Interval cancers after negative colonoscopy: population-based case-control study

Hermann Brenner,1 Jenny Chang-Claude,2 Christoph M Seiler,3 Michael Hoffmeister1

ABSTRACT
Objective The risk of colorectal cancer after a previous negative colonoscopy is very low. Nevertheless, interval cancers occur. We aimed to assess the characteristics and predictors of interval cancers after negative colonoscopy.
Methods A population-based case-control study was conducted in Southern Germany in 2003–7. Sociodemographic and tumour characteristics were compared among 78 patients with interval cancers occurring 1–10 years after a negative colonoscopy and 433 colorectal cancers detected at screening. In addition, the indication for the preceding negative colonoscopy and its completeness were compared between patients with interval cancers and 515 controls with a preceding negative colonoscopy.
Results 56.4% of interval cancers occurred among women compared with 33.7% of cases detected by screening (p=0.0001). After adjustment for covariates, female sex (OR 2.28, 95% CI 1.35 to 3.83) and location in the caecum or ascending colon (OR 1.98, 95% CI 1.17 to 3.35) were independently associated with occurrence of interval cancers. The preceding negative colonoscopy was more commonly conducted because of a positive faecal occult blood test (26.0% vs 12.9%, p=0.009) and was more often incomplete (caecum not reached: 18.1% vs 6.7%, p=0.001) among interval cancer cases than among controls. Characteristics of the preceding negative colonoscopy strongly and independently associated with occurrence of interval cancers were follow-up of a positive faecal occult blood test among men (OR 5.49, 95% CI 2.10 to 14.35) and incompleteness among women (OR 4.38, 95% CI 1.69 to 11.30).
Conclusions The observed patterns suggest that a substantial proportion of interval cancers are due to neoplasms missed at colonoscopy and are potentially preventable by enhanced performance of colonoscopy.

INTRODUCTION
A number of observational studies have shown the risk of colorectal cancer (CRC) to be low within the 10-year screening interval commonly recommended after a negative colonoscopy.1–4 Nevertheless, interval cancers occur, especially in the right colon,5 and, given limited empirical evidence, it is uncertain to what degree they result from neoplasms missed at the preceding negative colonoscopy or represent cancers that have developed since. A recent study from Canada, which was based on physicians’ billing claims, hospital discharge and cancer registry databases, suggested that a deficiency in colonoscopy quality rather than accelerated tumour biology was the cause of the majority of interval cancers occurring within 3 years after a negative colonoscopy.5 6 Furthermore, female sex and older age of the patients and performance of the colonoscopy by a non-gastroenterologist were identified as predictors of missed/early CRC after negative colonoscopy.

However, most previous studies on interval cancers after colonoscopy relied on registry and administrative data,5–8 were restricted to the initial 3–5 years after colonoscopy,6–10 did not specifically focus on interval cancers occurring after a negative colonoscopy (ie, a colonoscopy with no detection of adenomatous polyps)6–12 and provided limited information on possible predictors of interval cancers. Furthermore, most previous reports came from Canada or the USA.5–7 The quality of colonoscopies might differ between countries. For example, recent evidence suggests that, compared with Canada,13 14 the risk of CRC after preceding colonoscopy may be more substantially reduced,
even in the right colon, in Germany where the nationwide introduction of screening colonoscopy in 2002 was accompanied by major efforts of quality assurance.\textsuperscript{15} We aimed to assess characteristics and predictors of interval cancers occurring within 10 years after a negative colonoscopy in a large population-based case-control study from Germany.

**METHODS**

**Study design and study population**

Our analysis is based on data from the “Darmkrebs: Chancen der Verhütung durch Screening” (DACHS) study, a population-based case-control study conducted in the Rhine-Neckar region located in the south-west of Germany and covering a population of about 2 million people. Details of the study design have been reported elsewhere.\textsuperscript{2 3 15} Briefly, the study area includes 22 hospitals where patients with CRC are treated, and all of them agreed to participate in the study. Patients with a first diagnosis of primary invasive CRC aged 30 or older living in the study area are eligible for recruitment. Control subjects are randomly selected from population registers using frequency matching with respect to age, sex and county of residence. We excluded subjects with a history of inflammatory bowel disease who are typically under frequent colonoscopic surveillance. The study was approved by the ethical committees of the Medical Faculty of the University of Heidelberg and of the Medical Chambers of Baden-Württemberg and Rhineland-Palatinate. Recruitment for this study is ongoing. The current analysis is based on cases and controls recruited between January 2003 and December 2007. Overall, 4344 persons (1945 cases and 2399 controls) were recruited. Based on the statistics of patients with CRC treated in the hospitals, recruited patients constitute about 50% of the expected total number of eligible patients in the study area. The participation rate among eligible controls (n=4769) was 50.3%. Written informed consent was obtained from each participant.

