Title:
Risk of post-colonoscopy colorectal cancer following screening colonoscopy with low-risk or no adenomas: a population-based study.

Authors:
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What does this paper add to the literature?
This study directly compares the post colonoscopy colorectal cancer risk between individuals with either no or low risk adenomas in a faecal test positive screening population. We find no difference in cancer occurrence between these two groups suggesting that screening recall procedures should not be differentiated by this.
Introduction:

The Danish national colorectal cancer (CRC) screening program was initiated in 2014. Citizens aged 50-74 years were invited to submit a faecal immunochemical test (FIT) and FIT positive individuals (100 ng/ml hemoglobin per ml buffer - equivalent to 20 µg/g feces) scheduled for colonoscopy within two weeks. Based on the adenoma findings, individuals are risk stratified, and their appropriate recall procedure and interval is determined (1). If no adenomas are detected, an 8-year repeated FIT is scheduled while in case of low-risk adenoma findings (less than 3 tubular adenomas, all smaller than 10 mm and all low-grade neoplasia), a repeated FIT is scheduled after two years instead (1). Despite the described planned recall procedure, the first screening round was rolled out over four years, with all screening eligible individuals invited in that time span, and no re-invitations made in that period. This was done to accommodate the increasing colonoscopy resource demand. The prolonged interval renders a unique opportunity to investigate the interval cancer rates beyond the planned biennial recall. The impact of this large difference in FIT recall intervals between individuals with low-risk adenomas (two years) and individuals with no adenomas (eight years) on post colonoscopy colorectal cancer (PCCRC) occurrence was the focus of this study.

The Danish Colorectal Cancer Screening database monitors the screening program and reports annually on selected quality indicators. The quality of the Danish screening program has been found satisfactory due to fulfillment of the majority of quality criteria stated in the European screening quality guidelines (2). In 2014-2015 the adenoma detection rate (ADR) was 49-52% and 91% of colonoscopies were complete (3). An individual registration of bowel preparation quality score, withdrawal time or individual endoscopist quality measures is not performed.

Recent ESGE guidelines have changed focus from the post colonoscopy risk of advanced adenomas to the risk of CRC when determining the appropriate recall intervals (2). Studies have demonstrated a reduced incidence of CRC following a negative screening colonoscopy (4, 5), and a CRC incidence similar to that of the background population after excision of low-risk adenomas (6-9). But there is no comparable evidence in these two groups on post colonoscopy colorectal cancer (PCCRC) to support the actual time intervals on re-invitation currently chosen. That PCCRC does occur (10-12) may be due to missed lesions, regrowth or to newly developed neoplasms and highlight the need to accurately monitor and evaluate the recall procedure.

The primary aim of this study was to determine if the planned recall procedure, distinguishing between individuals with either no or low-risk adenomas, can be supported by differences in their PCCRC rate. The secondary aim was to investigate the impact of sex, age and index FIT value on the PCCRC rate,
analyzing that they all significantly affect the risk and thus should be considered when designing the optimal recall procedures.

**Material and methods:**
This is a retrospective cohort study comprising nationwide data from the Danish Colorectal Cancer Screening Database and the Danish Colorectal Cancer Group (DCCG) database. From the screening database all individuals invited for screening in 2014 and 2015 who submitted a positive faecal test were identified. Age, sex, FIT value, investigational dates and risk stratification were recorded. Individuals completing the screening and risk stratified to either no or low-risk adenomas were included in the analysis. Individuals were excluded if they had been diagnosed with colorectal cancer prior to their enrollment in the screening program. This group is already subject to a follow-up program due to their risk of developing metachronous cancer and are not encouraged to participate in screening. Additionally, individuals diagnosed with colorectal cancer within four weeks after the screening investigations were excluded, due to suspected registration error. Individuals not registered with a complete screening investigation were excluded.

The colorectal cancer registry was then crosschecked based on social security numbers of included individuals to find those diagnosed with CRC in a period beginning four weeks after the completed screening and running for the following three years. The primary outcome was the three-year PCCRC rate.

