Published in final edited form as:
N Engl J Med. 2013 September 19; 369(12): . doi:10.1056/NEJMoa1301969.

Long-Term Colorectal-Cancer Incidence and Mortality after Lower Endoscopy

Reiko Nishihara, Ph.D., **Kana Wu, M.D., Ph.D.**, **Paul Lochhead, M.B., Ch.B.**, **Teppei Morikawa, M.D., Ph.D.**, **Xiaoyun Liao, M.D., Ph.D.**, **Zhi Rong Qian, M.D., Ph.D.**, **Kentaro Inamura, M.D., Ph.D.**, **Sun A. Kim, M.D., Ph.D.**, **Aya Kuchiba, Ph.D.**, **Mai Yamauchi, Ph.D.**, **Yu Imamura, M.D., Ph.D.**, **Walter C. Willett, M.D., Dr.P.H.**, **Bernard A. Rosner, Ph.D.**, **Charles S. Fuchs, M.D., M.P.H.**, **Edward Giovannucci, M.D., Sc.D., M.P.H.**, **Shuji Ogino, M.D., Ph.D.**, and **Andrew T. Chan, M.D., M.P.H.**

From the Department of Medical Oncology, Dana–Farber Cancer Institute and Harvard Medical School (R.N., P.L., T.M., X.L., Z.R.Q., K.I., S.A.K., A.K., M.Y., Y.I., C.S.F., S.O.); the Departments of Nutrition (R.N., K.W., A.K., W.C.W., E.G.), Epidemiology (W.C.W., E.G., S.O.), and Biostatistics (B.A.R.), Harvard School of Public Health; the Channing Division of Network Medicine, Department of Medicine (K.W., W.C.W., B.A.R., C.S.F., E.G., A.T.C.), and Department of Pathology (S.O.), Brigham and Women's Hospital and Harvard Medical School; and the Division of Gastroenterology, Massachusetts General Hospital (A.T.C.) — all in Boston; the Gastrointestinal Research Group, Institute of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom (P.L.); the Department of Pathology, University of Tokyo Hospital, Tokyo (T.M.); and Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, MD (K.I.)

Abstract

BACKGROUND—Colonoscopy and sigmoidoscopy provide protection against colorectal cancer, but the magnitude and duration of protection, particularly against cancer of the proximal colon, remain uncertain.

METHODS—We examined the association of the use of lower endoscopy (updated biennially from 1988 through 2008) with colorectal-cancer incidence (through June 2010) and colorectal-cancer mortality (through June 2012) among participants in the Nurses' Health Study and the Health Professionals Follow-up Study.

RESULTS—Among 88,902 participants followed over a period of 22 years, we documented 1815 incident colorectal cancers and 474 deaths from colorectal cancer. With endoscopy as compared with no endoscopy, multivariate hazard ratios for colorectal cancer were 0.57 (95% confidence interval [CI], 0.45 to 0.72) after polypectomy, 0.60 (95% CI, 0.53 to 0.68) after negative sigmoidoscopy, and 0.44 (95% CI, 0.38 to 0.52) after negative colonoscopy. Negative colonoscopy was associated with a reduced incidence of proximal colon cancer (multivariate hazard ratio, 0.73; 95% CI, 0.57 to 0.92). Multivariate hazard ratios for death from colorectal

Address reprint requests to Dr. Chan at the Division of Gastroenterology, Massachusetts General Hospital, 55 Fruit St., GRJ-825C, Boston, MA 02114, or at achan@partners.org.

Drs. Nishihara, Wu, Lochhead, and Morikawa and Drs. Ogino and Chan contributed equally to this article.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH).

Dr. Chan reports receiving consulting fees from Bayer Health-care, Pfizer, Millennium Pharmaceuticals, and Pozen. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

cancer were 0.59 (95% CI, 0.45 to 0.76) after screening sigmoidoscopy and 0.32 (95% CI, 0.24 to 0.45) after screening colonoscopy. Reduced mortality from proximal colon cancer was observed after screening colonoscopy (multivariate hazard ratio, 0.47; 95% CI, 0.29 to 0.76) but not after sigmoidoscopy. As compared with colorectal cancers diagnosed in patients more than 5 years after colonoscopy or without any prior endoscopy, those diagnosed in patients within 5 years after colonoscopy were more likely to be characterized by the CpG island methylator phenotype (CIMP) (multivariate odds ratio, 2.19; 95% CI, 1.14 to 4.21) and microsatellite instability (multivariate odds ratio, 2.10; 95% CI, 1.10 to 4.02).

CONCLUSIONS—Colonoscopy and sigmoidoscopy were associated with a reduced incidence of cancer of the distal colorectum; colonoscopy was also associated with a modest reduction in the incidence of proximal colon cancer. Screening colonoscopy and sigmoidoscopy were associated with reduced colorectal-cancer mortality; only colonoscopy was associated with reduced mortality from proximal colon cancer. Colorectal cancer diagnosed within 5 years after colonoscopy was more likely than cancer diagnosed after that period or without prior endoscopy to have CIMP and microsatellite instability. (Funded by the National Institutes of Health and others.)

