Potential for Colorectal Cancer Prevention of Sigmoidoscopy Versus Colonoscopy: Population-Based Case Control Study

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Abstract

We aimed to estimate the proportions of colorectal cancer cases that might be prevented by sigmoidoscopy compared with colonoscopy among women and men. In a population-based case control study conducted in Germany, 540 cases with a first diagnosis of primary colorectal cancer and 614 controls matched for age, sex, and county of residence were recruited. A detailed lifetime history of endoscopic examinations of the large bowel was obtained by standardized personal interviews, validated by medical records, and compared between cases and controls, paying particular attention to location of colorectal cancer and sex differences. Overall, 39%, 77%, and 64% of proximal, distal, and total colorectal cancer cases were estimated to be preventable by colonoscopy. The estimated proportion of total colorectal cancer cases preventable by sigmoidoscopy was 45% among both women and men, assuming that sigmoidoscopy reaches the junction of the descending and sigmoid colon only and findings of distal polyps are not followed by colonoscopy. Assuming that sigmoidoscopy reaches the splenic flexure and colonoscopy is done after detection of distal polyps, estimated proportions of total colorectal cancer preventable by sigmoidoscopy increase to 50% and 55% (73% and 91% of total colorectal cancer preventable by primary colonoscopy) among women and men, respectively. We conclude that colonoscopy provides strong protection against colorectal cancer among both women and men. The proportion of this protection achieved by sigmoidoscopy with follow-up colonoscopy in case of distal polyps may be larger than anticipated. Among men, this regimen may be almost as effective as colonoscopy, at least at previous performance levels of colonoscopy. (Cancer Epidemiol Biomarkers Prev 2007;16(3):494–9)

Introduction

With more than 1 million new cases and more than 500,000 deaths yearly, colorectal cancer is the third most common cancer and the fourth most common cancer cause of death globally (1). Due to its typically slow development, there is a large potential to reduce the burden of the disease by early detection and removal of precancerous lesions or early cancer stages. Endoscopic screening examinations seem to have a particularly large potential to reduce colorectal cancer incidence and mortality by early detection (and removal) of colorectal adenomas and carcinomas. However, there is ongoing debate on the endoscopic examination best suited for screening purposes (2). In particular, while there seems to be consensus that screening by both sigmoidoscopy and colonoscopy are cost effective, results concerning relative effectiveness and cost effectiveness of sigmoidoscopy compared with colonoscopy have not been consistent (3).

An assumption that was explicitly or implicitly made in most pertinent previous analyses was that colonoscopy with polypectomy was equally effective for the reduction of proximal and distal colorectal cancer. However, risk reduction might be different for both locations of colorectal cancer for several reasons, including incompleteness of colonoscopy (4) or suggested differences in mechanisms of tumorigenesis (5-7). Furthermore, recent studies have suggested that the diagnostic yield of sigmoidoscopy, and hence the potential for colorectal cancer prevention, might substantially vary between women and men (8, 9). We aimed to estimate the proportions of colorectal cancer that could be prevented by sigmoidoscopy or colonoscopy among women and men based on detailed sex-specific estimates of risk reduction of proximal and distal colorectal cancer by colonoscopy from a large population-based case control study.

Materials and Methods

Study Design and Study Population. We conducted a population-based case-control study in the Rhine-Neckar region located in the southwest of Germany and covering a population of ~2 million people. Details of the study design have been reported elsewhere (10, 11). Briefly, patients with a first diagnosis of invasive primary colorectal cancer ages 30 years or older between January 2003 and June 2004 were eligible for recruitment. To avoid potential bias due to higher detection rates of asymptomatic colorectal cancer among people undergoing screening, only patients whose cancer was detected due to symptoms or incidentally (rather than by screening) were included in this analysis (additional sensitivity analyses also including patients whose cancer was detected by screening yielded similar results). All of the 22 hospitals in the study area where patients with colorectal cancer were treated were involved in recruitment. Community-based control subjects, matched with respect to age, sex, and county of residence, were randomly selected from population registers.

Data Collection. Patients were informed about the study by the physicians in charge of their treatment, in most cases during hospital stay a few days after surgery. Personal

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interviews were conducted by trained interviewers during hospitalization or, if patients had already left hospital, at their homes. The standardized interviews included a detailed medical and family history, as well as a lifetime history of sociodemographic and lifestyle factors. Controls were contacted by the study center through mail and follow-up calls, and interviews were scheduled at their homes. In addition, blood samples were taken from both cases and controls.

