surveillance by regular colonoscopy.[9,10] Surveillance of moderate to high risk groups by regular colonoscopy significantly reduces the incidence of CRC and CRC-related mortality.[11,12] It is considered cost-effective to recommend a colonoscopy every 6 years from the age of 45 years to individuals with a moderate familial CRC risk of 10–15%.[9,10,13,14] For individuals with a high familial CRC risk above 15%, referral to a clinical geneticist is recommended for more precise risk assessment and determination of individualised preventive measures.[9,10,15]

However, many individuals with an increased familial CRC risk are still unidentified. If they are invited for population CRC screening, three scenarios can occur: (1) they decline to participate; (2) they have a negative FOBT; or (3) they have a positive FOBT. With the current design of the screening programme, only participants with a positive FOBT are invited for colonoscopy and familial risk assessment. Thus, individuals with an increased familial CRC risk in the first two groups will remain unidentified as being high-risk. As a consequence, they cannot benefit from surveillance by regular colonoscopies; nor can their close relatives, who may also have an increased risk of developing CRC.

Table 1 – Variables measured in the study.

Variable	Definition
FOBT results	
True positive	CRC and/or advanced adenoma(s) upon colonoscopy
False positive	All other or no pathology upon colonoscopy
Pathology results	
Colorectal carcinoma	Adenocarcinoma of the colorectum
Advanced adenoma	Adenomas $\geqslant$10 mm, with high-grade dysplasia or a villous component $\geqslant$20%[19]
Other lesions	Any lesion except for colorectal carcinoma or advanced adenoma (e.g. benign polyps, inflammations)
Personal history of	
Any cancer	Any malignant tumour
CRC	Adenocarcinoma of the colorectum
Definite LSAT	Epithelial ovarian carcinoma (including fallopian tube and primary peritoneal cancer), and malignancies of the endometrium, stomach, biliary tract, small intestine, upper urinary tract and benign and malignant tumours of the sebaceous glands[9]
Possible LSAT	Abdominal tumours NOS, kidney tumours NOS, pancreatic cancer, and carcinomas of the brain and urinary bladder
Family history	
Family size	The number of first-, second-, and third-degree relatives
Family history of CRC	CRC in first-, second-, and/or third-degree relatives
Family history of LSAT	LSAT in first-, second-, and/or third-degree relatives
Family history of other cancers	Other cancers than CRC or LSAT in first-, second-, and/or third-degree relatives
Familial CRC risk[a]	
Average (CRC risk <10%)	Negative family history for CRC and LSAT; or one relative with CRC > 50 years
Moderate (CRC risk 10–15%)	One relative with CRC < 50 years, or two first- or second-degree relatives with CRC between 50 and 70 years
High (CRC risk >15%)	Meeting Amsterdam I/II or Bethesda criteria[9,15,20,21]
Confounders	
Possible signs of CRC	Changed bowel habits, rectal blood loss[b], melena, abdominal pain, feeling of incomplete bowel movement, unintentional weight loss
Medication use	Use of NSAIDS and/or anticoagulants
Smoking	Smoking of any amount of tobacco-containing products
Alcohol use	Drinking of any amount of alcohol-containing beverages

CRC = colorectal cancer; FOBT = faecal occult blood test; LSAT = Lynch syndrome associated tumours; NOS = not otherwise specified; and NSAIDs = non-steroidal anti-inflammatory drugs.

[a] Familial CRC risk = cumulative lifetime risk of developing CRC.

[b] Excluding bleeding from known haemorrhoids.

Two previous studies have assessed familial risk among participants in an FOBT screening programme.[16,17] In both studies, familial CRC risk was assessed using questionnaires, which were sent along with the invitation for participation in the screening programme. However, Navarro et al. excluded individuals meeting criteria for Lynch syndrome, and only determined whether participants had a positive family history, defined as having a family member with CRC, endometrial or kidney cancer.[17] Worthley et al. found that 4.2% of Australian participants had a familial CRC risk above 10%, warranting increased surveillance.[16] In the present study, familial risk assessment was performed among participants with a positive FOBT by an experienced nurse or gastroenterologist to determine the percentage of – previously unidentified-participants in a Dutch CRC screening programme who have an increased familial CRC risk.