Randomized, controlled trials have shown that screening with flexible sigmoidoscopy reduces the incidence of colorectal cancer and associated mortality, albeit with diminished effectiveness for cancers of the proximal colon.[1–3] Although comparable data from randomized, controlled trials of screening colonoscopy are not yet available,[4] colonoscopy is also widely endorsed by expert bodies for population-based screening, largely on the basis of case–control studies that show associations with reduced colorectal-cancer incidence and mortality.[5–9] However, as with flexible sigmoidoscopy, there is uncertainty about the effectiveness of colonoscopy in reducing the incidence of and mortality associated with proximal colon cancer[10–19] and about the frequency and interval at which testing should be offered.[5–9] Moreover, it remains unclear why a considerable proportion of colorectal cancers are diagnosed in persons who have recently undergone colonoscopy.[5] Such cancers may result from missed lesions or from the rapid progression of new neoplasia,[20–25] which may be associated with specific molecular characteristics.[25]

To address these uncertainties, we conducted a prospective analysis of the association between lower gastrointestinal endoscopy and the long-term risk of incident colorectal cancer in two large U.S. cohorts prospectively followed over a period of 22 years. We also comprehensively examined the molecular features in a subset of tumors.

METHODS

STUDY POPULATION

We used data from two prospective cohort studies: the Nurses' Health Study, which included 121,700 U.S. female nurses, 30 to 55 years of age at enrollment in 1976; and the Health Professionals Follow-up Study, which included 51,529 U.S. male health professionals, 40 to 75 years of age at enrollment in 1986.[26,27] The return of mailed questionnaires was considered to constitute written informed consent.

The study protocol was approved by the institutional review boards of the Harvard School of Public Health and Brigham and Women's Hospital. The authors assume full responsibility for the analyses and interpretation of these data.

ASSESSMENT OF LOWER ENDOSCOPY AND POLYPECTOMY

Details of the endoscopy assessment are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. In both cohorts, beginning in 1988 and continuing through 2008, as part of a questionnaire administered every 2 years, participants

were asked whether they had undergone either sigmoidoscopy or colonoscopy and, if so, the reason for the investigation. In 2004, we additionally collected comprehensive information on whether previously reported lower endoscopies were colonoscopies or sigmoidoscopies.[26,27] Every cycle thereafter, responses for sigmoidoscopy and colonoscopy were recorded separately.

When participants reported a diagnosis of colorectal polyps, consent was obtained to review medical records and pathology reports.[26,27] Study physicians, who were unaware of all the data obtained from the questionnaires, confirmed adenomatous polyps. Persons with polyps that met one or more of the criteria for advanced adenoma (≥10 mm in diameter, tubulovillous or villous histologic features, or high-grade dysplasia) and persons with three or more adenomatous polyps were classified as having high-risk adenoma.[5] Colonoscopic polypectomy was defined as the excision of one or more confirmed adenomatous polyps, excluding hyperplastic polyps. A negative endoscopy was defined as a procedure that did not result in the diagnosis of adenomas or colorectal cancer.

COLORECTAL-CANCER ASCERTAINMENT AND MOLECULAR ANALYSES

Detailed descriptions of cancer ascertainment and molecular analyses are provided in the Supplementary Appendix. A diagnosis of colorectal cancer was confirmed with the use of the National Death Index, medical records, and pathology reports. We extracted DNA from paraffin-embedded tumor specimens and normal tissue specimens. Microsatellite instability status and mutation status for *BRAF* (codon 600), *KRAS* (codons 12 and 13), and *PIK3CA* (exons 9 and 20) were determined as previously described.[28,29] DNA methylation was quantified at eight CpG island methylator phenotype (CIMP)–specific promoters (*CACNA1G*, *CDKN2A* [p16], *CRABP1*, *IGF2*, *MLH1*, *NEUROG1*, *RUNX3*, and *SOCS1*) and in long interspersed nucleotide element 1 (LINE-1), with the use of the MethyLight technique or pyrose-quencing.[28,30]

STATISTICAL ANALYSIS

A detailed description of the statistical analysis is provided in the Supplementary Appendix. We followed participants from the month of return of the 1988 baseline questionnaire through June 2010 for the incidence analysis and through June 2012 for the mortality analysis. We excluded participants with a baseline history of cancer (except for nonmelanoma skin cancer), ulcerative colitis, colorectal polyps, familial polyposis syndromes, or previous lower endoscopy (Fig. S1 in the Supplementary Appendix). We used Cox proportional-hazards models to calculate hazard ratios and 95% confidence intervals. All analyses were stratified according to age (in months), sex (in the combined cohort analysis), and calendar year of the questionnaire cycle. Multivariate models were adjusted for known or suspected risk factors for colorectal cancer, listed in Table 1.

For the incidence analysis, to minimize the influence of endoscopies performed for the diagnostic evaluation of colorectal cancer, we examined the association of endoscopy status reported on the biennial questionnaire before the diagnosis of colorectal cancer, death from any cause, or the end of follow-up, whichever came first. We used the most recently updated information for all variables before each 2-year follow-up and treated all variables as time-varying to account for changes during follow-up. For the mortality analysis, we evaluated the association of screening sigmoidoscopy or screening colonoscopy with mortality on the basis of the endoscopy status reported up to and including the date of diagnosis of colorectal cancer, death from any cause, or the last follow-up cycle, whichever came first.

We calculated the population-attributable risk, estimated as the proportion of incident colorectal cancers that would have been prevented in our population if all participants had

undergone colonoscopy (with negative results or polypectomy) at least once and risk factors had not changed.[31] We also conducted a case–case analysis using a logistic-regression model to examine whether specific molecular features were associated with cancer occurring within 5 years after colonoscopy. All statistical analyses were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

INCIDENT COLORECTAL CANCER

Among 88,902 participants (31,736 men and 57,166 women), we documented a total of 1815 incident cases of colorectal cancer (in 714 men and 1101 women) during 22 years of follow-up, encompassing a total of 1,738,396 person-years. Age-adjusted demographic characteristics at the midpoint of follow-up (1998), according to endoscopy status, are described in Table 1.

