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Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths

Ann G. Zauber, Ph.D., Sidney J. Winawer, M.D., Michael J. O'Brien, M.D., M.P.H., Iris Lansdorp-Vogelaar, Ph.D., Marjolein van Ballegooijen, M.D., Ph.D., Benjamin F. Hankey, Sc.D., Weiji Shi, M.S., John H. Bond, M.D., Melvin Schapiro, M.D., Joel F. Panish, M.D., Edward T. Stewart, M.D., and Jerome D. Waye, M.D.

ABSTRACT

BACKGROUND

In the National Polyp Study (NPS), colorectal cancer was prevented by colonoscopic removal of adenomatous polyps. We evaluated the long-term effect of colonoscopic polypectomy in a study on mortality from colorectal cancer.

METHODS

We included in this analysis all patients prospectively referred for initial colonoscopy (between 1980 and 1990) at NPS clinical centers who had polyps (adenomas and nonadenomas). The National Death Index was used to identify deaths and to determine the cause of death; follow-up time was as long as 23 years. Mortality from colorectal cancer among patients with adenomas removed was compared with the expected incidence-based mortality from colorectal cancer in the general population, as estimated from the Surveillance Epidemiology and End Results (SEER) Program, and with the observed mortality from colorectal cancer among patients with nonadenomatous polyps (internal control group).

RESULTS

Among 2602 patients who had adenomas removed during participation in the study, after a median of 15.8 years, 1246 patients had died from any cause and 12 had died from colorectal cancer. Given an estimated 25.4 expected deaths from colorectal cancer in the general population, the standardized incidence-based mortality ratio was 0.47 (95% confidence interval [CI], 0.26 to 0.80) with colonoscopic polypectomy, suggesting a 53% reduction in mortality. Mortality from colorectal cancer was similar among patients with adenomas and those with nonadenomatous polyps during the first 10 years after polypectomy (relative risk, 1.2; 95% CI, 0.1 to 10.6).

CONCLUSIONS

These findings support the hypothesis that colonoscopic removal of adenomatous polyps prevents death from colorectal cancer. (Funded by the National Cancer Institute and others.)

From the Departments of Epidemiology and Biostatistics (A.G.Z., W.S.) and Medicine (S.J.W.), Memorial Sloan-Kettering Cancer Center; and the Department of Medicine, Mt. Sinai Medical Center (J.D.W.) — both in New York; the Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston (M.J.O.); the Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands (I.L.-V., M.B.); CANSTAT, Plano, TX (B.F.H.); the Department of Medicine, Minneapolis Veterans Affairs Medical Center, Minneapolis (J.H.B.); the Department of Medicine, Valley Presbyterian Hospital, Van Nuys, CA (M.S.); the Department of Medicine, Cedars–Sinai Medical Center, Los Angeles (J.F.P.); and the Department of Radiology, Medical College of Wisconsin, Milwaukee (E.T.S.). Address reprint requests to Dr. Zauber at the Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 E. 63rd St., New York, NY 10065, or at zaubera@mskcc.org.

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It has been a long-standing belief that screening for colorectal cancer can affect mortality from the disease in two ways: by detecting cancers at an early, curable stage and by detecting and removing adenomas.[1] Detection of early-stage colorectal cancer has been shown to be associated with a reduction in mortality from colorectal cancer in screening trials.[2-4] However, an adenomatous polyp is a much more common neoplastic finding on endoscopic screening. We previously reported that colonoscopic polypectomy in the National Polyp Study (NPS) cohort reduced the incidence of colorectal cancer.[5] An important question is whether the cancers prevented by colonoscopic polypectomy in the cohort were those that had the potential to cause death. To estimate the effect of colonoscopic detection and removal of adenomatous polyps on mortality from colorectal cancer, we examined mortality in the study cohort during a surveillance period of up to 23 years after colonoscopic polypectomy.

METHODS

STUDY DESIGN

We conducted a long-term follow-up study of the NPS cohort using the National Death Index (NDI) to determine the death rate among patients with adenomatous polyps that had been removed, as compared with mortality from colorectal cancer in the general population and in an internal concurrent control group of patients with nonadenomatous polyps.[6]

The NPS was a multicenter postpolypectomy surveillance study of patients with one or more newly diagnosed adenomas; it involved seven clinical centers that represent a wide range of endoscopic practices (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients in the randomized, controlled trial were assigned either to surveillance colonoscopy at 1 and 3 years after polypectomy or to first surveillance colonoscopy at 3 years; both groups were offered surveillance colonoscopy at 6 years. Previous reports have detailed the study design and methods.[5,7-9]