2. Patients and methods

2.1. Study design and setting

From June 2006 to February 2007, a random sample of 10,569 individuals aged 50–75 in Nijmegen and surrounding areas were invited to a pilot CRC screening programme. Individuals were randomised to receive either a guaiac-based FOBT (gFOBT) (Hemoccult II®) or an immunochemical FOBT (iFOBT) (OC-sensor®). This population-based study is described in detail elsewhere.[18]

Individuals with a positive FOBT were invited for colonoscopy. Everyone who accepted the invitation was seen by a specialised nurse or gastroenterologist who took a medical and family history, with the aid of a checklist. If the family history was positive for cancer, a more detailed pedigree was drawn.

Colonoscopy was performed by an experienced gastroenterologist. If possible, all observed neoplasms were removed, and other lesions were biopsied, if necessary. Histology was evaluated by an experienced pathologist. All colonoscopies were completed in May 2007.

The study was reviewed and approved by the Dutch Health Council. All participants gave written informed consent for the FOBT and, if applicable, for colonoscopy.

2.2. Data collection

From the checklists filled in during the visit and medical records, the following items were collected: demographical data (such as age and gender), FOBT results, pathology results, personal and family history of cancer and possible confounders. Details and definitions are shown in Table 1. Familial CRC risks were calculated from these data. Increased familial CRC risk was defined as a cumulative lifetime risk of CRC of at least 10%, i.e. a moderate or high familial CRC risk.[9]

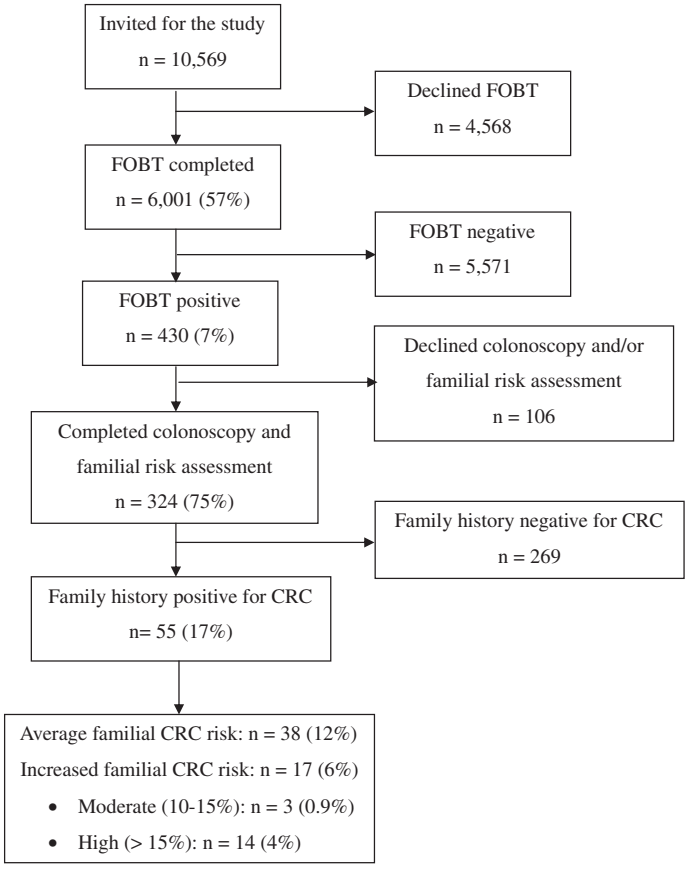

Fig. 1 – Flow chart from invitation to familial risk assessment. Average familial CRC risk = cumulative lifetime risk of developing colorectal cancer below 10%; CRC = colorectal cancer; FOBT = faecal occult blood test; increased familial CRC risk: cumulative lifetime risk of developing colorectal cancer of at least 10%.