As the primary outcome measure, the three-year PCCRC rate (measured from the time of individual screening completion) in the group with no adenomas was compared to the three-year PCCRC rate in the group with low-risk adenomas. Subsequently, individuals with PCCRC were compared to individuals without PCCRC displaying the distribution of sex, age and FIT value. Binary variables were reported with proportions and 95% confidence intervals and compared using χ² test. Normally distributed continuous variables were reported with means and 95% confidence intervals and compared using student’s t-test. Non-normally distributed continuous variables were reported with medians and inter quartile ranges and compared using Mann-Whitney U test. A multivariable cox proportional hazards regression model on the primary outcome (PCCRC) was planned if more than 40 PCCRCs were identified. This lower limit was set to allow for a minimum of ten outcome occurrences for each of our four independent variables investigated (age, sex, FIT-value and risk stratification group). A p value ≤.05 was considered statistically significant. STATA 15 (Stata corp, Texas, USA) was used for analysis. Data extraction was conducted by a registry data manager upon approval by the database scientific committees and data management was approved by the regional data protection agency (18/25740). No ethical committee approval was needed for this study according to Danish legislation.
Results:

A total of 533,023 screening invitees submitted a FIT in the study period. There were 36,673 positive tests, of which 17,910 individuals (48.8 %) were screened and risk stratified with either no or low risk adenomas. Eighty-one individuals were excluded due to a previous diagnosis of colorectal cancer. Four individuals were excluded due to diagnosis of colorectal cancer within four weeks after the screening investigations. An additional 198 individuals were excluded due to a registration of an incomplete colonoscopy with no subsequent record of any additional completed examination being performed. A total of 17,627 individuals were included in the analysis.

Table 1 demonstrates the distribution of the collected demographic variables according to the two risk stratification groups. The proportion of males was significantly higher in the low-risk adenomas group (p<0.001) and the individuals with low-risk adenomas were significantly older (p<0.001).

<table>
<thead>
<tr>
<th></th>
<th>Individuals with low-risk adenomas at screening</th>
<th>Individuals with no adenomas at screening</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6,123</td>
<td>11,504</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3,617 (59 %)</td>
<td>5,603 (49 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years), median (IQR*)</td>
<td>65 (57-70)</td>
<td>63 (54-70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FIT~-value (ng/ml), median (IQR*)</td>
<td>243 (156-525)</td>
<td>244 (152-554)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*IQR: Inter quartile range, **FIT: Fecal immunochemical test

There were a total of 60 PCCRC occurrences within three years. Table 2 demonstrates the cumulated PCCRC occurrences in both groups after one, two and three years respectively. After three years there were 18 (0.29 %) cancers found in the group with low-risk adenomas and 42 (0.37 %) cancers found in the group with no adenomas (p=0.44)

Table 2: Three year cumulated post colonoscopy colorectal cancer occurrences.

<table>
<thead>
<tr>
<th></th>
<th>Individuals with low-risk adenomas at screening</th>
<th>Individuals with no adenomas at screening</th>
<th>All individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year PCCRC*, n (%)</td>
<td>0 (0 %)</td>
<td>7 (0.06%)</td>
<td>7 (0.04 %)</td>
</tr>
<tr>
<td>2 year PCCRC*, n (%)</td>
<td>7 (0.11 %)</td>
<td>18 (0.16 %)</td>
<td>25 (0.14 %)</td>
</tr>
</tbody>
</table>

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Table 3 demonstrates the distribution of sex, age and FIT value between those with PCCRC occurrence and those without. In univariate comparison individuals with PCCRC was significantly older (p<0.001) and had a higher FIT-value (p=0.007). The risk stratification group of either no or low risk adenomas was not statistically significantly different.

Table 3: Demographic overview of individuals with a 3-year post colonoscopy colorectal cancer.

<table>
<thead>
<tr>
<th></th>
<th>Individuals with PCCRC</th>
<th>Individuals without PCCRC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>17,567</td>
<td></td>
</tr>
<tr>
<td>Male sex, N (%)</td>
<td>36 (60 %)</td>
<td>9,184 (52 %)</td>
<td>0.23</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>69 (64.5-74)</td>
<td>63 (65-70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FIT-value (ng/ml), median (IQR)</td>
<td>436.5 (197-1000)</td>
<td>243 (153-545)</td>
<td>0.007</td>
</tr>
<tr>
<td>Risk stratification with no adenomas, N (%)</td>
<td>42 (70%)</td>
<td>11,462 (65%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*IQR: Inter quartile range, ^PCCRC: Post colonoscopy colorectal cancer, ~FIT: Fecal immunochemical test

The results of the cox proportional hazards regression on the three-year PCCRC occurrence are displayed in table 4. Time at risk was 19,279,610 days. Overall model fit probability was p<0.001.

