Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study

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Background: Colonoscopy with a possible polypectomy is an efficient and preferred screening method to reduce the incidence of colorectal cancer (CRC). However, critics argue that, to date, a reduction of incidence and mortality from CRC has not been demonstrated in a population-based setting.

Objective: To compare the incidence of and mortality from CRC among individuals screened by colonoscopy and non-screened individuals.

Design: A closed cohort study.

Setting: Population-based setting in a precisely defined area with a low level of population migration.

Patients: This study involved 1912 screened and 20,774 control participants.

Intervention: CRC cases in this closed cohort study were prospectively collected during the screening period of 1 year and the follow-up period of 6 years.

Main Outcome Measurements: Follow-up data were corrected for negligible migration balance in the area. Tumor characteristics and risk or protective factors, age and sex, participation in general health screening examinations, history of CRC in a first-degree relative, smoking status, body mass index, frequency of sports activity, eating habits, and patients' professions were recorded.

Results: Overall cancer incidence was significantly lower in the screened group compared with the non-screened group (adjusted odds ratio [OR] 0.31; 95% confidence interval [CI], 0.16-0.59; \( P < .001 \)). Colon cancer–associated mortality also was clearly lower (adjusted OR 0.12; 95% CI, 0.01-0.93; \( P = .04 \)). Risk factors such as lifestyle, smoking, and body mass index as well as family history were similar in both groups. Blue-collar workers had a higher incidence of CRC compared with professionals. The risk factors for CRC were a positive family history and smoking.

Limitations: Number and ethnicity of the participants, non-randomized study.

Conclusion: Colonoscopy with polypectomy significantly reduces CRC incidence and cancer-related mortality in the general population. (Gastrointest Endosc 2012;76:110-7.)

Colorectal carcinoma (CRC) has a very high incidence in Switzerland as well as in other European countries and is the second most frequent cause of cancer-related deaths in Europe. It is detected in approximately 413,000 people in Europe every year,1 half of whom die during the course of the disease. Hence, there is a need for efficient strategies for prevention and early detection of carcinomas. Colonoscopy with the possibility of an immediate

Abbreviations: CRC, colorectal cancer.

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polypectomy is a recommended and preferred screening method due to the knowledge of colorectal carcinogenesis by adenoma-carcinoma sequence, which takes place over the course of years to decades.\(^1\)\(^2\)\(^5\)

Despite the growing number of studies examining the role of colonoscopy screening, evidence is conflicting. Critics argue that most studies have methodologic weaknesses. Some studies, for example,\(^6\) that establish a correlation between the number of colonoscopies performed and colon carcinoma mortality, or that demonstrate an incidence reduction of colorectal cancer after polypectomy,\(^7\)\(^8\) used mainly historical controls that differ from screened participants with respect to prognosis. A recent, randomized, controlled trial provided evidence that a single sigmoidoscopy significantly reduces the incidence of later cancer in the rectosigmoid colon\(^9\) that has not yet been seen significantly in other trials at an interim evaluation; however, these findings were questioned on methodologic grounds.\(^10\) In addition, retrospective studies suggested that the efficiency of colonoscopy screening in the proximal colon may be poor.\(^11\)\(^12\)

In contrast to earlier CRC screening studies that used colonoscopy, this population-based closed cohort observational study aimed to obtain complete and comparable data on CRC incidence and CRC-related mortality after a single screening colonoscopy compared with no screening, while taking into account the potential differences in risk profiles between the screened and non-screened participants.