2.3. Data analysis

Descriptive statistics were used to characterise the study population, family history and familial CRC risk. Age comparisons between the groups with true and false positive FOBTs were performed using independent samples *T*-tests (two-tailed). Gender (male/female), test type (iFOBT/gFOBT), personal and family history of any cancer/CRC/Lynch syndrome associated tumour (LSAT) (yes/no) and possible signs of CRC, smoking and alcohol use (yes/no) were analysed as dichotomous variables. These variables, as well as medication use (none/non-steroidal anti-inflammatory drugs (NSAIDs)/anticoagulants/combined use of NSAIDs and anticoagulants) and familial CRC risk categories (not increased [average] and increased [moderate or high]), were compared between participants with true and false positive FOBTs, and between participants with an average versus an increased familial CRC risk, using Pearson Chi-Square tests.

Significance was defined at the $p \leqslant 0.05$ level. All statistical analyses were performed using SPSS version 16.0.

3. Results

3.1. Study population

Of the 10,569 participants, 57% ($n = 6001$) completed FOBT (Hemoccult® 51%, OC-Sensor® 62%) (Fig. 1). A positive FOBT was found in 430 participants (7%). The study population of the present study consists of the 324 participants with a positive FOBT (75%) who completed colonoscopy and familial risk assessment. The study population was predominantly male (63%) with a mean age of 63 years (standard deviation [SD] = 6.9) (Table 2).

CRC ($n = 22$) and/or advanced adenomas ($n = 122$) were found in 133 participants. Thus, 41% of participants had a true positive FOBT. The remaining 191 individuals had a false positive FOBT, with minor adenomas ($n = 77$) and/or other pathology ($n = 81$), or no pathology detected ($n = 55$).

No significant relevant differences were found between participants with true versus false positive FOBTs.

3.2. Personal history of cancer

Details of personal and family history are shown in Table 3. Approximately 10% of all participants reported a personal history of cancer (other than CRC and Lynch syndrome associated tumours). Three participants had a positive history of CRC or LSAT.

3.3. Family history of colorectal cancer

Information on family size was reported in pedigrees of 38 participants (12%) and in most cases, only included the number of brothers, sisters and/or children. One participant was adopted; no information on her biological relatives was known. Fifty-five participants (17%) had a positive family his-

Table 2 – Baseline characteristics of 324 individuals with a positive FOBT in a CRC screening programme.

	False positive FOBT		True positive FOBT		Total	
	N	%	*N*	%	*N*	%
Number of individuals (% of total)	191	59.0	133	41.0	324	100
Male gender	115	60.2	90	77.7	205	63.3
Mean age (SD)	62.1 (7.0)		63.4 (6.7)		62.6 (6.9)	
Number of iFOBTs (versus gFOBTs)[a]	173	90.6	108	81.2	281	86.7
Colonoscopy results[b]						
CRC	0	0	22	16.5	22	6.8
Advanced adenoma	0	0	122	91.7	122	37.7
Minor adenoma	67	20.7	10	30.9	77	23.8
Other pathology	59	30.9	22	16.5	81	25.0
No pathology	55	28.8	0	0	55	17.0
Possible signs of CRC						
Changed bowel habits	9	4.7	7	5.3	16	4.9
Rectal blood loss[c]	19	10.0	24	18.0	43	13.3
Melena	1	0.5	1	0.8	2	0.6
Abdominal pain	14	7.3	8	6.0	22	6.8
Feeling of incomplete bowel movement	9	4.7	7	5.3	16	4.9
Unintentional weight loss	8	4.2	4	3.0	12	3.7
Medication use						
NSAIDs	37	19.4	28	21.1	65	20.1
Anticoagulants	7	3.7	2	1.5	9	2.8
Smoking	44	23.0	43	32.3	87	26.9
Alcohol use	153	80.1	102	76.7	255	78.7

CRC = colorectal cancer; FOBT = faecal occult blood test; gFOBT = guaiac-based FOBT; iFOBT = immunochemical FOBT; NA = not applicable; NSAIDs = non-steroidal anti-inflammatory drugs; and SD = standard deviation.

