Risk profiling and screening for colorectal cancer
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Colorectal cancer risk factors in the detection of advanced adenoma and cancer


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Abstract

Several risk factors for colorectal cancer (CRC) have been identified. If individuals with risk factors are more likely to harbor cancer or its precursors, screening programs should be targeted towards this population. We evaluated the predictive value of colorectal cancer risk factors for the detection of advanced colorectal adenoma in a population-based CRC colonoscopy screening program.

Data were collected in a multicentre trial conducted in the Netherlands, in which 6,600 asymptomatic men and women between 50 and 75 years of age were randomly selected from a population registry. They were invited to undergo a screening colonoscopy. Based on a review of the literature, CRC risk factors were selected. Information on risk factors was obtained from screening attendees through a questionnaire. For each CRC risk factor, we estimated its odds ratio (OR) relative to the presence of advanced neoplasia as detected at colonoscopy.

Of the 1,426 screening participants who underwent a colonoscopy, 1,236 (86%) completed the risk questionnaire. 110 participants (8.9%) had advanced neoplasia. The following risk factors were significantly associated with advanced neoplasia detected by colonoscopy: age (OR: 1.06 per year; 95% CI: 1.03 to 1.10) calcium intake (OR: 0.99 per mg; 95% CI: 0.99 to 1.00), positive CRC family history (OR: 1.55 per first degree family member; 95% CI: 1.11 to 2.16) and smoking (OR: 1.75 95% CI: 1.09 to 2.82).

Elderly screening participants, participants with lower calcium intake, a CRC family history, and smokers are at increased risk of harboring detectable advanced colorectal neoplasia at screening colonoscopy.
Background

Colorectal cancer (CRC) is one of the leading causes of cancer related death. Over the years, several risk factors for CRC have been identified in epidemiologic studies. These include, amongst others, physical inactivity, smoking, BMI, and nutritional habits.

Information about modifiable risk factors, combined with personalized risk communication, can improve health literacy, positively affecting health behavior. Addressing lifestyle habits during screening can have a positive effect on health behavior. Communication about risk factors can improve awareness and participation in screening participants, especially in those at higher risk.

In order to communicate an individuals’ risk, one first has to determine these risk factors. Risk based screening can be used not just to detect disease while still preclinical but also to improve health literacy and health behavior. This can be embedded in a screening setting.

Risk factors could additionally be used in risk stratification in order to target high risk populations in screening programs, or to tailor screening in these programs to calculated risk. Such initiatives would only be valid if individuals with risk factors are more likely to harbor cancer or its precursors at screening. If colorectal cancer risk factors are merely associated with a more rapid growth of adenomas, preferential screening of individuals with risk factors would not necessarily be unjustified, because of the relatively shorter dwell time. On the other hand, if individuals with more risk factors are also more likely to have (advanced) adenoma at colonoscopy, the benefits of screening would indeed be higher for them.

So far, most of the CRC risk factors have been identified in longitudinal studies, where baseline information on risk factors was associated with the incidence of clinical cancer during follow-up. Lieberman and colleagues evaluated risk factors associated with advanced colorectal neoplasia in asymptomatic persons undergoing colonoscopy, but included a selected group of predominantly male US veterans. Larsen et al. conducted a cross-sectional study in a general population but only evaluated life style factors. We conducted a study to evaluate the association of CRC risks factors and colorectal neoplasia in the general population within a pilot population based CRC screening program, in which a random selection of the general Dutch population was invited for a screening colonoscopy.
Methods
Study population
Data were collected in the Colonoscopy or Colonography for Screening (COCOS) study, a multicenter population-based CRC screening pilot in two academic centers in the Netherlands. At the time of the study, the Netherlands had no nationwide CRC screening program. In the COCOS trial participation and yield in a population based CRC screening program were compared between colonoscopy and CT colonography as primary screening methods. The trial is described in detail elsewhere12. For our study we only include data from invitees randomly selected and invited for primary colonoscopy. This included 6,600 asymptomatic men and women between 50 and 75 years of age. Subjects who had a full colonic examination in the previous 5 years were excluded as well as subjects who were in a colonoscopy surveillance program and those with a life-expectancy below 5 years.

Invitation procedure
Invitations were sent by mail by the Regional Comprehensive Cancer Centres in Amsterdam and Rotterdam. Two weeks before the invitation all invitees received a preannouncement. Invitees had three options to respond: using the reply card, by calling or emailing the Comprehensive Cancer Centre. The Comprehensive Cancer Centre made an appointment for a prior consultation. Non-responders received a reminder 4 weeks after the invitation.