**METHODS**

**Study area and participants**

This closed cohort study was performed in a precisely defined, mainly rural area of Switzerland (cantons of Uri and Glarus), which is surrounded by mountains to a substantial degree. Whereas the canton of Uri consists of an area of 415.5 square miles and a population of around 35,000 people, the area and population of Glarus are 264.7 square miles and 38,000 people, respectively. For geographic reasons, these regions have extremely low levels of population migration of 0.255% and between 0.07% and 0.09%, respectively, among individuals aged >50 years in urban and rural areas. Medical and endoscopic care in the study area is provided by two hospitals and one gastroenterologist in private practice, which allowed for a comprehensive overview. During the initial screening, they were supported by gastroenterologists and trainees from the University Hospitals of Basel and Zurich, who had performed at least 200 procedures. Enrollment started on June 1, 2000 and ended 1 year later (for further details see reference 13). Patients screened by colonoscopy constituted the screened group, whereas the 20,774 patients who had been contacted but had refused to participate in the screening program comprised the control group. Colonoscopies were performed by 11 board-certified gastroenterologists, including the 3 local gastroenterologists who were supported in addition by 10 gastroenterology trainees from the University Hospitals of Basel and Zurich, who had performed at least 200 procedures. Enrollment started on June 1, 2000 and ended 1 year later (for further details see reference 13). The information from the participants in the study was gathered by the family doctor and the endoscopists and sent in an anonymous format to the central secretariat of the study. The study protocol had been approved by the Institutional Ethic Committee of central Switzerland in Lucerne. In addition, the study protocol had been controlled and approved by the data protection officer of the canton Uri.

**Follow-up**

After enrollment, the occurrence of colon carcinoma in this closed cohort was prospectively investigated in both groups during the follow-up period from June 1, 2001 to May 31, 2007. There are only 3 gastroenterology centers in the area (including those in the two hospitals), and it is only in these centers that colorectal carcinoma can be

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**Take-home Message**

- Colorectal cancer screening by colonoscopy markedly reduces not only the incidence of colorectal cancer but also cancer-related mortality.
Diagnosed. Data from the registry offices were obtained to ensure that only those patients who had access to the initial information campaign were included in the statistical analysis. The earlier-mentioned low migration rate minimized the possibility of losing a non-screened colorectal carcinoma patient to follow-up. All 1912 screened individuals were contacted by personal correspondence over a 5-year period after screening for the collection of follow-up data. To minimize possible missing data, the responsible general practitioners were contacted in writing with regard to each participant.

The tumor stage and location as well as accompanying diseases, body mass index, family tumor history, lifestyle factors, smoking habits, medication, professions, and symptoms were evaluated. Further progression was covered by reports from the involved centers as well as the inquiries made to the hospitals and practitioners.

**Statistical analysis**

Comparisons between groups at baseline were statistically tested by using parametric or nonparametric methods as appropriate. A $P$ value of $< 5\%$ was considered significant. Any occurrence of colorectal cancer and colorectal cancer–related deaths were recorded for all participants. Salient risk parameters as well as suspected or known protective factors at screening were obtained from each screening participant, including information on age and sex, participation in general health screening examinations, history of colorectal cancer in a first-degree relative, smoking status, and body mass index as well as the frequency of sports activity and eating habits (vegetarian, consumption of fruit and vegetables). We also assessed the patient’s profession. All CRC patients (screened and not screened) were assessed for these parameters at the time of hospitalization. To obtain the distribution of risk profiles in the non-screening population at baseline, we extrapolated the profiles of the non-screening cancer cases and used resampling procedures to reconstruct the complete non-screening population. We created a virtual population of approximately 100,000 persons with exactly the same distribution of risk parameters as the non-screened hospitalized patients. From that population, we randomly drew 3 subgroups of approximately 21,000 patients, each sample representing the total number of non-screened inhabitants of Uri and Glarus, fulfilling the inclusion criteria of this study. The first set of patients was used to assess the effects of screening. Sets 2 and 3 were used for sensitivity analyses. Furthermore, we specified which risk parameters were used to correct for differences in the distribution of screened and non-screened participants. Performance parameters of colonoscopy in the reduction of colon cancer occurrence and colorectal cancer–related deaths were assessed by using multivariate regression models in which we corrected for baseline differences in risk profiles between the screened and non-screened populations. In addition, we performed survival analysis and produced Kaplan-Meier survival curves. All analyses were performed by using the Stata 11.2 statistics software package (StataCorp LP, College Station, TX).
RESULTS

Initial findings from the screening for colorectal cancer by colonoscopy were shown in detail earlier.13 A total of 132 of the 2044 persons who chose screening by colonoscopy (1071 men, 973 women) had to be excluded because of insufficient bowel preparation or incomplete colonoscopy but were also followed-up. None of these persons developed a colorectal cancer later on. Polyps were found in 565 of the 1912 screened individuals (29.6%), including 374 persons (19.6%) with adenomas by histology (Table 1). All polyps found in the colonoscopy were removed during endoscopy or later by surgery in 7 cases (0.36%), except for the very small lesions in the rectum. Overall, 1279 polyps were removed (Table 2).