In the combined cohorts, the multivariate hazard ratios for colorectal cancer among participants who had undergone endoscopy, as compared with those who had not, were 0.57 (95% confidence interval [CI], 0.45 to 0.72) after removal of adenomatous polyps, 0.60 (95% CI, 0.53 to 0.68) after negative sigmoidoscopy, and 0.44 (95% CI, 0.38 to 0.52) after negative colonoscopy (Table 2). These associations were consistent among men and women and were evident for all disease stages at presentation. A reduced incidence of distal colorectal cancer was observed with polypectomy (multivariate hazard ratio, 0.40; 95% CI, 0.27 to 0.59), negative sigmoidoscopy (multivariate hazard ratio, 0.44; 95% CI, 0.36 to 0.53), and negative colonoscopy (multivariate hazard ratio, 0.24; 95% CI, 0.18 to 0.32). However, only negative colonoscopy was associated with a significantly reduced risk of proximal colon cancer (multivariate hazard ratio, 0.73; 95% CI, 0.57 to 0.92).

In analyses restricted to endoscopy for screening, the results were similar to those obtained in our analyses of endoscopy for any indication (Table S1 in the Supplementary Appendix). In addition, we observed consistent results in the analysis that used propensity-score adjustment and in the subanalyses excluding cases of colorectal cancer diagnosed within 2 years after a previously reported initial endoscopy and excluding those for which the participant or medical record indicated that the diagnosis had been made at the initial screening endoscopy (Table S2 in the Supplementary Appendix). We estimated that the population-attributable risk of colorectal cancer (the proportion of incident cancers that would have been prevented with colonoscopy) was 40% (95% CI, 32 to 46) for all colorectal cancers, 22% (95% CI, 10 to 34) for proximal colon cancers, and 61% (95% CI, 52 to 69) for distal colorectal cancers.

SCREENING COLONOSCOPY INTERVAL

To gain insight into the recommended screening interval for low-risk persons, we evaluated colorectal-cancer incidence according to the time since the last negative colonoscopy (Table 3). The multivariate hazard ratios for colorectal cancer were 0.35 (95% CI, 0.28 to 0.45) for an interval of 3.0 years or less after a negative colonoscopy as compared with no endoscopy, 0.40 (95% CI, 0.31 to 0.52) for 3.1 to 5.0 years, 0.52 (95% CI, 0.38 to 0.70) for 5.1 to 10.0 years, and 0.26 (95% CI, 0.12 to 0.59) for 10.1 to 15.0 years. In addition, reduced risks were observed up to 15.0 years after the last negative colonoscopy for both proximal colon cancer (multivariate hazard ratio for 5.1 to 15.0 years, 0.60; 95% CI, 0.38 to 0.94) and distal colorectal cancer (multivariate hazard ratio for 5.1 to 15.0 years, 0.35; 95% CI, 0.22 to 0.54).

SURVEILLANCE COLONOSCOPY INTERVAL

Among participants who had undergone endoscopy with removal of adenomatous polyps, as compared with those who had not undergone endoscopy, a lower incidence of colorectal cancer was observed with a surveillance interval of 3.0 years or less (multivariate hazard ratio, 0.48; 95% CI, 0.33 to 0.69) and with an interval of 3.1 to 5.0 years (multivariate hazard ratio, 0.49; 95% CI, 0.33 to 0.73) (Table S3 in the Supplementary Appendix). Similar risks across time intervals were observed among participants with a history of adenoma in the proximal colon or distal colorectum. For participants with high-risk adenoma, the association was attenuated and of shorter duration, with a multivariate hazard ratio of 0.70 (95% CI, 0.43 to 1.14) for colonoscopy performed within 3.1 to 5.0 years after the last colonoscopy.

SUBGROUP ANALYSES

The inverse association of colonoscopy with colorectal cancer appeared to be similar across subgroups defined according to age, body-mass index, smoking status, and status with respect to regular use of aspirin (Table S4 in the Supplementary Appendix). Among participants with a family history of colorectal cancer, a significant association was no longer observed beyond 5 years after colonoscopy (multivariate hazard ratio, 0.91; 95% CI, 0.55 to 1.52). By contrast, there was a sustained association beyond 5 years among persons without a family history of colorectal cancer (multivariate hazard ratio, 0.43; 95% CI, 0.32 to 0.58) (P = 0.04 for interaction).

LIFETIME COLONOSCOPY HISTORY AND CANCER INCIDENCE

We considered only negative colonoscopies that occurred at least 4 years apart to account for repeat examinations performed within a shorter interval owing to inadequate bowel preparation. As compared with no endoscopy, the multivariate hazard ratios for colorectal cancer were 0.43 (95% CI, 0.35 to 0.51) after one negative colonoscopy, 0.32 (95% CI, 0.22 to 0.48) after two negative colonoscopies, and 0.23 (95% CI, 0.08 to 0.67) after three negative colonoscopies (Table S5 in the Supplementary Appendix).

MOLECULAR CHARACTERISTICS OF CANCERS

We identified 62 cancers diagnosed within 5 years after colonoscopy for which molecular data were available (Table S6 in the Supplementary Appendix). As compared with cancers diagnosed in patients more than 5 years after colonoscopy or without any prior endoscopy, those diagnosed in patients within 5 years after colonoscopy were more likely to be characterized by CIMP (multivariate odds ratio, 2.19; 95% CI, 1.14 to 4.21), microsatellite instability (multivariate odds ratio, 2.10; 95% CI, 1.10 to 4.02), and an increased LINE-1 methylation level (multivariate odds ratio for each 30% increment, 3.21; 95% CI, 1.29 to 8.00). *BRAF*, *KRAS*, and *PIK3CA* mutations were not significantly associated with cancer diagnosed within 5 years after colonoscopy.