PATIENTS

All patients referred for initial colonoscopy at the seven clinical centers between November 1980 and February 1990 who did not have a family or personal history of familial polyposis or inflammatory bowel disease or a personal history of prior polypectomy or colorectal cancer were prospectively evaluated for enrollment in the randomized, controlled trial of surveillance intervals and underwent a protocol-specified colonoscopy.[8,9] Patients had been referred for colonoscopy because of positive findings on barium enema examination (27%), sigmoidoscopy (15%), fecal occult-blood test (11%), or other tests (10%) or because of symptoms (32%) or a family history (5%) of colorectal cancer.[8] All identified polyps were removed and centrally reviewed according to NPS pathological criteria.[7] Patients were classified at the initial colonoscopy as having adenomatous polyps or only nonadenomatous polyps (i.e., mucosal tags or hyperplastic polyps) by pathological classification at the clinical center (Fig. 1). Patients with newly diagnosed adenomas were eligible for the randomized, controlled study if they underwent a complete colonoscopy to the cecum with removal of one or more adenomas and if all polyps detected were removed. Patients were ineligible if they had no polyps or had gross colorectal cancer, inflammatory bowel disease, malignant polyps (i.e., a polyp removed at colonoscopy that appeared to be benign on endoscopy but that was identified as invasive adenocarcinoma on pathological assessment[10]), or sessile polyps greater than 3 cm in diameter, or if the colonoscopy was incomplete. The current analysis of mortality from colorectal cancer included all patients with adenomas who were eligible for the randomized trial and all patients with only nonadenomatous polyps (Table 1 and Fig. 1).

COMPARISON GROUPS

General Population

To compare the observed mortality in the adenoma cohort with appropriately matched rates in the general population, we used incidence-based mortality to adjust the general-population rates for our exclusions. Incidence-based mortality, which is derived by following back deaths in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based registry program to their diagnosis (http://surveillance.cancer.gov/statistics/ibm), allows mortality to be partitioned by date of diagnosis.[12] We excluded deaths from colorectal cancer in the SEER database that occurred in cases that were diagnosed before the calendar year of enrollment in the NPS and those that were diagnosed within 3 years after enrollment. This 3-year time lag corresponds to the average

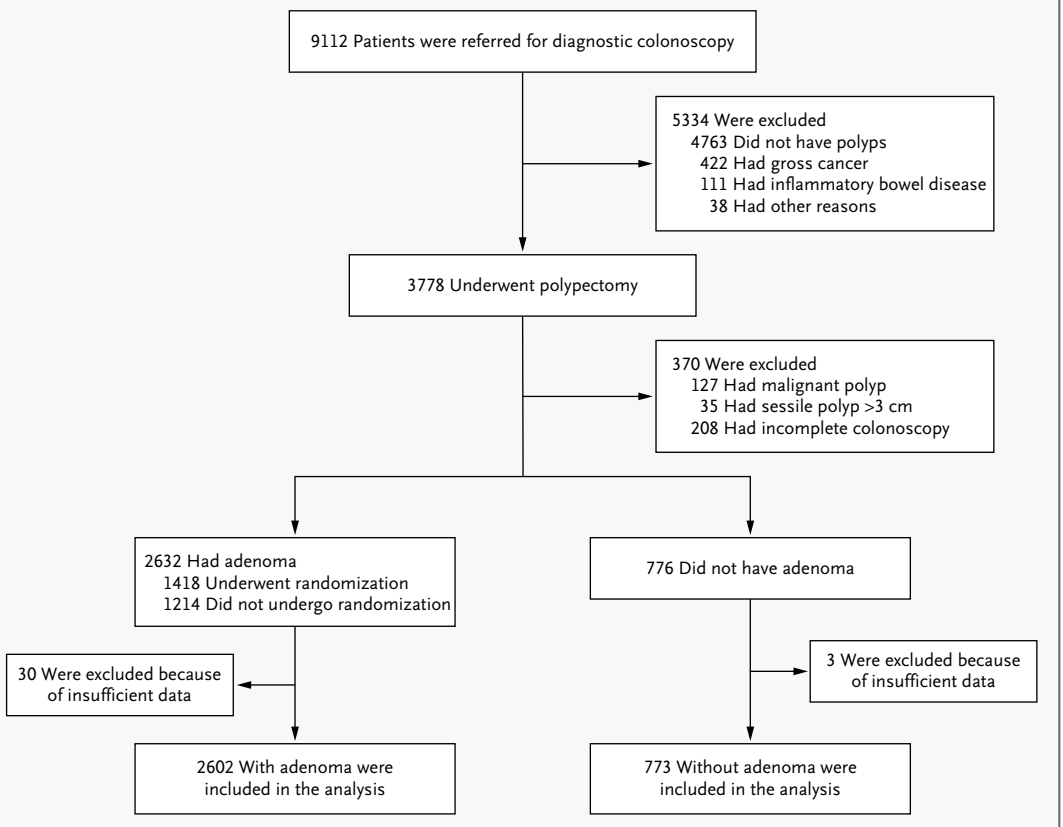

Figure 1. Study Enrollment.