Colorectal cancer incidence was significantly reduced by colonoscopy screening. Overall, 225 colorectal carcinomas were detected, one of which was found in a screened person (0.05% of screened persons, 60 months after screening [pT3 pN0 M0]) during follow-up, resulting in a total of 12 CRC cases in the screened group (0.6% of the screened persons).\(^11\) In the non-screened group, there were 213 cases of CRC (1.0%) (Table 3). None of the non-screened patients, of whom 5 presented with synchronous carcinomas, and none of the persons who had been excluded from screening, had previously undergone a colonoscopy. Baseline characteristics are shown in Table 3. The cumulative incidence for colorectal cancer was higher in the screened group in the initial phase of the study owing to the early detection of prevalent cancers among the screened participants during the screening period, as can be seen in Figure 2. During the study, however, the cumulative incidence in the control group increased, and the incidence numbers of cancer of the screened individuals and controls started to diverge. Overall, the incidence of colorectal cancer was significantly lower in the screened group compared with the non-screened group.\(^11\)

All except 1 patient of the screened group in whom a carcinoma or a high-grade dysplasia was found were male, whereas in the non-screened group almost two-thirds (61.6%) were male. The majority of cancers (57.9%) were located in the rectosigmoid colon, followed by cancers in the proximal colon (36.4%); only 5.7% of the cancers were located in the descending colon. This distribution pattern was similar in women and men and was comparable in screened and non-screened individuals. Five of 12 carcinomas in the screened group were located proximal to the rectosigmoid colon. The stages of detected carcinomas are shown in Table 3. A total of 72% of the screened-group cancers (66.7% including the one detected during follow-up) and 19.7% of the cancers in the control group were at stage T1/2. One of the 12 persons of the screened individuals with a colorectal cancer and 51 of the 213 persons of the non-screened individuals with a colorectal cancer died because of their cancers. Colorectal cancer–associated mortality was clearly lower in the screened group (OR 0.12; 95% CI, 0.01-0.93; \(P < .001\)).

The risk profile in the screened group was comparable to that in the general population. The characteristics and occupations of participants with and without screening are shown in Tables 4 and 5. The distribution of working professions was comparable except for farmers, who agreed less frequently to participate in the screening, compared with their proportion in the general population (3.7% vs 11.6%). Therefore, being a farmer could be considered a risk factor with regard to non-participation in the screening. Furthermore, participants undergoing screening showed a slight increase in health awareness compared with non-screened individuals. Persons with cancer in the screened group were slightly younger (60.6 \(\pm\) 7.7 years compared with 67.1 \(\pm\) 12.2 years), most likely reflecting the earlier detection of the cancer. Other factors, such as body weight and nutritional habits, did not differ between the two groups. Among the participants, 15.0% of persons with screening but only 10.0% without screening had a body mass index above 30. As expected, more persons with an increased familial risk for colorectal cancer joined the screened group. A total of 12.8% of people with screening but only 7.3% of those without screening had first-degree relatives with colorectal carcinoma. De-

![Table 1. Most advanced colorectal lesions found in the screening colonoscopy in 1912 participants](image)
spite a comparable degree of participation in screening, blue-collar workers had a higher colorectal cancer incidence (35% compared with 20.4% in the general population), which might be due to a higher proportion of smokers in this group. Conversely, cancers occurred least frequently in professionals, which might be for the same reason. Not smoking represented a protective factor with respect to advanced neoplasia (adjusted risk 0.50; 95% CI, 0.32-0.77). A total of 11.8% of the screened individuals and 25.8% of the cancer patients of the control group used aspirin regularly. Overall, a high proportion of patients developing cancer were smokers (45% and 48.8%, respectively, in screened and non-screened patients compared with 15.8% in patients without cancer), a behavior that, therefore, represents a risk factor for colorectal cancer.