Information on previous endoscopic examinations of the large bowel was obtained in detail during the interview. We excluded cases with endoscopic examinations <1 year ago to avoid consideration of endoscopies that might have been conducted during the diagnostic process leading to the current cancer diagnosis. To ensure comparability, controls with an endoscopic examination during the last 12 months were also excluded We also carried out additional sensitivity analyses, including cases and controls with a previous endoscopy <1 year ago, which yielded very similar results.

Whenever a previous endoscopy was reported by cases or controls, we sought to validate this information by pertinent medical records from participants' physicians. Medical records could be obtained for 80% and 89% of examinations reported by cases and controls, respectively, within the preceding 10 years (the time frame during which medical records have to be archived in Germany). The majority of these endoscopies were colonoscopies according to both self-reports (86%) and endoscopy reports (88%), and both data sources agreed about the type of endoscopy in 83% of examinations. Medical records were used for classification where available, otherwise self-reports were used.

Statistical Analysis. The statistical analysis was carried out using the SAS statistical software system, version 8.2. We first described cases and controls according to age and sex, and we assessed the distribution of the location of colorectal cancer among cases. Next, we assessed the risk of proximal, distal, and total colorectal cancer according to history of colonoscopy, using subjects without any previous endoscopy as the reference group. Relative risks [approximated by odds ratios (OR)] and their 95% confidence intervals (95% CI) for the association between history of colonoscopy and colorectal cancer risk were estimated from multiple logistic regression models, adjusting for the matching factors age and sex, as well as the following factors, which are known or have been suggested to be related to risk of colorectal cancer: level of school education (categories: ≤9, 10-11, and 12+ years), history of colorectal cancer among a first-degree relative, smoking (never, ever, and current), ever regular use (at least once monthly for at least 1 year) of nonsteroidal anti-inflammatory drugs, any hormone therapy, and body mass index (categories: <20, 20-24.9, 25-29.9, and 30+ kg/m^2). To avoid confounding by general health behavior, we additionally controlled for participation in a general health screening examination, offered to adults ages 36 years and older every 2 years in the German health care system (categories: ever and never).

Due to the small numbers of subjects with a previous sigmoidoscopy, the effect of sigmoidoscopy was not estimated directly by estimating the risk of these subjects compared with subjects without previous endoscopy. Rather, estimates were based on the proportions of proximal and distal colorectal cancer cases and on estimates of risk reduction of proximal and distal colorectal cancer by colonoscopy as outlined in the Appendix. In a first conservative approach, it was assumed that sigmoidoscopy would only prevent distal colorectal cancer by detection and removal of distal polyps. However, detection of distal polyps often prompts subsequent examination of the entire colon by colonoscopy. In a second approach, we therefore also considered the proportion of proximal cancer prevented by follow-up colonoscopies (for details, see Appendix A).

In the main analysis presented in this article, distal colon was conservatively defined as sigmoid colon or rectum because >50% of flexible sigmoidoscopic examinations reach only the junction of the sigmoid and descending colon (12, 13). Ideally, flexible sigmoidoscopy would reach the splenic flexure. Although this seems to be achieved in a minority of patients only, we carried out an additional analysis, in which distal colon was alternatively defined as rectum, sigmoid colon, or descending colon, to estimate the proportions of colorectal cancer that might be prevented by flexible sigmoidoscopy under ideal conditions. Results are presented in detail for the ''main definition'' of distal colon (sigmoid colon and rectum). All analyses were repeated using the ''alternative definition'' of distal colon (descending colon, sigmoid colon, and rectum), but, to save space, only the final results (estimates of the proportions of colorectal cancer cases that might be prevented by ''ideal'' sigmoidoscopy) are presented in detail.

Results

Overall, 540 cases and 614 controls were recruited. According to estimates from the population-based cancer registry of the nearby state of Saarland, ~50% of eligible patients were recruited. The participation rate among controls was 44% (with higher proportions among younger controls and lower proportions in the oldest age groups), but an additional 25% of controls provided information on key variables, including history of endoscopic examinations of the large bowel. After exclusion of cases detected by screening (n = 108), people with history of inflammatory bowel disease (n = 1) or previous endoscopy <1 year ago (n = 44) or unknown (n = 2), or whose last endoscopy was a rectoscopy or sigmoidoscopy rather than colonoscopy (n = 48), 411 cases and 540 controls were retained for this analysis. Their age and sex distribution is shown in Table 1. Mean age of cases and controls was 67.8 and 66.6 years, respectively, ~40% of both cases and controls were 60 to 69 years old. The sample included more men than women. Due to matching, age and sex distribution was very similar among cases and controls.