**Data collection**

Patients were informed about the study by their treating physicians, in most cases during hospital stay a few days after surgery. They were notified to the study centre upon receipt of informed consent. Personal interviews were conducted by trained interviewers who visited the patients during hospitalisation or, if they had already left the hospital, at their homes. The standardised interviews, which lasted for about 1 h, included a detailed medical and family history as well as a lifetime history of socio-demographic and lifestyle factors. Controls were contacted by the study centre by mail and follow-up calls, and interviews were scheduled at their homes among controls with no history of CRC. The interviews were conducted in the same way as for cases. A self-administered questionnaire that included key information was obtained from a minority of control participants who were not willing to participate in a personal interview.

Detailed information on any previous endoscopic examinations of the large bowel was obtained during the interview. Whenever a previous endoscopy (ie, an endoscopy that was not part of the diagnostic process leading to the current diagnosis) with or without polypectomy was reported by cases or controls, we sought to validate this information by pertinent medical records from the subject’s physician.

**Statistical analysis**

From 1945 cases of CRC we identified 78 interval cancer cases with a validated negative colonoscopy within 10 years prior to diagnosis, as shown in figure 1. In case of multiple preceding endoscopies, only the most recent one was considered.

In a first set of analyses we compared patients with interval cancers with 433 cases whose cancer was detected at screening (figure 1, left side) with respect to the distribution of sex, age, cancer site, stage and grade. Differences between patients with interval cancers and cases detected by screening were tested for statistical significance using $\chi^2$ tests. In addition to showing results for all interval cancers, interval cancers were stratified according to time since negative colonoscopy (<3 years, 3–10 years). Multiple logistic regression was used to identify independent associations (ORs and 95% CIs) of sex, age, tumour location and grade with the occurrence of interval cancers.

In a second set of analyses we compared the 78 patients with interval cancers with 515 controls with a validated negative colonoscopy within 10 years prior to recruitment, who were selected in the same way as the cases with a history of negative colonoscopy (figure 1, right side). Cases and controls with a preceding negative colonoscopy were compared with respect to indication (as reported by the study participants) as well as
completeness (caecum reached: yes/no, taken from medical records) of that colonoscopy. Again, differences between the groups were assessed for statistical significance by $\chi^2$ tests, and multiple logistic regression was employed to assess independent associations of indication and completeness of the preceding colonoscopy with the occurrence of interval cancers, quantified by sex and age-adjusted ORs and their 95% CIs. In addition to analyses for all cases and controls meeting the inclusion criteria, analyses for subgroups defined by sex, age (<70 and $\geq$70 years), time since preceding negative colonoscopy (<10 years) and location of cancer (proximal: caecum or ascending colon; distal: other).

Table 2

Crude and adjusted associations of sociodemographic factors and tumour characteristics with the occurrence of interval cancers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Interval cancers &lt;3 years</th>
<th>Interval cancers 3–10 years</th>
<th>Interval cancers 1–10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude analysis</td>
<td>Adjusted analysis*</td>
<td>Crude analysis</td>
</tr>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Women</td>
<td>2.33 1.17 to 4.67</td>
<td>1.98 0.94 to 4.15</td>
<td>2.73 1.44 to 5.17</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>$\geq$70 years</td>
<td>0.92 0.46 to 1.84</td>
<td>0.77 0.37 to 1.64</td>
<td>0.88 0.47 to 1.66</td>
</tr>
<tr>
<td>Location†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Proximal</td>
<td>2.94 1.43 to 6.02</td>
<td>2.54 1.20 to 5.35</td>
<td>1.76 0.93 to 3.35</td>
</tr>
<tr>
<td>Grade‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1 and G2</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>G3 and G4</td>
<td>2.36 1.13 to 4.90</td>
<td>2.04 0.94 to 4.43</td>
<td>1.44 0.68 to 3.01</td>
</tr>
</tbody>
</table>

*Adjusted for other variables listed in the table.
†Proximal: caecum to ascending colon; distal: other.
‡G1—well differentiated, G2—moderately differentiated, G3—poorly differentiated, G4—undifferentiated.
(47.4%) of the interval cancers were located in the caecum or ascending colon compared with 29.1% of screening detected cancers. This proportion was particularly high (54.5%) among interval cancers occurring <3 years after a negative colonoscopy. The proportions of stage I cancers and of low-grade cancers (G1 or G2) were much higher among screening detected cancers (41.3% and 79.2%, respectively) than among interval cancers (15.4% and 67.6%, respectively), especially interval cancers occurring <3 years after a negative colonoscopy (14.3% and 61.8%, respectively).