**DISCUSSION**

We found in this closed cohort study a substantial reduction of colon cancer incidence and colorectal cancer–related mortality in a sample of asymptomatic individuals undergoing a single colonoscopy screening compared with non-screened individuals. We are unaware of any other long-term prospective study assessing the role of colonoscopy screening for the reduction of colon cancer incidence and mortality in a well-defined, population-based setting under real-life conditions. About 10% of the population included in the study participated in the screening, which had been offered during a 1-year period only. This demonstrates realistic, real-life conditions. Contrary to previous studies, we directly compared tumor incidence among people undergoing screening to people refusing to participate after receiving the same information. Not only 213 participants without screening were included because of incongruent reports on tumor stage in 3 individuals. Furthermore, we adjusted for differences in the cancer-related risk profiles.
The findings of the retrospective data suggested that colonoscopy screening is of little use when assessing the proximal colon. In our study, however, colonoscopy was efficient for the entire colon, a fact that also has been shown recently in another case-control study. There are many possible explanations for this discrepancy. Besides for methodologic issues, the quality of endoscopy and colon preparation could arguably be an important reason. In a recent study, Singh et al showed that the quality of endoscopy and sufficient training for endoscopists are pivotal for an adequate assessment of the colon. In addition, the retrospective analysis of a screening study in Poland showed that the recurrence of colorectal cancer during the follow-up period occurred almost only in those cases in which an endoscopist had found adenomas in fewer than 20% of the colonoscopies, which was a critical number that our study came close to reaching (19.6% adenomas). Compared with a recently published case-control study with a risk reduction of 77%, our results emphasize even more clearly the effect of a colonoscopy on the incidence of colorectal cancer of the distal as well as the proximal colon in a population-based setting. Our findings also are consistent with a British randomized, controlled trial offering flexible sigmoidoscopy screening. Concordant with our results, within the first years after screening, the cumulative incidence was higher in the screened group because of the early detection of prevalent cancers. In our study, the reduction of colon cancer was more extensive than in the sigmoidoscopy trial. However, the reduction of the rectosigmoid tumor incidence of 50% by sigmoidoscopy was seen after an enema as preparation. Theoretical knowledge about colon cancer formation has made colonoscopy an ideal screening tool to fight colon cancer. Slow formation of the tumor permits its colonoscopic detection at a prognostically advantageous early stage. Moreover, it allows for the removal of adenomas and thus prevents the later occurrence of cancers. In fact, the U.S. National Polyp Study showed that adenoma patients had a 76% to 90% reduction of cancer incidence after colonoscopic polypectomy, and a European study showed similar results. However, these studies used epidemiologic data as a reference for comparison, which can be problematic because these data might represent a population with a different prognostic pattern compared with the screened population. In addition, the U.S. National Polyp Study used randomized patients who had undergone a colonoscopic polypectomy, thus ignoring cancer cases identified in the screening, which have been included in our study. Our study, however, confirmed the data of the U.S. National Polyp Study.

<table>
<thead>
<tr>
<th>Variable, %</th>
<th>General population (n = 20774)</th>
<th>With screening (n = 1912)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
<td>77.3</td>
<td>84.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sporting activities &gt; twice a week</td>
<td>21.2</td>
<td>36.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Regular consumption of fruits and vegetables</td>
<td>65.4</td>
<td>29.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vegetarian</td>
<td>3.0</td>
<td>1.65</td>
<td>=.001</td>
</tr>
<tr>
<td>Screening of the prostate gland</td>
<td>53.8</td>
<td>41.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Testing of cholesterol</td>
<td>30.7</td>
<td>30.8</td>
<td>=.925</td>
</tr>
<tr>
<td>Gynecologic screening</td>
<td>64.8</td>
<td>84.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable, %</th>
<th>General population screening</th>
<th>With screening screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profession of men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional (such as university graduate, teacher, clergyman)</td>
<td>30.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Farmer</td>
<td>11.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Trader, retail dealer, commercial clerk</td>
<td>33.7</td>
<td>35.6</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>20.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Other professions</td>
<td>3.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Profession of women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional (such as university graduate, teacher)</td>
<td>8.2</td>
<td>12.7</td>
</tr>
<tr>
<td>Farmer</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Commercial clerk, tradesperson</td>
<td>5.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Shop assistant, waitress, factory worker</td>
<td>11.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Housewife</td>
<td>71.6</td>
<td>66.1</td>
</tr>
<tr>
<td>Other profession</td>
<td>2.9</td>
<td>2.0</td>
</tr>
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</table>

TABLE 4. Baseline characteristics of the population participating in the screening and the general population

TABLE 5. Professions of the population participating in the screening and the general population
The main strength of our study was its implementation set-up in a clearly defined region with low population migration and characterized by very similar living conditions among residents. The design of this closed cohort observational study underlines the clinical relevance of the data. Moreover, comparable levels of information on colon cancer prevention and early symptoms of colon cancer were collected for persons with and without screening.