MORTALITY AFTER SCREENING ENDOSCOPY

During follow-up, we identified a total of 474 deaths attributable to colorectal cancer. We observed lower mortality from colorectal cancer among participants who had undergone screening sigmoidoscopy (multivariate hazard ratio, 0.59; 95% CI, 0.45 to 0.76) and among those who had undergone screening colonoscopy (multivariate hazard ratio, 0.32; 95% CI, 0.24 to 0.45) than among those who had never undergone screening endoscopy (Table 4). Screening colonoscopy was associated with reduced mortality from both distal colorectal cancer (multivariate hazard ratio, 0.18; 95% CI, 0.10 to 0.31) and proximal colon cancer (multivariate hazard ratio, 0.47; 95% CI, 0.29 to 0.76), whereas screening sigmoidoscopy

was associated only with reduced mortality from distal colorectal cancer (multivariate hazard ratio, 0.31; 95% CI, 0.20 to 0.49).

DISCUSSION

In two large, U.S. prospective cohort studies, we found that the long-term incidence of colorectal cancer was lower among men and women who had a history of negative sigmoidoscopy, negative colonoscopy, or polypectomy for adenoma than among those who had no history of endoscopy. Negative colonoscopy was associated with a lower incidence of both distal colorectal cancer and proximal colon cancer, whereas negative sigmoidoscopy and colonoscopy with polypectomy were associated primarily with a lower incidence of distal colorectal cancer. We estimated that 40% of colorectal cancers (including 61% of distal colorectal cancers and 22% of proximal colon cancers) that developed during follow-up would have been prevented if all the participants in our study had undergone colonoscopy. Moreover, screening sigmoidoscopy and screening colonoscopy were associated with lower mortality from colorectal cancer, as compared with no endoscopy, although only screening colonoscopy was associated with lower mortality from proximal colon cancer.

Previous randomized, controlled trials have had inconsistent findings regarding the influence of sigmoidoscopy on the incidence of proximal colon cancer,[1–3,32] probably owing to differences in subsequent exposure to colonoscopy. In the U.K. Flexible Sigmoidoscopy Screening Trial, no reduction in the incidence of proximal cancer was detected; however, only 5% of participants underwent follow-up colonoscopy on the basis of sigmoidoscopic findings.[2] By contrast, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial showed a 14% reduction in the incidence of proximal colon cancer, potentially owing to the 21.9% of participants who underwent colonoscopy for follow-up of sigmoidoscopic findings or outside the study protocol.[1] As is consistent with the findings in previous randomized, controlled trials,[2,3] our results suggest that screening sigmoidoscopy alone is probably insufficient for reducing the incidence of proximal colon cancer and associated mortality.

Our results are consistent with the findings of the National Polyp Study, which showed a lower incidence of colorectal cancer among persons after colonoscopic polypectomy, as compared with population-based estimates of expected rates.[16,33] Our study expands on these results, since we were able to directly compare actual incidences of cancer among persons after polypectomy with the incidences among persons from the same background population who did not undergo endoscopy, while adjusting for potential confounders. We did not observe a significantly reduced incidence of proximal colon cancer in association with polypectomy. This result might be due, in part, to limited statistical power. Alternatively, the presence of an adenoma may be a marker of an increased risk of subsequent proximal colon cancer that is not completely mitigated by polypectomy. A recent case–control study also showed a smaller reduction in the incidence of proximal colon cancer, as compared with distal colorectal cancer, after polyp-ectomy.[14]

In our analysis, negative colonoscopy was associated with a significantly reduced incidence of distal colorectal cancer or proximal colon cancer up to 15 years after the procedure. Previous estimates of the duration of protection associated with a negative colonoscopy have varied widely, ranging from 5 to 20 years.[11–13,34] These inconsistent results may be due to relatively short follow-up[12,13,34] or the limitations of a case–control design,[11] including biases related to selection of controls. Our findings support the 10-year examination interval recommended by existing guidelines for persons at average risk who have a negative colonoscopy.[5–9] Our study suggests that even a single negative colonoscopy is associated

with a very low long-term risk of colorectal cancer.[2,3] However, our data support screening at more frequent intervals for persons with a family history of colorectal cancer.

Among participants with a history of adenoma, we observed a reduced incidence of cancer up to 5 years after colonoscopy, which supports current surveillance guidelines.[5,6] However, we found that the apparent reduction in risk was attenuated among participants with high-risk adenomas, a finding that is consistent with the results of other studies.[15] This observation may reflect a persistently elevated incidence of cancer associated with predisposing host or lifestyle risk factors, the biologic characteristics of high-risk adenomas, or the uncertain quality of colonoscopic detection and clearance of neoplasia in persons with high-risk lesions.[20–25]

Our finding that cancer diagnosed within 5 years after colonoscopy was associated with specific molecular features (CIMP, microsatellite instability, and high-level LINE-1 methylation) complements the existing literature.[20–25,35] Serrated lesions, particularly sessile serrated adenomas, are widely considered to be probable precursors of colorectal cancers characterized by CIMP, and these lesions may be particularly difficult to detect endoscopically or remove adequately.[36–38] It remains unclear whether any of the challenges posed by these biologic differences can be addressed by improvements in colonoscopic technique, including more meticulous inspection or improved bowel cleansing.