Overall, ~40% of cancers were located in the proximal colon, 18% were located in the sigma, and 41% were rectum cancers. The proportion of cancers located in the proximal colon was much higher (50% versus 33%), and the proportion of cancers located in the rectum was much lower (32% versus 48%) among women compared with men (P = 0.002; see Table 2).

A much higher proportion of controls (35.0%) than of cases (14.8%) had a previous colonoscopy, resulting in an OR of 0.32 as an estimate of relative risk among those who underwent colonoscopy after control for the matching factors age and sex. Additional control for a variety of potential confounding factors only slightly changed this estimate to 0.36 (see Table 3). With adjusted ORs of 0.32 and 0.39, the estimated risk reduction among those who had undergone colonoscopy was similar for women and men.

Table 1. Age and sex distribution of cases and controls

Characteristic	Level	Cases, n (%)	Controls, n (%)
Age (y)	30-49	20 (4.9)	31 (5.7)
	50-59	59 (14.4)	90 (16.7)
	60-69	164 (39.9)	210 (38.9)
	70-79	111 (27.0)	150 (27.8)
	80+	57 (13.9)	59 (10.9)
Sex	Women	179 (43.6)	237 (43.9)
	Men	232 (56.5)	303 (56.1)

Table 2. Location of cancer according to sex

	n (%)	*P*
Both		
Proximal colon	158 (40.4)	
Sigma	72 (18.4)	
Rectum	161 (41.2)	
Women		
Proximal colon	84 (49.7)	
Sigma	31 (18.3)	
Rectum	54 (32.0)	
Men		
Proximal colon	74 (33.3)	
Sigma	41 (18.5)	
Rectum	107 (48.2)	0.002

However, risk reduction was much stronger for distal colorectal cancer (defined as located in the sigma or rectum) than for proximal colorectal cancer (adjusted ORs 0.23 and 0.61, respectively), and this difference was particularly pronounced for women (adjusted ORs 0.10 and 0.69, respectively; see Table 4).

Consequently, >70% of cancers preventable by colonoscopy (and 46% of cancers overall) were estimated to be preventable by sigmoidoscopy alone, even if sigmoidoscopy was assumed to reach the junction of the sigmoid and the descending colon only and detection of distal polyps did not prompt colonoscopy (see Table 5). Under this assumption, estimates were quite similar for women and for men. However, taking follow-up colonoscopies after detection of a distal polyp into account, it is estimated that 68% and 84% of cancers preventable by primary colonoscopy (45% and 52% of all colorectal cancer) would be preventable by primary sigmoidoscopy among women and men, respectively.

With the alternative definition of distal colon (including descending and sigmoid colon and rectum), assuming that sigmoidoscopy reaches the splenic flexure, these proportions would increase to 73% and 91% (50% and 55% of all colorectal cancers) among women and men, respectively (see Table 6).

Discussion

According to this large population-based study with careful validation of self-reported previous endoscopic examinations of the large bowel, about two thirds of colorectal cancer cases could be prevented by colonoscopy with removal of precancerous lesions. The vast majority of these cancers could also be prevented by primary sigmoidoscopy screening with a follow-up colonoscopy among people with distal polyps only. The relative effectiveness of sigmoidoscopy compared with colonoscopy is estimated to be 76% if sigmoidoscopy reaches the junction of the descending colon and the sigmoid colon only and 83% if sigmoidoscopy reaches the splenic flexure. The corresponding figures are even higher among men (84% and 91%, respectively).

Our estimates of the proportion of colorectal cancer that might be prevented by colonoscopy are in line with previous studies from the United States (14), Germany (15), and Italy (16). An even stronger risk reduction had been observed in the United States National Polyp Study (17). Our estimates of the proportions of colorectal cancer that might be prevented by sigmoidoscopy, in particular if followed by colonoscopy in case of distal polyps, are considerably higher than previously assumed levels. For example, Sonnenberg et al. (18) assumed that 75% of colorectal cancer cases might be prevented by a colonoscopy-based screening program with 10-year screening intervals compared with only 34% prevented cases by sigmoidoscopy-based screening with 5-year screening intervals. Frazier et al. (19) assumed the reductions of colorectal cancer incidence by a single colonoscopy or a single sigmoidoscopy at age 55 years to be ~27% and 14% to 15% (latter depending on rules for follow-up colonoscopy after detection of polyps) and by colonoscopy or sigmoidoscopy repeated every 10 years to be ~58% and 28% to 32%, respectively.