Table 4: Cox proportional hazards regression model of post colonoscopy cancer occurrence over three years.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Hazard ratio</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>1.310</td>
<td>0.308</td>
<td>0.780-2.200</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.079</td>
<td>&lt;0.001</td>
<td>1.042-1.118</td>
</tr>
<tr>
<td>FIT*-value, ng/ml</td>
<td>1.001</td>
<td>0.002</td>
<td>1.0004-1.0018</td>
</tr>
<tr>
<td>Risk stratification group, low-risk adenomas</td>
<td>0.729</td>
<td>0.264</td>
<td>0.419-1.269</td>
</tr>
</tbody>
</table>

*FIT: Fecal immunochemical test
We found advancing age (p<0.001) and increasing FIT-value (p=0.002) significantly associated to the hazard of PCCRC. The risk stratification group showed no statistically significant impact on PCCRC occurrence.

Discussion:

The removal of low risk adenomas at index screening colonoscopy did not show any associations with the risk of three-year PCCRC (p=0.264). Instead, PCCRC was significantly associated with advanced age (p<0.001) and increased FIT-value (P=0.002). These results challenge the current recall procedure where individuals with low-risk adenomas are re-invited after two years while individuals with no adenomas must wait eight years for their re-invitation.

In this cohort, the higher number of PCCRC’s found in older individuals and in individuals with high FIT-values, suggests that the risk of PCCRC is related to the overall risk of having or developing CRC. Theoretically, the risk of PCCRC after a screening colonoscopy is determined by the sum of several factors. One factor is the risk of developing new pathology after colonoscopy, again dependent on findings at the primary investigation and patient related factors. Another, is the risk associated to the examination quality of the primary endoscopy and the conferred risk of missed lesions.

Male sex, advanced age and higher FIT value are all independent patient related risk factors of advanced colorectal neoplasia (13-16). This could suggest that a negative colonoscopy in an aged male with a high FIT value may pertain a higher risk of a missed lesion and also that this individual carries a higher risk of developing new pathology in the interval before any planned re-invitation. More frequent FIT testing following a colonoscopy with no or low-risk adenomas might reduce the rate of PCCRC (17) but will render an additional burden of futile colonoscopies on society and patients (18, 19). Instead, a stratified FIT recall procedure, based on index FIT value, age and sex, might reduce the PCCRC rate, without increasing the colonoscopy burden, allowing high risk individuals to be re-invited earlier while lower risk individuals could do with a longer re-invitation interval.

Although post colonoscopy cancer is associated with the initial FIT-value, a seemingly patient-related factor, a significant part of the explanation is likely due to missed lesions and the risk of PCCRC associated with the examination quality of the primary endoscopy. Indeed, repeat colonoscopy in FIT positive asymptomatic individuals, has a high yield of CRC and advanced adenomas (20). It is likely that the associated variables lie, not at the patient level, but within endoscopist and procedural related factors. Examining these factors, the individual ADR of the endoscopist, has been found to be the strongest predictive factor for PCCRC (21-23), while also bowel preparation quality (24) caecal intubation rate (25) and withdrawal time (26) has been shown to be a predictive factor of PCCRC (27).
An important limitation to this study is the lack of data on individual endoscopist performance and data on the bowel preparation quality of completed endoscopies. While the overall ADR and completion rates of the Danish screening program are considered acceptable, data on individual endoscopist performance and bowel preparation quality scores of individual colonoscopies would be valuable when determining predictive factors of post colonoscopy colorectal cancer.

The results presented indicate the importance of high quality endoscopies, and that care should be taken before accepting a clean colon in a screening patient. At an institutional level, it necessitates comprehensive quality assurance, to ensure that the endoscopist quality and bowel preparation quality is at a sufficient level. Efforts like these, are tightly linked to training and skills, which has been shown to reduce the PCCRC rate (28). In the run-in phase of the national screening program presented here, the colonoscopy capacity and demands for skilled endoscopists might have been challenged. But with an increased focus over the last years, courses and training programs have been implemented.

In conclusion our study shows that the PCCRC rate is not affected by the findings of low-risk adenomas, in a cohort of FIT-positive screening individuals. These findings do not support the current recall procedure and suggest that the time to re-invitation should not be differentiated between those with no adenomas and those with low-risk adenomas. The fact that age and primary FIT value show association with the PCCRC rate, suggests that a significant part of interval cancers are due to missed lesions, and underlines the importance of continued focus on optimizing the endoscopy quality.

We acknowledge the Danish Colorectal Cancer Group Database and the Danish Quality Database for Colorectal Cancer Screening for providing registry data.


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