Risk factors
Based on a review of the literature, a set of putative risk factors were selected. This set included only variables that could be collected through medical history and questionnaires, without additional testing. We evaluated age, sex, CRC family history10,13, alcohol intake4,10,14, current smoking, history of smoking5,10, BMI6,15,16, regular Aspirin or NSAID use10,17,18, total calcium intake10,19,20 and physical activity10,11,21.

Risk factor information was collected with a ten item questionnaire, which was based on three existing validated questionnaires: the Prevention Compass22, the Municipal Health Agency23, and the Interheart questionnaire24. The questionnaire was handed out to the participants after arrival in the hospital and completed and collected immediately before the screening colonoscopy.

The ten factors were operationalized as follows. Family history was defined as having one or more first degree relatives with a previous CRC diagnosis. Aspirin/NSAID use was defined as the current use of either aspirin, ascal, diclofenac, ibuprofen or naproxen, etoricoxib, meloxicam. Smoking behavior was evaluated as present or past smoking. Years
of smoking were asked in order to estimate pack years. Alcohol intake was measured in number of units of alcohol per week. Exercise was evaluated as physical activity of at least 30 minutes a day for at least 5 days a week, as is recommended in the Dutch guidelines. Questions about calcium addressed the consumption of dairy products, vegetables and bread, allowing us to estimate intake in milligram of calcium. Fibre intake was estimated in grams of fibre in fruits, vegetables, bread and cereals a day. Sleep was measured as hours of sleep per 24 hours. Information on the hormonal status of women was assessed through questions about the time of the last menstrual period and the use of hormone replacement therapy.

Colonoscopy
All colonoscopies were performed at one of the two screening centers by gastroenterologists with an experience of more than 1,000 colonoscopies. Colonoscopies were done using the standard quality aspects defined by the American Society for Gastrointestinal Endoscopy. Participants were prepared for colonoscopy by a low fiber diet, 2 L of hypertonic polyethylene glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) and 2 L of fluids. The procedure was performed under conscious sedation using intravenous midazolam (Dormicum, Actavis, Baarn, The Netherlands) and fentanyl (Bipharma, Weesp, The Netherlands) at the discretion of the participant and the endoscopist. In case of poor bowel preparation the colonoscopy was interrupted and re-scheduled. Cecal intubation was confirmed by still images of the appendiceal orifice and ileocecal valve or by intubation of the ileum. Insertion and withdrawal times were recorded separately. At the start of withdrawal of the endoscope, butylscopalamine bromide (Buscopan, Boehringer Ingelheim bv, Alkmaar, the Netherlands) was given intravenously at the discretion of the endoscopist to reduce colonic motility and repeated if necessary. Withdrawal time was at least 6 minutes. All detected lesions were removed during the same procedure if possible. If immediate endoscopic treatment was impossible, biopsies were obtained. Pathological assessment of tissue samples provided a definitive diagnosis.

Lesions
Of all lesions detected during colonoscopy, the size (millimeters), morphology (pedunculated, sessile, flat or depressed), localization (segment of the colon) and macroscopic features (hyperplastic, adenomatous, carcinomatous) were noted. The size of each lesion was measured using an open biopsy forceps with 7 mm span. Data on additional diagnostic or therapeutic procedure (biopsy, piecemeal polypectomy, coagulation or cold-snare total polypectomy), macroscopic involvement of margins, use of submucosal saline and/or epinephrine injection, and time needed for polypectomy were also recorded.
Pathology
Histology was defined according to the Vienna criteria. Dysplasia was categorized as either low grade or high grade. All lesions were classified as normal mucosa, hyperplastic, tubular adenoma, tubulovillous adenoma, villous adenoma, or carcinoma. Histopathology was processed and stained using standard methods and evaluated by two expert pathologists (one in each center). All cases of advanced neoplasia and a random selection of 10% of all other lesions evaluated in each center were revised by the pathologist of the other center. In case of inconsistency, a definitive diagnosis was made in a consensus reading.

Statistical analysis
The main outcome measure was the association between each of the putative risk factors and the detection of advanced neoplasia, on a per patient basis, based on the colonoscopy results. In these analyses the most advanced lesion per patient was used. Advanced neoplasia was defined as at least one CRC or advanced adenoma (adenoma of 10 mm or larger, ≥ 25% villous histology or high grade dysplasia).

For each risk factor we calculated the corresponding odds ratio relative to the colonoscopy outcome, and the associated 95% confidence interval, to express the association with the presence of advanced neoplasia. Odds ratios for continuous variables were estimated using univariate logistic regression analyses, assuming the relation to be linear. Missing data in the questionnaires were handled by multiple imputation. In multiple imputation, missing values are estimated from other related variables in the dataset. With this several complete datasets are created, in which different imputations are based on a random draw from different estimated underlying distributions.