Our study has several strengths. First, because we collected information biennially for a period of 22 years, we were able to update endoscopy status in order to accurately assess associations with the subsequent risk of colorectal cancer or death. Second, our detailed exposure information, including lifestyle factors, enabled us to finely adjust for potential confounders. Third, our prospective design minimized biases inherent in case–control studies, including recall and selection biases. Fourth, we were able to directly compare the incidence of colorectal cancer and mortality associated with colorectal cancer among persons who underwent endoscopy with the incidence and mortality among persons from the same background population who did not undergo endoscopy. By contrast, previous cohort studies have used comparisons with population-based estimates.[12,16,33] Fifth, since all study participants were health care professionals, the accuracy of our classification according to endoscopy status was high. Finally, our comprehensive molecular profiling of tumors allowed us to elucidate molecular features of cancer occurring within 5 years after colonoscopy, adjusting for other potential confounding factors.

There are limitations to our study. As with all observational studies, we cannot rule out unmeasured confounding, including potential bias introduced by the pooling of data from two separate cohorts. Second, our participants were health care professionals, and our findings may not be generalizable to other populations. However, previous studies have shown that the prevalences of risk factors for colorectal cancer, including smoking and body-mass index, among our participants are consistent with those of the broader population,[39,40] and the incidence and stage distribution of colorectal cancers in our cohorts are similar to those in other population-based registries. Moreover, there is little evidence to suggest that the putative mechanisms by which endoscopy is associated with a reduced incidence of colorectal cancer would differ according to occupation or educational background.

In conclusion, as compared with no endoscopy, colonoscopy and sigmoidoscopy were associated with a lower incidence of distal colorectal cancer, whereas only colonoscopy was associated with a reduced incidence of proximal colon cancer, and that reduction was modest. As compared with no screening endoscopy, screening colonoscopy and sigmoidoscopy were associated with lower mortality from colorectal cancer, whereas only

colonoscopy was associated with lower mortality from proximal colon cancer. Tumor molecular features of the serrated pathway might be involved in the development of cancer within 5 years after colonoscopy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants from the NIH (P01 CA87969; P01 CA55075 and 1UM1 CA167552, to Dr. Willett; P50 CA127003, to Dr. Fuchs; R01 CA151993, to Dr. Ogino; R01 CA137178, to Dr. Chan; and K24 DK098311, to Dr. Chan) and from the Bennett Family Foundation and the Entertainment Industry Foundation through the National Colorectal Cancer Research Alliance. Dr. Chan is a Damon Runyon Clinical Investigator, Dr. Lochhead is a Scottish Government Clinical Academic Fellow and was supported by a Harvard University Frank Knox Memorial Fellowship, Dr. Inamura was supported by a Japan Society for the Promotion of Science Postdoctoral Fellowship for Research Abroad, and Dr. Kim was supported by an Early Exchange Postdoctoral Fellowship Grant from Asan Medical Center, Seoul, Korea.

We thank the participants and staff of the Nurses' Health Study and the Health Professionals Follow-up Study for their valuable contributions; and Scott G. Smith of the Department of Nutrition, Harvard School of Public Health, for assistance with data management.

References

1. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012; 366:2345–57. [PubMed: 22612596]
2. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010; 375:1624–33. [PubMed: 20430429]
3. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial — SCORE. J Natl Cancer Inst. 2011; 103:1310–22. [PubMed: 21852264]
4. Bretthauer M. The capsule and colorectal-cancer screening — the crux of the matter. N Engl J Med. 2009; 361:300–1. [PubMed: 19605836]
5. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastro-enterology. 2012; 143:844–57.
6. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008; 58:130–60. [PubMed: 18322143]
7. McFarland EG, Levin B, Lieberman DA, et al. Revised colorectal screening guidelines: joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. Radiology. 2008; 248:717–20. [PubMed: 18710970]
8. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009. Am J Gastroenterol. 2009; 104:739–50. [Erratum, Am J Gastroenterol 2009;104: 1613.]. [PubMed: 19240699]
9. Screening for colorectal cancer: U S Preventive Services Task Force recommendation statement. Ann Intern Med. 2008; 149:627–37. [PubMed: 18838716]
10. Inadomi JM. Why you should care about screening flexible sigmoidoscopy. N Engl J Med. 2012; 366:2421–2. [PubMed: 22612597]
11. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Long-term risk of colorectal cancer after negative colonoscopy. J Clin Oncol. 2011; 29:3761–7. [PubMed: 21876077]

12. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin Gastroenterol Hepatol. 2008; 6:1117–21. [PubMed: 18691942]

13. Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA. 2006; 295:2366–73. [PubMed: 16720822]

14. Brenner H, Chang-Claude J, Rickert A, Seiler CM, Hoffmeister M. Risk of colorectal cancer after detection and removal of adenomas at colonoscopy: population-based case-control study. J Clin Oncol. 2012; 30:2969–76. [PubMed: 22826281]

15. Cottet V, Jooste V, Fournel I, Bouvier AM, Faivre J, Bonithon-Kopp C. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. Gut. 2012; 61:1180–6. [PubMed: 22110052]

16. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med. 1993; 329:1977–81. [PubMed: 8247072]

17. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst. 2010; 102:89–95. [PubMed: 20042716]

18. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology. 2007; 133:1077–85. [PubMed: 17698067]

19. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol. 2012; 30:2664–9. [PubMed: 22689809]

20. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy — results of the Complete Adenoma Resection (CARE) Study. Gastroenterology. 2013; 144(1):74. e1–80.e1. [PubMed: 23022496]

21. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. Gut. 2012; 61:1576–82. [PubMed: 22200840]

22. Bressler B, Paszat LF, Chen Z, Roth-well DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology. 2007; 132:96–102. [PubMed: 17241863]

23. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010; 362:1795–803. [PubMed: 20463339]