[a] $p = 0.021$.

[b] Results exceed 100%, since participants may have had more than one type of pathology.

[c] Excluding bleeding from known haemorrhoids.

Table 3 – Personal and family history in 324 individuals with a positive FOBT in a CRC screening programme.

	False positive FOBT (n = 191)		True positive FOBT (n = 133)[a]		Total (n = 324)	
	N	%	N	%	N	%
Number of patients with personal history of						
Any cancer	14	7.3	18	13.5	32	9.9
CRC/LSAT	1	0.5	2	1.5	3	0.9
Number of patients with FH of CRC						
Positive FH of CRC	36	18.8	19	14.3	55	17.0
⩾1 FDR with CRC	36	18.8	19	14.3	55	17.0
⩾1 SDR with CRC	11	5.8	0	0	11	3.4
Unknown[a]	0	0	1	0.8	1	0.3
Number of patients with FH of definite/possible LSAT[b]						
Positive FH of LSAT	5	2.6	0	0	5	1.5
⩾1 FDR with LSAT	5	2.6	0	0	5	1.5
⩾1 SDR with LSAT	0	0	0	0	0	0
Unknown[a]	0	0	1	0.8	1	0.3
Number of patients with FH of other cancers						
Positive FH of cancer	15	7.9	5	3.8	20	6.2
⩾1 FDR with cancer	15	7.9	5	3.8	20	6.2
⩾1 SDR with cancer	1	0.5	0	0	1	0.3
Unknown[a]	0	0	1	0.8	1	0.3
Familial CRC risk						
Average	180	94.2	126	94.7	306	94.4
Moderate	2	1.0	1	0.8	3	0.9
High	9	4.7	5	3.8	14	4.3
Unknown[a]	0	0	1	0.8	1	0.3

CRC = colorectal cancer; FDR = first degree relative; FH = family history; FOBT = faecal occult blood test; LSAT = Lynch syndrome associated tumours; definite LSAT = epithelial ovarian carcinoma (including fallopian tube and primary peritoneal cancer), and malignancies of the endometrium, stomach, biliary tract, small intestine, upper urinary tract and benign and malignant tumours of the sebaceous glands; possible LSAT = abdominal tumours not otherwise specified (NOS), kidney tumours NOS, pancreatic cancer, and carcinomas of the brain and urinary bladder; and SDR = second degree relative.

[a] 1 Missing: family history unknown because of adoption.

[b] 3 Definite, 2 possible.

tory of CRC; 36 with a false positive FOBT and 19 with a true positive FOBT.

3.4. *Increased familial colorectal cancer risk*

Six percent of participants had an increased familial CRC risk, i.e. a familial CRC risk above 10% (n = 6 and n = 11 among participants with true and false positive FOBTs, respectively). Familial CRC risk was above 15% in 14 participants. In the other 38 participants with a positive family history of CRC, familial CRC risk was below 10%. No significant differences were found between participants with an average versus an increased familial CRC risk (data not shown).

4. Discussion

In this study, 17% of participants with a positive FOBT in a CRC screening programme had a positive family history of CRC. Six percent of participants had a familial CRC risk of at least 10%. These prevalences are higher than previously reported in the general Dutch population by de Jong et al.[7] They performed a study among 5072 Dutch individuals aged 45–70, who filled in a questionnaire about the occurrence of CRC in their first-degree relatives (FDRs). Eleven percent of the 3973 responders reported at least one FDR with CRC, while 2.3% of unaffected responders reported FDR with CRC diagnosed before the age of 50, or two or more FDRs with CRC (i.e. a familial CRC risk above 10%). We cannot exclude that a positive family history of CRC is one of the reasons to participate in a screening programme.[22] Also, advanced adenomas and CRCs might occur more often in participants with an increased familial CRC risk compared to those with a negative family history.[23,24] Since family history was not assessed in participants with a negative FOBT and decliners, the number of individuals with an increased familial CRC risk may therefore be higher in our study.