The results of multiple logistic regression are shown in table 2. Female sex and location of cancer in the caecum or ascending colon were strongly and independently associated with occurrence of interval cancers (adjusted OR 2.28 (95% CI 1.35 to 3.83) and 1.98 (95% CI 1.17 to 3.55), respectively). For cancer location, the association was stronger and statistically significant only for interval cancers occurring <3 years after a negative colonoscopy.

Comparison of patients with interval cancer and controls with a preceding negative colonoscopy (table 3) showed that the preceding negative colonoscopy was less often conducted as a primary screening examination (39.0% vs 50.9%) and more often conducted as a follow-up examination for a positive faecal occult blood test (FOBT, 26.0% vs 12.9%) in patients with interval cancers (p=0.009). Furthermore, the colonoscopy had been more often incomplete (ie, the caecum had not been reached) among patients with interval cancers (18.1% vs 6.7%, p=0.001). Differences in incompleteness of the preceding colonoscopy between patients with interval cancers and controls were particularly pronounced among women (25.0% vs 8.3%, p=0.002), whereas differences in the indication for the preceding colonoscopy were most pronounced among men. Among men with interval cancers, the preceding colonoscopy had been conducted to follow up a positive FOBT in 35.3% of cases compared with only 10.6% among male controls with a preceding negative colonoscopy (p=0.001). Differences in indication and completeness of the preceding negative colonoscopy between patients with interval cancers and controls were more pronounced among participants aged <70 years.

With adjusted ORs of 2.26 (95% CI 1.16 to 4.42) and 2.63 (95% CI 1.25 to 5.0), respectively, indication by positive FOBT and incompleteness of a preceding negative colonoscopy remained strong and independent predictors of interval cancers after controlling for each other as well as for age and sex (table 4). With adjusted ORs of 2.93 (95% CI 1.13 to 7.61) and 7.24 (95% CI 1.78 to 30.5), respectively, associations were particularly strong with interval cancers occurring <3 years after a negative colonoscopy. Positive associations were also observed with interval cancers occurring 3–10 years after a negative colonoscopy, but they were much weaker and did not reach statistical significance in stratum-specific analysis. Although age and sex were adjusted for in the multiple regression models, estimation of the association of these covariates with occurrence of interval cancers in the case-control analyses would not be meaningful, given that these factors were matched for in recruitment of controls.

Stratified analyses by sex showed very distinct patterns of covariate adjusted associations with indication and completeness of the preceding negative colonoscopy (table 5). Among men, the risk of interval cancers was more than fivefold increased when the preceding colonoscopy had been performed because of a positive FOBT, whereas no significant association was seen with completeness of the colonoscopy. By contrast, incompleteness of the preceding negative colonoscopy was associated with a more than fourfold increase in the risk of interval cancers among women, for whom no association was seen with indication. Differences by age were much less pronounced even though associations with indication and completeness were somewhat stronger in participants aged <70 years and did not reach statistical significance in those aged ≥70 years. Somewhat unexpectedly, the association of incompleteness of the preceding colonoscopy was slightly weaker for interval cancers located in the caecum and ascending colon than for those located in more distal parts of the colon and rectum. The latter interval cancers also showed a much stronger association with a positive FOBT prior to the preceding negative colonoscopy.

**DISCUSSION**

Using data from a large population-based case-control study from Germany, we provide a detailed comparison of patients with interval CRC occurring within 10 years after a negative colonoscopy both with patients whose CRC was detected at screening colonoscopy and with controls who had a negative colonoscopy within the previous 10 years and no diagnosis of...
CRC. The former comparison indicates strong over-representation of cancers in the caecum and ascending colon among patients with interval CRC, particularly when the interval cancer occurred <3 years after the negative colonoscopy. Furthermore, a more than twofold higher risk of interval cancers was observed in women than in men. The latter comparison indicates that, in men, a preceding positive FOBT and, in women, incompleteness of colonoscopy are strong predictors of the occurrence of CRC after a negative colonoscopy.

Our finding of over-representation of proximal colon cancer among interval cancers is consistent with a previous analysis in a much smaller subset of our study population (including cases and controls recruited in 2003 and the first half of 2004 only) which found that risk reduction after negative colonoscopy was less pronounced for proximal colon cancer, especially cancer in the caecum and ascending colon. Likewise, over-representation of interval cancers in the right colon has been reported in colonoscopy cohorts from Canada, where colonoscopy was also found to be associated with reduced mortality from left-sided but not right-sided CRC.