Results
Of the 6,600 persons invited for primary colonoscopy screening, 1,426 (22%) agreed to undergo the procedure (See figure 1). In this group, 1,236 (87%) individuals completed the questionnaire; their data were included in the analysis. Table 1 summarizes the background characteristics of the study participants. Their mean age was 60.5 (SD 6.2); 600 (48%) were female. Their mean BMI was 26.7 kg/m² (SD 5.6). Smoking status was available for 1,222 participants; 15% is a current smoker. In women, 3.6% was pre-menopausal. Reported mean alcohol consumption was 7.8 glasses a week (SD 9.0).
Of the 1,236 respondents, 110 (8.9%) had advanced neoplasia detected during colonoscopy as most advanced lesion: 7 (0.6%) had CRC (3 men, 4 women) and 103 (8.3%) advanced adenoma (57 men, 46 women).

**Risk factors**
Table 1 shows the univariate and multivariate odds ratios (OR) for advanced neoplasia and no-pathology.

**Patient characteristics**
More males had advanced neoplasia, but the association was not statistically significant. Increasing age had a weak, but significant association with advanced neoplasia. In our study group, 185 persons had one or more first degree family members with colorectal cancer. Number of family members with CRC was strongly and significantly associated with an increased risk of CRC, with an odds ratio of 1.55 per additional family member. For women pre-menopausal status had a strong but non-significant association, with an OR of 0.24 (95% CI: 0.03 to 1.76).
Table 1 Descriptive statistics of the population and odds ratios (OR) for the risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>N</th>
<th>No neoplasia</th>
<th>Advanced neoplasia</th>
<th>OR (95% CI) Univariate</th>
<th>OR (95% CI) Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1236</td>
<td>649</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>636 (52%)</td>
<td>298 (46%)</td>
<td>61 (55%)</td>
<td>0.63 (0.12-3.43)</td>
<td>1.19 (0.81-1.77)</td>
</tr>
<tr>
<td>Female</td>
<td>600 (48%)</td>
<td>351 (54%)</td>
<td>49 (45%)</td>
<td></td>
<td>1.05 (0.67-1.65)</td>
</tr>
<tr>
<td>Age in years*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>633 (51%)</td>
<td>366 (56%)</td>
<td>38 (35%)</td>
<td>0.94 (0.91-0.98)</td>
<td>1.06 (1.03-1.10)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>603 (49%)</td>
<td>267 (44%)</td>
<td>72 (65%)</td>
<td></td>
<td>1.04 (1.00-1.11)</td>
</tr>
<tr>
<td>No. of relatives with CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1051 (85%)</td>
<td>562 (87%)</td>
<td>87 (79%)</td>
<td>0.70 (0.46-1.07)</td>
<td>1.55 (1.11-2.16)</td>
</tr>
<tr>
<td>1</td>
<td>152 (12%)</td>
<td>74 (11%)</td>
<td>14 (13%)</td>
<td></td>
<td>1.53 (0.85-2.74)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>33 (3%)</td>
<td>9 (1.3%)</td>
<td>9 (8.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI kg/m²*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>30 (2.4%)</td>
<td>19 (2.9%)</td>
<td>1 (1.0%)</td>
<td>0.96 (0.91-1.01)</td>
<td>0.99 (0.96-1.04)</td>
</tr>
<tr>
<td>20-25</td>
<td>425 (34%)</td>
<td>242 (37%)</td>
<td>34 (31%)</td>
<td></td>
<td>1.00 (0.92-1.08)</td>
</tr>
<tr>
<td>25-30</td>
<td>559 (45%)</td>
<td>277 (43%)</td>
<td>53 (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>203 (16%)</td>
<td>102 (16%)</td>
<td>18 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>49 (4%)</td>
<td>22 (3.3%)</td>
<td>4 (3.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre menopausal status in women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (8.3%)</td>
<td>30 (8.5%)</td>
<td>17 (2.0%)</td>
<td>0.83 (0.41-1.67)</td>
<td>0.24 (0.03-1.76)</td>
</tr>
<tr>
<td>No</td>
<td>424 (71%)</td>
<td>240 (68%)</td>
<td>47 (16%)</td>
<td></td>
<td>0.96 (0.31-2.98)</td>
</tr>
<tr>
<td>missing</td>
<td>126 (21%)</td>
<td>81 (23%)</td>
<td>47 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>187 (15%)</td>
<td>62 (9.6%)</td>
<td>25 (23%)</td>
<td>0.21 (0.11-0.40)</td>
<td>1.75 (1.09-2.82)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>588 (48%)</td>
<td>315 (49%)</td>
<td>57 (52%)</td>
<td></td>
<td>3.59 (1.61-8.02)</td>
</tr>
<tr>
<td>No</td>
<td>447 (39%)</td>
<td>264 (41%)</td>
<td>27 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>14 (1.1%)</td>
<td>8 (1.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For the purpose of clarity this table shows threshold values for several variables. In the analysis these variables were used as continues variables. The odds ratio's mentioned account for continues variables.