24. Sanduleanu S, Masclee AM, Meijer GA. Interval cancers after colonoscopy — insights and recommendations. Nat Rev Gastroenterol Hepatol. 2012; 9:550–4. [PubMed: 22907162]

25. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol. 2010; 105:1189–95. [PubMed: 20010923]

26. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med. 1995; 122:327–34. [PubMed: 7847643]

27. Wark PA, Wu K, van 't Veer P, Fuchs CF, Giovannucci EL. Family history of colorectal cancer: a determinant of advanced adenoma stage or adenoma multiplicity? Int J Cancer. 2009; 125:413–20. [PubMed: 19358277]

28. Ogino S, Nosho K, Kirkner GJ, et al. CpG island methylator phenotype, micro-satellite instability, BRAF mutation and clinical outcome in colon cancer. Gut. 2009; 58:90–6. [PubMed: 18832519]

29. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor *PIK3CA* mutation, and colorectal-cancer survival. N Engl J Med. 2012; 367:1596–606. [PubMed: 23094721]

30. Ogino S, Nishihara R, Lochhead P, et al. Prospective study of family history and colorectal cancer risk by tumor LINE-1 methylation level. J Natl Cancer Inst. 2013; 105:130–40. [PubMed: 23175808]

31. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. Cancer Causes Control. 2007; 18:571–9. [PubMed: 17387622]

32. Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ. 2009; 338:b1846. [PubMed: 19483252]
33. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012; 366:687–96. [PubMed: 22356322]
34. Imperiale TF, Glowinski EA, Lin-Cooper C, Larkin GN, Rogge JD, Ransohoff DF. Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med. 2008; 359:1218–24. [Erratum, N Engl J Med 2009;361:2004.]. [PubMed: 18799558]
35. Shaukat A, Arain M, Anway R, Manaktala S, Pohlman L, Thyagarajan B. Is KRAS mutation associated with interval colorectal cancers? Dig Dis Sci. 2012; 57:913–7. [PubMed: 22138963]
36. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012; 107:1315–29. [PubMed: 22710576]
37. Burnett-Hartman AN, Newcomb PA, Phipps AI, et al. Colorectal endoscopy, advanced adenomas, and sessile serrated polyps: implications for proximal colon cancer. Am J Gastroenterol. 2012; 107:1213–9. [PubMed: 22688851]
38. Burnett-Hartman AN, Newcomb PA, Potter JD, et al. Genomic aberrations occurring in subsets of serrated colorectal lesions but not conventional adenomas. Cancer Res. 2013; 73:2863–72. [PubMed: 23539450]
39. Sarna L, Bialous SA, Cooley ME, Jun HJ, Feskanich D. Impact of smoking and smoking cessation on health-related quality of life in women in the Nurses' Health Study. Qual Life Res. 2008; 17:1217–27. [PubMed: 18931942]
40. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ. 2008; 337:a1440. [PubMed: 18796495]

N Engl J Med. Author manuscript; available in PMC 2014 March 19.

Table 1

Age-Adjusted Demographic and Clinical Characteristics According to Status with Respect to Lower Endoscopy and Polypectomy in 1998.*

Characteristic	Men				Women			
	No Lower Endoscopy (N = 14,287)	Polypectomy (N = 1259)	Negative Sigmoidoscopy (N = 8091)	Negative Colonoscopy (N = 3578)	No Lower Endoscopy (N = 31,423)	Polypectomy (N = 1481)	Negative Sigmoidoscopy (N = 16,748)	Negative Colonoscopy (N = 3957)
Age (yr)	62.5±8.9	68.3±8.8	64.8±9.1	65.8±9.0	63.4±7.1	66.4±6.7	65.0±6.9	64.3±6.8
Body-mass index†	25.9±3.4	26.2±3.3	25.7±3.3	25.8±3.2	25.4±4.5	25.7±4.5	25.1±4.2	25.2±4.3
History of colorectal cancer in first-degree relative (%)	9	25	13	19	10	33	17	29
Smoking status (%)								
Never smoked	46	40	47	46	45	40	46	44
Former smoker	47	53	48	49	43	50	46	48
Current smoker	7	6	5	5	12	10	7	8
Weekly physical activity level (METs)‡	32.9±28.6	31.0±28.0	33.3±28.4	32.7±26.7	17.5±16.9	16.5±14.7	17.4±16.4	17.3±16.1
Red-meat intake (servings/day)	1.2±0.9	1.1±0.8	1.1±0.8	1.1±0.8	0.9±0.4	0.9±0.4	0.9±0.4	0.9±0.4
Folate intake (μg/day)	532±226	540±222	558±230	562±231	432±164	431±149	456±167	448±164
Calcium intake (mg/day)	918±346	903±331	934±342	936±340	965±327	994±332	1031±342	1019±342
Total caloric intake (kcal/day)	2004±543	1961±546	1954±523	1967±520	1716±415	1715±395	1719±408	1716±411
Alcohol intake (g/day)	10.8±13.6	11.8±14.1	10.3±12.3	10.9±12.8	5.7±8.5	6.1±8.8	5.7±8.3	5.8±8.3
Current multivitamin use (%)	56	57	60	61	58	56	64	65
Regular use of aspirin (%)§	55	57	57	57	41	40	43	44
Nonsteroidal antiinflammatory drug use (%)¶	17	19	19	19	31	33	35	34

Characteristic	Men				Women			
	No Lower Endoscopy (N = 14,287)	Polypectomy (N = 1259)	Negative Sigmoidoscopy (N = 8091)	Negative Colonoscopy (N = 3578)	No Lower Endoscopy (N = 31,423)	Polypectomy (N = 1481)	Negative Sigmoidoscopy (N = 16,748)	Negative Colonoscopy (N = 3957)
Cholesterol-lowering drug use (%)[¶]	12	18	17	17	14	19	17	17
History of postmenopausal hormone use (%)	NA	NA	NA	NA	67	78	80	81

[*] Plus–minus values are means ±SD. Values were standardized to the age distribution of the study population, except for the values for age. Data were for the midpoint of the follow-up period (1998) for the Health Professionals Follow-up Study for men and the Nurses' Health Study for women. Polypectomy was defined as removal of an adenoma. Percentages do not always sum to 100 owing to rounding. NA denotes not applicable.