Our study, however, has certain potential limitations. The first limitation is the participation rate of 10% for the screening with colonoscopy. This represents a real-life situation, however, because screening was offered during a 1-year period only. The second limitation is the size of the cohort. We found only one colorectal cancer in the screened group in the distal colon during follow-up. These data are too scarce, however, for us to make a clear distinction of efficacy in respect to location of the cancer. A third limitation is the duration of the follow-up period, which might be too short to demonstrate all the limitations of the screening. A fourth limitation is the lack of randomization. A large, prospective, randomized, controlled study testing the value of colonoscopy as a screening method to detect colorectal cancer and its precursors would be desirable, but the results of sufficiently large, randomized, controlled studies are not to be expected in the near future. However, our study design is that of a closed cohort study representing the real-life situation even more accurately. We were able to control for potential differences in the risk profiles between screened and non-screened participants. We used a multivariate approach in which we corrected for differences in salient prognostic parameters between screened and non-screened participants and thus reduced the potential for confounding. Screened participants, on the one hand, might have been slightly more health-conscious. They smoked slightly less and played more sports. On the other hand, they more frequently had a familial risk of colorectal cancer. The professions of screened individuals were comparable to those of the general population, with the exception of farmers, whose participation in the screening program was low. There were more cancer patients among blue-collar workers despite equal participation in screening. The use of aspirin was even higher in cancer patients most likely because of more comorbidities and higher age. Thanks to the clear definition of the participating individuals and the control group followed in this closed area, this study design mimics the actual clinical situation even more closely. A fifth shortcoming of our study is that our population consisted almost exclusively of Swiss people of the white population. Results may not be applicable directly to other ethnic groups. A sixth limitation is the quality of the colonoscopy and bowel preparation, which is crucial for the success of the endoscopic screening. In addition, the effects on incidence and mortality reduction cannot exclusively be ascribed to the initial colonoscopic screening. Participants in whom polyps were found in the screening were subsequently followed-up endoscopically according to the guidelines of the Swiss Society for Gastroenterology (www.sggssg.ch). Thus, the efficiency of the screening must be considered as a combined result of the initial endoscopy with a high quality and follow-up monitoring of those with abnormal findings. Therefore, our results cannot be generalized to every screening for colorectal cancer by colonoscopy, especially if done without quality control and subsequent surveillance of the patients. Moreover, any colonoscopy done in the control group would have been a potential confounder. We could rule this out, however, by asking every person specifically after the detection of a cancer by previously performed endoscopic or radiologic examination of the colon. Finally, generalizability might be limited owing to our exclusion criteria, which encompassed persons with a history of familial tumor syndromes such as familial polyposis or hereditary colon cancer syndrome. We also excluded patients with inflammatory bowel disease or previous colon cancer. We decided to do so to reduce the extent of the potential bias if these patients were not equally distributed between the screened and non-screened groups. Furthermore, our study design provided an even better control of the participants during the follow-up period, which excluded a potential information bias as the reason for the higher cancer occurrence in the control group. We did not find any relevant factor putting the control group at a greater risk to develop a colorectal cancer compared with the participants in the screening group, but an additional residual bias influencing the results of our study cannot be ruled out completely.

In conclusion, to date, there has been only limited evidence regarding the efficiency of colonoscopy in the reduction of the occurrence of colon cancer and colorectal cancer–related deaths. Our well-defined closed cohort observational study design provides clinically relevant data substantially favoring a single colonoscopic colorectal cancer screening program for healthy middle-aged participants, on the condition that it includes a qualitatively well-performed colonoscopy.

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REFERENCES


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