The much higher estimates of proportions of colorectal cancer preventable by sigmoidoscopy derived in our study result from the combination of the large proportion of colorectal cancer located in the sigma and rectum (~60%; i.e., within the reach of sigmoidoscopy) and the particularly strong risk reduction for distal colorectal cancer. Similar predominance of distal location has been reported for colorectal adenomas and colorectal carcinomas (20). The finding of particularly strong risk reduction for distal colorectal cancer is consistent with results of previous studies (14, 15, 21, 22), including a very large case-control study from the United States (23).

The much stronger risk reduction for distal than for proximal cancer is the main reason for the considerably smaller difference in the effects of sigmoidoscopy and colonoscopy estimated in our study than assumed in most previous analyses of effectiveness and cost effectiveness of various screening strategies. One possible reason could be missed proximal polyps due to the incompleteness of colonoscopies. In our study, 12% of colonoscopies were recorded to be incomplete in medical charts, and completeness was not recorded in another 11% of colonoscopies. These findings may therefore explain some proportion of the large difference in risk reduction of proximal and distal colorectal cancer, suggesting a major potential for improvement in quality of colonoscopy. Nevertheless, additional factors, such as potential differences in tumor biology (5-7), might also play a role.

Clearly, colonoscopy with removal of adenomas provides the strongest protection against colorectal cancer. However, the advantage in terms of risk reduction compared with sigmoidoscopy has to be weighed against increased inconvenience, risks, and costs. The risk of perforation after colonoscopy is approximately double that after sigmoidoscopy (24). Although estimates vary both between and within countries, costs of colonoscopy are about two to four times higher than costs of flexible sigmoidoscopy (3, 25). If, as suggested by our analysis, its disadvantage in terms of risk reduction is much lower than commonly assumed, the relative merits of sigmoidoscopy compared with colonoscopy require careful reevaluation, which should also pay particular attention to gender-specific patterns.

Another important aspect is acceptability and feasibility of and compliance with screening examinations. Sigmoidoscopy was found to be acceptable, feasible, and safe in ongoing trials in the United Kingdom, Italy, Norway, and the United States (26-29). Acceptability and feasibility may be lower for colonoscopy, partly due to limited resources in highly

Table 3. Association of history of colonoscopy with risk of colorectal cancer

Sex	History of colonoscopy	Cases, *n* (%)	Controls, *n* (%)	Adjusted OR* (95% CI)
Both	No	350 (85.2)	351 (65.0)	$1.00^{Reference}$
	Yes	61 (14.8)	189 (35.0)	0.36 (0.26-0.50)
Women	No	155 (86.6)	148 (62.5)	$1.00^{Reference}$
	Yes	24 (13.4)	89 (37.6)	0.32 (0.19-0.56)
Men	No	195 (84.1)	203 (67.0)	$1.00^{Reference}$
	Yes	37 (16.0)	100 (33.0)	0.39 (0.25-0.60)

*Adjusted for age, sex (in analysis for both sexes combined only), education, participation in general health screening examination, family history of colorectal cancer, smoking, body mass index, ever regular use of nonsteroidal anti-inflammatory drugs, and ever regular use of hormone replacement therapy.

Table 4. Association of history of colonoscopy with risk of proximal and distal colorectal cancer (both groups of cases compared with all controls)

Sex	History of colonoscopy	Proximal cancer*		Distal cancer*	
		Cases, *n* (%) †	Adjusted OR (95% CI) ‡	Cases, *n* (%) †	Adjusted OR (95% CI) ‡
Both	No	125 (79.1)	1.00[Reference]	208 (89.3%)	1.00[Reference]
	Yes	33 (20.9)	0.61 (0.39-0.95)	25 (10.7%)	0.23 (0.14-0.37)
Women	No	66 (78.6)	1.00[Reference]	80 (94.1%)	1.00[Reference]
	Yes	18 (21.4)	0.69 (0.36-1.30)	5 (5.9%)	0.10 (0.03-0.29)
Men	No	59 (79.7)	1.00[Reference]	128 (86.5%)	1.00[Reference]
	Yes	15 (20.3)	0.55 (0.29-1.03)	20 (13.5%)	0.32 (0.18-0.55)