[†] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] Metabolic equivalents (METs) are defined for each type of physical activity as a multiple of the number of metabolic equivalents for sitting quietly for 1 hour. For example, a participant who walked at a rate of 3.0 miles per hour for 1 hour once per week would have a MET score of 3.3.

[§] Regular aspirin use was defined as current use of two or more aspirin tablets per week for the Nurses' Health Study and use of aspirin at least two times per week for the Health Professionals Follow-up Study.

[¶] Drug use was defined as current, regular use of the agent.

Table 2

Incident Colorectal Cancer after No Lower Endoscopy, Negative Lower Endoscopy, or Polypectomy.*

Variable	No Lower Endoscopy	Polypectomy	Negative Sigmoidoscopy	Negative Colonoscopy
All participants				
No. of person-yr	980,154	72,375	381,093	304,774
No. of cases of colorectal cancer	1164	82	348	221
Age-adjusted incidence rate†	45.7	31.4	19.3	14.1
Age-adjusted hazard ratio (95% CI)	1.00	0.60 (0.47–0.76)	0.59 (0.52–0.66)	0.44 (0.37–0.51)
Multivariate hazard ratio (95% CI)‡	1.00	0.57 (0.45–0.72)	0.60 (0.53–0.68)	0.44 (0.38–0.52)
Disease stage§				
I or II				
No. of cases	484	38	143	89
Age-adjusted hazard ratio (95% CI)	1.00	0.68 (0.48–0.96)	0.57 (0.47–0.69)	0.42 (0.32–0.54)
Multivariate hazard ratio (95% CI)‡	1.00	0.62 (0.44–0.88)	0.57 (0.47–0.70)	0.41 (0.32–0.53)
III				
No. of cases	253	12	72	41
Age-adjusted hazard ratio (95% CI)	1.00	0.43 (0.23–0.81)	0.59 (0.45–0.77)	0.40 (0.28–0.58)
Multivariate hazard ratio (95% CI)‡	1.00	0.43 (0.23–0.80)	0.62 (0.47–0.81)	0.42 (0.29–0.62)
IV				
No. of cases	159	7	55	26
Age-adjusted hazard ratio (95% CI)	1.00	0.34 (0.15–0.74)	0.66 (0.48–0.91)	0.35 (0.22–0.55)
Multivariate hazard ratio (95% CI)‡	1.00	0.34 (0.15–0.75)	0.70 (0.51–0.97)	0.36 (0.23–0.58)
Tumor location¶				
Proximal colon				
No. of cases	379	40	179	119
Age-adjusted hazard ratio (95% CI)	1.00	0.88 (0.63–1.25)	0.90 (0.75–1.08)	0.72 (0.57–0.92)
Multivariate hazard ratio (95% CI)‡	1.00	0.83 (0.59–1.18)	0.92 (0.77–1.11)	0.73 (0.57–0.92)
Distal colorectum				
No. of cases	650	28	136	61
Age-adjusted hazard ratio (95% CI)	1.00	0.41 (0.28–0.61)	0.43 (0.35–0.52)	0.24 (0.18–0.31)
Multivariate hazard ratio (95% CI)‡	1.00	0.40 (0.27–0.59)	0.44 (0.36–0.53)	0.24 (0.18–0.32)
Men				
No. of person-yr	318,287	31,455	120,016	114,284
No. of cases of colorectal cancer	471	38	109	96
Age-adjusted hazard ratio (95% CI)	1.00	0.55 (0.39–0.78)	0.47 (0.37–0.58)	0.46 (0.36–0.58)
Multivariate hazard ratio (95% CI)‡	1.00	0.52 (0.37–0.74)	0.47 (0.38–0.59)	0.46 (0.36–0.58)
Women				
No. of person-yr	661,868	40,921	261,077	190,490

Variable	No Lower Endoscopy	Polypectomy	Negative Sigmoidoscopy	Negative Colonoscopy
No. of cases of colorectal cancer	693	44	239	125
Age-adjusted hazard ratio (95% CI)	1.00	0.63 (0.46–0.86)	0.66 (0.57–0.77)	0.42 (0.34–0.52)
Multivariate hazard ratio (95% CI)[‡]	1.00	0.61 (0.44–0.83)	0.69 (0.59–0.81)	0.43 (0.35–0.54)

[*] Endoscopy status was assigned on the basis of the biennial questionnaire that was returned before a diagnosis of colorectal cancer, death from any cause, or the end of follow-up, whichever came first. Negative sigmoidoscopy and negative colonoscopy were defined as lower endoscopy without detection of an adenoma.

[†] Age-adjusted incidence rates (per 100,000 person-years) were standardized to the age distribution of the population.