** Present or past smoking.
<table>
<thead>
<tr>
<th>Sleep in hours*</th>
<th>≤7</th>
<th>&gt;7</th>
<th>Missing</th>
<th>≥7 (53%)</th>
<th>&gt;7 (41%)</th>
<th>Missing (61%)</th>
<th>1.01 (0.86-1.19)</th>
<th>57 (52%)</th>
<th>43 (39%)</th>
<th>10 (9.0%)</th>
<th>0.97 (0.82-1.17)</th>
<th>0.93 (0.73-1.19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous exercise h/wk</td>
<td>Yes</td>
<td>No</td>
<td>≤15 units per week</td>
<td>1023 (82%)</td>
<td>151 (12%)</td>
<td>62 (5.0%)</td>
<td>1.30 (0.85-2.01)</td>
<td>89 (81%)</td>
<td>15 (14%)</td>
<td>6 (5.5%)</td>
<td>1.00 (0.98-1.03)</td>
<td>0.85 (0.24-3.06)</td>
</tr>
<tr>
<td>Alcohol in units per week*</td>
<td>≤15 units per week</td>
<td>&gt;15</td>
<td>Missing</td>
<td>1094 (89%)</td>
<td>142 (12%)</td>
<td>727 (59%)</td>
<td>380 (59%)</td>
<td>269 (41%)</td>
<td>34 (5.2%)</td>
<td>0.91 (0.43-1.89)</td>
<td>0.99 (0.99-1.00)</td>
<td>0.84 (0.26-2.68)</td>
</tr>
<tr>
<td>Red meat in servings per week*</td>
<td>≤3</td>
<td>&gt;3</td>
<td>Missing</td>
<td>779 (63%)</td>
<td>412 (33%)</td>
<td>45 (3.6%)</td>
<td>408 (63%)</td>
<td>214 (33%)</td>
<td>27 (4.2%)</td>
<td>1.02 (0.91-1.16)</td>
<td>0.95 (0.85-1.06)</td>
<td>0.94 (0.77-1.16)</td>
</tr>
<tr>
<td>Aspirin/NSAID</td>
<td>User</td>
<td>Non-user</td>
<td>≤3</td>
<td>968 (78%)</td>
<td>268 (22%)</td>
<td>654 (53%)</td>
<td>351 (54%)</td>
<td>261 (40%)</td>
<td>37 (5.7%)</td>
<td>1.07 (0.59-1.93)</td>
<td>0.90 (0.55-1.47)</td>
<td>0.83 (0.32-2.17)</td>
</tr>
</tbody>
</table>

*For the purpose of clarity this table shows threshold values for several variables. In the analysis these variables were used as continues variables.
The odds ratio’s mentioned account for continues variables.

** Present or past smoking.
Diet
Of the dietary information available only calcium intake was significantly associated with advanced neoplasia: high calcium intake had a small protective effect. Consumption of fiber and meat were not significantly associated with advanced neoplasia.

Lifestyle
Smoking was a statistically significant risk factor for advanced neoplasia, with an OR of 1.75. Associations for BMI and alcohol intake were not significant. Sixty-two percent of participants had enough physical exercise according to the Dutch guidelines. Physical activity had a small but non-significant protective effect on the presence of advanced neoplasia. Similarly, hours of sleep had a weak but non-significant association with advanced neoplasia. Regular NSAID-use, defined as 3 or more times a week, was not significantly associated with advanced neoplasia.

Discussion
In this study of the predictive value of colorectal cancer risk factors in a screening population we found age, calcium intake, family history and smoking to be significantly associated with CRC or advanced adenoma, as detected during a screening colonoscopy. In contrast, sex, BMI, post menopausal status, fibre intake, aspirine/nsaid use and red meat intake were not significantly associated with advanced neoplasia.

Strengths of this study are that all participants underwent colonoscopy examination, that the study included a random sample from a Dutch population registry, and the high response rate for the questionnaires, with almost ninety percent of participants completing the risk factor questionnaire. In addition, the distribution of life style factors in our study group is representative of that in the general Dutch population30,31.