*Distal cancer includes sigma and rectum cancer, and proximal cancer includes all other colorectal cancers.
† For numbers and proportion of controls in respective categories, see Table 3.
‡ Adjusted for age, sex (in analysis for both sexes combined only), education, participation in general health screening examination, family history of colorectal cancer, smoking, body mass index, ever regular use of nonsteroidal anti-inflammatory drugs, and ever regular use of hormone therapy.

qualified personnel (30), but pertinent data are sparse. Taking likely differences in compliance into account, the proportion of colorectal cancer prevented in the total population (i.e., in screened and unscreened people) may therefore be even larger for screening with sigmoidoscopy as the primary screening tool.

In the interpretation of our study, several limitations have to be kept in mind. Only ~50% of eligible patients could be recruited. As discussed in detail elsewhere (10), incomplete cases ascertainment was primarily due to work overload of physicians in charge of case notifications and is unlikely to be related to history of colonoscopy. Response rate among controls was <50% in this study, which had no upper age limit and included quite extensive data collection and drawing of a blood sample. However, data from a short questionnaire obtained from about half of nonparticipating controls yielded no indication of major distortion of history of colonoscopy among controls.

We did not distinguish between previous colonoscopies primarily conducted for screening purposes and other specific indications, such as symptoms, a positive family history or control of a positive fecal occult blood test, which may limit generalizability of our results to a primary screening setting. Because the latter indications are likely to be associated with an increased risk of colorectal cancer, risk reduction may have been underestimated to some extent, and true risk reduction by sigmoidoscopy and colonoscopy might even be somewhat greater than estimated in our study. On the other hand, risk reduction might have been overestimated if colonoscopy had more commonly been applied in more health conscious people, who have lower risk of colorectal cancer. We tried to minimize potential bias from this source by controlling for factors that might reflect or be related to health consciousness. Control for multiple potential confounders only had a minor effect on estimates of ORs, but one can never rule out residual confounding by imperfectly measured confounders or unmeasured confounders by an observational study like this one. The results of the randomized controlled trials, which are under way in Europe and the United States (26-29), will have to be awaited to obtain more definitive answers on the risk reduction that may be achieved by endoscopic screening.

Our estimates of risk reduction of distal colorectal cancer by sigmoidoscopy are actually based on data from colonoscopy. A similar approach has been taken in other studies aimed to compare the role of sigmoidoscopy and colonoscopy in colorectal cancer screening (8, 9, 31, 32). These estimates might be slightly too optimistic assuming that sedation and more vigorous colonic lavage applied with colonoscopy might lead to more complete detection and removal of polyps. In addition, variation in qualification of endoscopists, which is likely to be as important for the effectiveness of sigmoidoscopy (33, 34) as it is for the effectiveness of colonoscopy, was not accounted for in our analyses.

Despite these limitations, our study suggests that both screening sigmoidoscopy and screening colonoscopy may strongly reduce incidence of colorectal cancer. The potential of sigmoidoscopy compared with colonoscopy may be considerably larger than commonly assumed, particularly for men, but also for women, due to the very strong risk reduction for distal colorectal cancer achieved with endoscopic screening. For men, primary screening by sigmoidoscopy, followed by colonoscopy in case of detection of distal adenomas, may be almost as effective as primary colonoscopy, at least at previously achieved performance levels of colonoscopy. Taking likely differences in compliance into account, offer of sigmoidoscopy as a primary screening tool may even have a larger effect on reduction of colorectal cancer incidence than screening by primary colonoscopy. These findings may have important implications for comparative evaluations of cost effectiveness of screening sigmoidoscopy and screening colonoscopy and for screening recommendations and implementation of screening programs.

Finally, it should be noted that our analyses refer to previously established endoscopic procedures. It is well known that some proportion of lesions are missed by endoscopy (35). This fact should be reflected in the ORs derived in our analyses, which reflect the effect of less than perfect endoscopic examinations. Enhancements in both endoscopy technology and qualification of endoscopists may lead to higher proportions of colorectal cancer that may be prevented by colonoscopy and sigmoidoscopy in the future. In addition, advancements in virtual colonoscopy may open further avenues for effective alternative ''endoscopic'' colorectal cancer screening in the future (36).