In this context, the contribution of the quality of the colonoscopy and biological factors to the site differences are of major interest. In a previous study from New Zealand, nine of 17 interval cancers occurred after an incomplete colonoscopy. Although this proportion was lower among the 78 interval cancers included in our study (18%), a clear association between interval cancers and completeness of the preceding negative colonoscopy emerged. The occurrence of proximal interval cancers with a preceding positive FOBT in men.

### Table 4
Crude and adjusted associations of indication and completeness with the occurrence of interval cancers

<table>
<thead>
<tr>
<th>Indication</th>
<th>Location of interval cancer</th>
<th>Sex</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caecum or ascending colon</td>
<td>Other</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>OR* 95% CI</td>
<td>OR* 95% CI</td>
<td>OR* 95% CI</td>
</tr>
<tr>
<td>Screening</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Positive FOBT</td>
<td>1.41 0.47 to 4.26</td>
<td>3.31 1.47 to 7.44</td>
<td>5.49 2.10 to 14.35</td>
</tr>
<tr>
<td>Other</td>
<td>1.64 0.74 to 3.63</td>
<td>0.53 0.21 to 1.39</td>
<td>2.04 0.82 to 5.04</td>
</tr>
<tr>
<td>Complete</td>
<td>Yes 1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td></td>
<td>No 2.51 0.94 to 6.70</td>
<td>3.46 1.30 to 9.24</td>
<td>1.32 0.33 to 5.25</td>
</tr>
</tbody>
</table>

*Adjusted for indication or completeness of previous colonoscopy, as well as for age and sex.

### Table 5
Risk of interval cancers with respect to indication and completeness of preceding negative colonoscopy in preceding 1–10 years in defined subgroups

<table>
<thead>
<tr>
<th>Indication</th>
<th>Location of interval cancer</th>
<th>Sex</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caecum or ascending colon</td>
<td>Other</td>
<td>Men</td>
</tr>
<tr>
<td>Screening</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Positive FOBT</td>
<td>1.41 0.47 to 4.26</td>
<td>3.31 1.47 to 7.44</td>
<td>5.49 2.10 to 14.35</td>
</tr>
<tr>
<td>Other</td>
<td>1.64 0.74 to 3.63</td>
<td>0.53 0.21 to 1.39</td>
<td>2.04 0.82 to 5.04</td>
</tr>
<tr>
<td>Complete</td>
<td>Yes 1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td></td>
<td>No 2.51 0.94 to 6.70</td>
<td>3.46 1.30 to 9.24</td>
<td>1.32 0.33 to 5.25</td>
</tr>
</tbody>
</table>

*Adjusted for indication or completeness of previous colonoscopy, as well as for age and sex (as applicable).

FOBT, faecal occult blood test.
Taken together, the associations with a preceding positive FOBT and incompleteness of the previous negative colonoscopy support suggestions recently expressed based on model calculations that missed detection rather than biological factors may be the main cause for the occurrence of interval cancers after a negative colonoscopy.24

Nevertheless, biological factors undoubtedly contribute to the occurrence of interval cancers, particularly in the right colon. For example, microsatellite instability (MSI) and the CpG island methylator phenotype, which are more common among cancers in the right colon than in the left colorectum,25 26 have been shown to be associated with interval cancers.27 28 In our study, MSI and CpG island methylator phenotype status were not available. However, interval cancers—particularly those occurring <3 years after a negative colonoscopy—were more commonly grade 3 or 4 than cancers detected by screening, and this difference was even more pronounced among cancers located in the caecum and ascending colon (data not shown).

Higher tumour grade is associated with advanced stage and worse prognosis.29 30 and faster growth of these cancers may make their detection (or detection of their precursors) at colonoscopy less likely. Nevertheless, in multivariate analysis, cancer site and sex remained strong predictors of interval cancers even after control for tumour grade.

Our study has specific strengths and limitations. The strengths include its reliance on detailed data collected in a large population-based case-control study that enabled comparison of patients with interval cancers after negative colonoscopy with patients whose cancer was detected by screening and with controls who also had a previous negative colonoscopy but no cancer. All self-reported previous colonoscopies were validated controls who also had a previous negative colonoscopy but no patients whose cancer was detected by screening and with

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was obtained from the Ethics Committees, Medical Faculty, University of Heidelberg, and Medical Chambers of Baden-Württemberg and Rhineland-Palatinate.

Contributors All authors have contributed to the conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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