A number of other methodological issues need to be addressed. The sample size of this study was set at about twelve hundred participants, which limits the power to detect risk factors with a more modest strength and those with a low prevalence. Our study was conducted with self-administered questionnaires, a method that may be susceptible to socially desirable answers, though all participants were aware of the fact that the questionnaires were handled anonymously.

The strongest predictors for the presence of advanced neoplasia in our study were smoking and a positive family history. In line with findings from previous studies10,13, having one or more first degree family members with CRC was associated with detection of advanced neoplasia32. This confirms the indication for screening persons with a first degree
family member with CRC. Butterworth et al.\textsuperscript{13} conducted a meta-analysis in 59 studies and reported a summary risk estimate of 2.24 for persons with at least one first-degree family member with CRC. Smoking is known for its effect on carcinogenesis, and was associated with increased risk for diagnosed advanced neoplasia in our study. This result is also in line with earlier studies.\textsuperscript{5,10,33} Liang et al.\textsuperscript{33} included 36 studies in a meta-analysis and examined the association between smoking and advanced neoplasia. They concluded that smokers had a significantly increased risk for CRC.

There were only few premenopausal women in the study, but pre-menopausal status, independent of age, had a strong, but not significant protective effect. Freedman et al.\textsuperscript{34} detected a significant difference in CRC risk for pre- and post-menopausal status\textsuperscript{34} and Akhter et al.\textsuperscript{35} a small protective effect of post-menopausal status.

Of all dietary variables, only calcium had a small protective effect on the detection of advanced neoplasia in our study. A meta-analysis of Huncharek et al.\textsuperscript{36} showed a protective effect of calcium intake on CRC. Their summary relative risk for calcium intake on colon cancer risk was 0.78 and 0.84 respectively. Fiber and red meat intake were both not significantly associated with advanced neoplasia. Lieberman et al.\textsuperscript{10} reported a significant but small association for fiber intake, in line with our data. Alexander et al.\textsuperscript{37} performed a meta-analysis of the results from 35 prospective studies and found no association between red meat consumption and advanced neoplasia. They demonstrated that co-linearity between red meat intake and other factors limited the ability to show associations. In contrast, Chan et al. showed that high intake of red meat was positively associated with increased risk of CRC, with a summary relative RR of 1.22. Our data suggest that there is no statistical significant association between red meat consumption and detection of advanced neoplasia.

This study shows that some of the well-known CRC risk factors are also associated with the detection of colorectal cancer precursors during screening. The fact that we found significant associations in this cross-sectional screening study suggests that their risk factor status cannot be exclusively explained by a more rapid growth of precursors in individuals with one or more risk factors.

What then is the value of information about these risk factors for advanced neoplasia? The associations observed could be an argument to target screening more towards persons at increased risk of harboring colorectal cancer precursors, rather than inviting the whole populations in the same way. By screening these high risk individuals more frequently, or earlier in their life, their risk could be controlled. Multivariable risk models can be developed and used for this purpose, to function as a triage instrument in CRC screening in efforts to increase the detection rate of FOBT screening. The model made by Freedman et al. showed good indications for such use as a screening methodology.\textsuperscript{34,38}
There are other potential uses for information about risk factors. Most of the risk factors found in this study are adjustable lifestyle and diet risk factors. Knowing an individual’s risk factors makes it possible to communicate a tailored lifestyle advice to an individual. Colorectal cancer screening could be used not just to detect preclinical forms of disease but also to improve health literacy and health behavior [39]. Embedded in a colorectal cancer screening trial, a tailored advice based on characteristics of the individual may improve long-term health behavior.

Several studies have demonstrated that providing information about risk factors in the communication around screening can increase the tendency to participate in invitees and strengthen adherence under participants, especially in those at higher risk [9]. A systematic review by Edwards et al [40] showed that personalized risk communication leads to a small increase in uptake in screening programs [40]. Since the effectiveness of population screening is affected by the participation rates, one could consider using personalized risk communication in population screening programs.

In summary, this study, designed to evaluate risk factors for the detection of advanced colonic neoplasia in an average risk population, showed that a positive family history for CRC, calcium intake, smoking and age are associated with the presence of advanced neoplasia in a screening population. With the current knowledge about risk factors for CRC, screening programs can target towards individuals at increased risk and encourage those considering a healthy change in lifestyle, which would thereby increase the effectiveness of those programs.
References


11 Larsen IK, Grotmol T, Almendingen K, Hoff G. Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals. BMC Gastroenterol 2006;6:5.