Table 5. Proportions (95% CIs) of colorectal cancer cases preventable by sigmoidoscopy and by colonoscopy: main analysis (assuming that sigmoidoscopy reaches the junction of the sigmoid and descending colon)

Sex	COL (%)	SIG only (%)	Ratio SIG/COL	SIG + COL if distal polyps (SIG+, %)	Ratio SIG+/COL
Both	64 (50-74)	45 (38-53)	0.71 (0.62-0.84)	49 (41-57)	0.76 (0.71-0.86)
Women	68 (44-81)	45 (36-54)	0.67 (0.54-0.91)	46 (37-55)	0.68 (0.56-0.90)
Men	61 (40-75)	45 (32-57)	0.74 (0.61-0.93)	51 (36-63)	0.84 (0.75-0.95)

Abbreviations: COL, colonoscopy; SIG, sigmoidoscopy; SIG+, sigmoidoscopy + colonoscopy if distal polyps.

Table 6. Proportions (95% CIs) of colorectal cancer cases preventable by sigmoidoscopy and by colonoscopy: main analysis (assuming that sigmoidoscopy reaches the splenic flexure)

Sex	COL (%)	SIG only (%)	Ratio SIG/COL	SIG + COL if distal polyps (SIG+, %)	Ratio SIG+/COL
Both	64 (50-74)	50 (42-57)	0.78 (0.69-0.91)	53 (44-61)	0.83 (0.77-0.91)
Women	68 (44-81)	49 (40-57)	0.72 (0.59-0.99)	50 (40-58)	0.73 (0.62-0.96)
Men	61 (40-75)	50 (37-61)	0.83 (0.70-1.02)	55 (39-67)	0.91 (0.82-1.00)

Abbreviations: COL, colonoscopy; SIG, sigmoidoscopy; SIG+, sigmoidoscopy + colonoscopy if distal polyps.

Appendix A

In the first, conservative approach, the proportion of colorectal cancer prevented by sigmoidoscopy was estimated as

$$P_{\text{distal}} * (1 - \text{RR}_{\text{distal}})$$

and the proportion of colorectal cancer prevented by colonoscopy was estimated as

$$(1 - \text{RR}_{\text{total}})$$

where P_{distal} represents the proportion of distal colorectal cancer among cases, and $\text{RR}_{\text{distal}}$ and RR_{total} represent the relative risks of distal and total colorectal cancer, respectively, of people who underwent colonoscopy compared with people who did not. All three parameters were directly estimated from our case-control study as described in the main text. This approach is based on the assumption that sigmoidoscopy would only prevent distal colorectal cancer by detection and removal of distal polyps.

In the second approach, taking follow-up colonoscopies after detection of distal polyps into account, the proportion of colorectal cancer prevented by sigmoidoscopy was estimated as

$$P_{\text{distal}} * (1 - \text{RR}_{\text{distal}}) + P_{\text{proximal}} * (1 - \text{RR}_{\text{proximal}}) * Q$$

where P_{proximal} and $\text{RR}_{\text{proximal}}$ represent the proportion of proximal colorectal cancer and the estimate of relative risk for proximal colorectal cancer of people who underwent colonoscopy compared with people who did not. These variables were again directly estimated from our case control-study. Q represents the proportion of people with advanced proximal adenomas who would receive colonoscopy as a follow-up examination after detection of distal adenomas through a primary screening sigmoidoscopy. This proportion was assumed to be 6% and 38% (8% and 45% in the alternative analyses, including the descending colon in the definition of distal colon) for women and men, respectively, based on results of studies reported from the United States (8, 9).