[‡] Models were further adjusted for body-mass index (<25.0 vs. 25.0–29.9 vs. ≥30.0), smoking status (never smoked vs. former smoker vs. current smoker), status with respect to a history of colorectal cancer in a first-degree relative, status with respect to regular use of aspirin, physical activity level (quintiles of mean METs per week), red-meat intake (quintiles of servings per day), total caloric intake (quintiles of kilocalories per day), alcohol intake (0 or quartiles of grams per day), folate intake (quintiles of micrograms per day), calcium intake (quintiles of milligrams per day), and status with respect to current multivitamin use, nonsteroidal antiinflammatory drug use, cholesterol-lowering drug use, and postmenopausal hormone use (for women only).

[§] Data on disease stage were available for 1379 of 1815 participants (76%): 896 participants who had not undergone lower endoscopy, 57 who had undergone polypectomy, 270 who had negative findings on sigmoidoscopy, and 156 who had negative findings on colonoscopy.

[¶] Data on tumor location were available for 1592 of 1815 participants (88%): 1029 participants who had not undergone lower endoscopy, 68 who had undergone polypectomy, 315 who had negative findings on sigmoidoscopy, and 180 who had negative findings on colonoscopy.

Table 3

Incident Colorectal Cancer, According to Time since Last Negative Colonoscopy.*

Variable	No Lower Endoscopy	Years since Last Negative Colonoscopy				
		≥15.1	15.0–10.1	10.0–5.1	5.0–3.1	≤3.0
No. of person-yr	980,154	1668	10,929	54,601	99,783	131,333
No. of cases of colorectal cancer	1164	3	8	51	70	77
Age-adjusted hazard ratio (95% CI)	1.00	0.69 (0.20–2.32)	0.26 (0.11–0.58)	0.50 (0.37–0.68)	0.40 (0.31–0.52)	0.35 (0.27–0.45)
Multivariate hazard ratio (95% CI)†	1.00	0.65 (0.19–2.23)	0.26 (0.12–0.59)	0.52 (0.38–0.70)	0.40 (0.31–0.52)	0.35 (0.28–0.45)

*The last negative colonoscopy was defined as the last colonoscopy without detection of an adenoma. Colonoscopy status was assigned on the basis of the biennial questionnaire that was returned before a diagnosis of colorectal cancer, death from any cause, or the end of follow-up, whichever came first.

†Models were further adjusted for body-mass index (<25.0 vs. 25.0–29.9 vs. ≥30.0), smoking status (never smoked vs. former smoker vs. current smoker), status with respect to a history of colorectal cancer in a first-degree relative, status with respect to regular use of aspirin, physical activity level (quintiles of mean METs per week), red-meat intake (quintiles of servings per day), total caloric intake (quintiles of kilo-calories per day), alcohol intake (0 or quartiles of grams per day), folate intake (quintiles of micrograms per day), calcium intake (quintiles of milligrams per day), and status with respect to current multivitamin use, nonsteroidal antiinflammatory drug use, and cholesterol-lowering drug use.

Table 4

Colorectal-Cancer Mortality after Screening Lower Endoscopy.

Variable	No Screening Lower Endoscopy	Screening Sigmoidoscopy	Screening Colonoscopy*
All participants			
All deaths from colorectal cancer			
No. of person-yr	1,182,248	302,330	357,008
No. of deaths	349	73	52
Age-adjusted hazard ratio (95% CI)	1.00	0.57 (0.44–0.73)	0.32 (0.24–0.44)
Multivariate hazard ratio (95% CI)†	1.00	0.59 (0.45–0.76)	0.32 (0.24–0.45)
Deaths from proximal colon cancer‡			
No. of deaths	121	46	25
Age-adjusted hazard ratio (95% CI)	1.00	1.04 (0.73–1.47)	0.49 (0.31–0.79)
Multivariate hazard ratio (95% CI)†	1.00	1.04 (0.73–1.48)	0.47 (0.29–0.76)
Deaths from distal colorectal cancer‡			
No. of deaths	195	21	16
Age-adjusted hazard ratio (95% CI)	1.00	0.29 (0.19–0.46)	0.18 (0.10–0.30)
Multivariate hazard ratio (95% CI)†	1.00	0.31 (0.20–0.49)	0.18 (0.10–0.31)
Men			
No. of person-yr	366,773	101,259	141,554
No. of deaths from colorectal cancer	131	30	26
Age-adjusted hazard ratio (95% CI)	1.00	0.57 (0.38–0.86)	0.34 (0.22–0.53)
Multivariate hazard ratio (95% CI)†	1.00	0.59 (0.39–0.90)	0.36 (0.23–0.56)
Women			
No. of person-yr	815,475	201,072	215,453
No. of deaths from colorectal cancer	218	43	26
Age-adjusted hazard ratio (95% CI)	1.00	0.56 (0.41–0.79)	0.31 (0.20–0.48)
Multivariate hazard ratio (95% CI)†	1.00	0.61 (0.43–0.85)	0.31 (0.20–0.48)

*Colonoscopy included removal of an adenoma.

†Models were further adjusted for body-mass index (<25.0 vs. 25.0–29.9 vs. ≥30.0), smoking status (never smoked vs. former smoker vs. current smoker), status with respect to a history of colorectal cancer in a first-degree relative, status with respect to regular use of aspirin, physical activity level (quintiles of mean METs per week), red-meat intake (quintiles of servings per day), total caloric intake (quintiles of kilocalories per day), alcohol intake (0 or quartiles of grams per day), folate intake (quintiles of micrograms per day), calcium intake (quintiles of milligrams per day), and status with respect to current multivitamin use, nonsteroidal antiinflammatory drug use, and cholesterol-lowering drug use.

‡Data on tumor location were available for 316 participants who had not undergone screening lower endoscopy, 67 who had undergone screening sigmoidoscopy, and 41 who had undergone screening colonoscopy.