However, our results are in line with two other studies. First, an Australian study, where 19.6% of 2538 participants in an FOBT screening programme reported a positive family history of CRC in a questionnaire.[16] Of these participants, 106 (4.2%) had a familial CRC risk high enough to warrant increased surveillance by colonoscopy rather than participation in a screening programme. However, of the 377 participants with an increased familial CRC risk, only 28 (7.4%) had a positive gFOBT or iFOBT. In a Spanish study, 731 of 18,405 participants (4.9%) in a gFOBT screening programme reported a positive family history, defined as having a family member with CRC, endometrial or kidney cancer.[17] Among those with a positive gFOBT, this percentage was 11.0%; 7.3% of participants with a negative gFOBT had a positive family history ($p < 0.005$).

Strengths of our study include the assessment of family history by a small number of nurses and gastroenterologists who are very experienced in familial and hereditary CRC and all determined familial CRC risk as defined by the most recent guidelines.[9] Moreover, the large number of participants make for a good representation of the general population eligible for FOBT screening.

A limitation of our study is that cancer diagnoses of relatives were not verified in medical records. The accuracy of a family history for CRC in first-degree relatives is very high, approximately 90%.[25,26] However, such accuracy is lower for second- and third-degree relatives, and for other cancer types, which can influence familial CRC risk. Since family history of colorectal cancer is correlated with family size, another limitation of our study could be that information about family size was mainly limited to first-degree relatives.[7] In addition, a quarter of all individuals with a positive FOBT did not complete colonoscopy and familial risk assessment, leading to a possible selection bias. We cannot be sure that no significant differences were present between individuals who underwent a colonoscopy and those who did not. Participants with a negative family history might feel that their risk of developing CRC is lower than in those with a positive family history and might, therefore, be less inclined to undergo colonoscopy and familial risk assessment.[22]

We estimated the number of CRCs that may be prevented by adding familial risk assessment to FOBT screening, based on the following assumptions. The first assumption is that the effectiveness of surveillance by regular colonoscopies in individuals with an increased familial CRC risk is identical to the effectiveness as described by Dove-Edwin et al. and Jarvinen et al.[11,12] In the study by Jarvinen et al., 6% of high-risk participants undergoing surveillance developed CRC during the 15-year follow-up of the trial, compared to 16% of participants who did not undergo surveillance.[12] Dove-Edwin et al. showed that the incidence of CRC was 43% lower in high-risk individuals, and 80% lower in participants with a moderate familial CRC risk, than the expected incidence in the absence of surveillance.[11] The second assumption is that participants have a mean number of three first-degree relatives (i.e. brothers, sisters and children) whose CRC risk is as high as that of the participant, and that these relatives do not yet participate in the screening programme.[13] Based on these assumptions, an additional 172–184 CRCs may be prevented annually among participants with a positive FOBT and their relatives in the eligible Dutch screening population of 3.5 million individuals (with an expected uptake of 60%). This is just a tip of the iceberg, since many participants with a negative FOBT, as well as non-participants, also have an increased familial CRC risk.[16,17]

In conclusion, 6% of participants with a positive FOBT in a CRC screening programme had a familial CRC risk above 10%. Although the FOBT screening programme may serve as a way to identify these individuals, they need referral for intensive surveillance by regular colonoscopies instead of participating in the FOBT screening programme. Adding familial risk assessment to population screening with FOBT may, therefore, lead to the prevention of a substantial number of CRCs. Other methods are needed to assess familial CRC risk among non-participants.

Conflict of interest statement

None declared.

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