To derive 95% CIs for the proportions of colorectal cancer prevented by sigmoidoscopy, bootstrap analyses of the case-control data were carried out. 95% CIs were derived as the range from the 2.5th to the 97.5th percentile of the point estimates obtained from 10,000 bootstrap samples. In these analyses, the parameter Q, which was obtained from external sources (8, 9), was held constant. Additional sensitivity analyses were carried out, in which Q was varied from 0.0 to 0.30 among women and from 0.30 to 0.60 among men. This variation only had a minor effect on the estimated proportions of colorectal cancer prevented by sigmoidoscopy with follow-up colonoscopy after detection of distal polyps (estimated proportions showed an overall variation of 5% units or less in all cases), and results of sensitivity analyses are therefore not presented in detail.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Ransohoff DF. Colon cancer screening in 2005: status and challenges. Gastroenterology 2005;128:1685–95.
3. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review of the U.S. Preventive Task Force. Ann Intern Med 2002;137:96–104.
4. Dafnis G, Granath F, Pahlman L, Ekbom A, Blomqvist P. Patient factors influencing the completion rate in colonoscopy. Dig Liver Dis 2005;37:113–8.
5. Ponz de Leon M, Sacchetti C, Sassatelli R, Zanghieri G, Roncucci L, Scalmati A. Evidence for the existence of different types of large bowel tumour: suggestions from the clinical data of a population-based registry. J Surg Oncol 1990;44:35–43.
6. Lindblom A. Different mechanisms in the tumourigenesis of proximal and distal colon cancers. Curr Opin Oncol 2001;13:63–9.
7. Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002;101: 403–8.
8. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G; for the Veterans Affairs Cooperative Study Group 380. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. N Engl J Med 2000;343: 162–8.
9. Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005;352:2061–8.
10. Brenner H, Chang-Claude J, Seiler CM, Stürmer T, Hoffmeister M. Does a negative screening colonoscopy ever need to be repeated? Gut 2006;55: 1145–50.
11. Verla-Tebit E, Lilla C, Hoffmeister M, Brenner H, Chang-Claude J. Cigarette smoking and colorectal cancer risk in Germany: a population-based study. Int J Cancer 2006;119:630–5.
12. Ott DJ, Wu WC, Gelfand DW. Extent of colorectal visualization with the fiberoptic sigmoidoscope. J Clin Gastroenterol 1982;4:337–41.
13. Painter J, Saunders DB, Bell GD, Williams CB, Pitt R, Bladen J. Depth of insertion at flexible sigmoidoscopy: implications for colorectal cancer screening and instrument design. Endoscopy 1999;31:227–31.
14. Müller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. Arch Intern Med 1995;155:1741–8.
15. Brenner H, Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G. Long-lasting reduction of risk of colorectal cancer following screening endoscopy. Br J Cancer 2001;85:972–6.
16. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M; The Italian Multicentre Study Group. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48: 812–5.
17. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977–81.
18. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. Ann Intern Med 2000;133:573–84.
19. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA 2000;284: 1954–61.
20. Patel K, Hoffman NE. The anatomical distribution of colorectal polyps at colonoscopy. J Clin Gastroenterol 2001;33:222–5.
21. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 1992;84: 1572–5.
22. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak M, Vatn H. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Scand J Gastroenterol 1999;34:414–20.
23. Newcomb PA, Storer BE, Morimoto LM, Templeton A, Potter JD. Long-term

efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst 2003;95:622–5.
24. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003;95:230–6.
25. O'Leary BA, Olynk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with faecal occult blood testing and colonoscopy. J Gastroenterol Hepatol 2004;19:38–47.
26. UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291–300.
27. Segnan N, Senore C, Andreoni B, et al. Baseline findings of the Italian multicenter randomized controlled trial of ''once-only sigmoidoscopy''—SCORE. J Natl Cancer Inst 2002;94:1763–72.
28. Bretthauer M, Gondal G, Larsen K, et al. Design, organization, and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). Scand J Gastroenterol 2002;37:568–73.
29. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst 2005;97:989–97.
30. Vijan S, Inadomi J, Hayward RA, Hofer TP, Fendrick AM. Projections of demand and capacity for colonoscopy related to increasing rates of colorectal cancer screening in the United States. Aliment Pharmacol Ther 2004;20:507–15.
31. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169–74.
32. Lieberman DA, Weiss DG; for the Veteran Affairs Cooperative Study Group 380. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001;345:555–60.
33. Atkin W, Rogers P, Cardwell C, et al. Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. Gastroenterology 2004;126:1247–56.
34. Pinsky PF, Schoen RE, Weissfeld JL, Kramer B, Hayes RB, Yokochi L; for the PLCO Project Team. Variability in flexible sigmoidoscopy performance among examiners in a screening trial. Clin Gastroenterol Hepatol 2005;3:792–7.
35. Ransohoff DF. Have we oversold colonoscopy? Gastroenterology 2005;129:1815.
36. Nicholson FB, Barro JL, Bartram CI, et al. The role of CT colonography in colorectal cancer screening. Am J Gastroenterol 2005;100:2315–23.