Of the 9112 patients referred for this study, 2602 with adenomatous polyps and 773 with only nonadenomatous polyps were included in the analysis. Diagnosis was made according to pathological classification at the clinical center. Only patients who provided sufficient demographic information (at least first and last names and either Social Security number or the month and year of birth) were matched against data from the National Death Index. These identifiers were not retained for patients with no polyps or with gross cancer; consequently, none of these patients were included in the analysis of mortality. In addition, 30 patients with adenomas and 3 with nonadenomas did not have sufficient demographic information and were not included in the analysis.

cancer sojourn time, as estimated from screening studies that use fecal occult-blood tests. The period during which a cancer can be detected by a screening test (e.g., the fecal occult-blood test) before entering a clinical phase is defined as the cancer sojourn time.[13] During the study-enrollment period (from 1980 through 1990), there was a small percentage of people who underwent screening for colorectal cancer, with screening performed predominantly by means of a guaiac fecal occult-blood test.[14,15] On the basis of the available literature, we estimated an average sojourn time for colorectal cancer of 3 years (range, 2 to 5).[13,16-18]

We used SEER*Stat with the SEER registries of nine areas (SEER9),[19] which included data from 1975 forward, for the analysis of incidence-based mortality from colorectal cancer. We used the National Center for Health Statistics database for the analysis of all causes of death in the general population.[20]

Nonadenoma Cohort as Internal Concurrent Control

Patients referred for initial colonoscopy at the participating centers from 1980 through 1990 who had only nonadenomatous polyps (including mucosal tags) were used as an internal concurrent control group for the adenoma cohort.[6,8] All hyperplastic polyps were reviewed in 2007 and were reclassified on the basis of criteria for the serrated polyp pathway.[21]

END POINTS

To ascertain mortality from colorectal cancer, we matched the NPS patient cohorts against records in the NDI, the registry of all deaths in the United States, from 1980 through 2003.[22] NPS records were matched against the NDI data on the basis of name, Social Security number, date of birth, sex, marital status, state of birth, and state of residence. Only records that included sufficient information — at least first and last names and either Social Security number or the month and year of birth — were matched against the NDI data (Fig. 1). The identifiers of date of birth and Social Security number were not collected for patients with no polyps or with gross cancer; consequently, data for these patients could not be matched against the NDI data and are not included in this study. In addition, a small number of patients in the adenoma and nonadenoma cohorts had insufficient information to allow a match with the NDI registry and were excluded from the analysis.

STUDY OVERSIGHT

The human subjects committee of the Memorial Sloan-Kettering Cancer Center approved the NPS. Patients provided authorization to release all medical and pathological reports to the study, as well as written informed consent to participate in the trial. In addition, the committee granted a waiver of authorization to conduct the search of the NDI.

Table 1. Baseline Characteristics of the Adenoma and Nonadenoma Cohorts.*

Characteristic	Adenoma (N=2602)	Nonadenoma (N=773)	P Value†
Age — yr‡	62.0±11.1	57.3±12.7	<0.001
Mean			
Age group — no. (%)			
<50 yr	327 (12.6)	193 (25.0)	<0.001
50–59 yr	682 (26.2)	223 (28.8)	
60–69 yr	926 (35.6)	233 (30.1)	
≥70 yr	657 (25.3)	124 (16.0)	
Sex — no. (%)§			
Male	1722 (66.2)	466 (60.3)	0.002
Female	878 (33.7)	307 (39.7)	
Race — no. (%)¶			
White	2143 (82.4)	640 (82.8)	0.39
Black	178 (6.8)	61 (7.9)	
Other	25 (1.0)	9 (1.2)	
Unknown	256 (9.8)	63 (8.2)	
No. of first-degree relatives with colorectal cancer — no. (%)			
0	2169 (83.4)	669 (86.5)	0.08
1	376 (14.5)	87 (11.3)	
≥2	57 (2.2)	17 (2.2)	
No. of colonoscopies to clear all detected polyps — no. (%)			
1	2320 (89.2)	757 (97.9)	<0.001
2	266 (10.2)	16 (2.1)	
≥3	16 (0.6)	0	
Participation in randomized follow-up surveillance study of patients with adenomas — no. (%)		NA	
Yes	1418 (54.5)		
No	1184 (45.5)		

Table 1. (Continued.)

Characteristic	Adenoma (N=2602)	Nonadenoma (N=773)	P Value†
Most advanced adenoma — no./total no. (%)‖		NA	
Nonadvanced	1075/2517 (42.7)		
Advanced**	1442/2517 (57.3)		
No. of adenomas — no./total no. (%)‖		NA	
1	1475/2517 (58.6)		
2	555/2517 (22.1)		
≥3	487/2517 (19.3)		
Location of adenomas — no./total no. (%)‖††		NA	
Distal only	1621/2517 (64.4)		
Any proximal	896/2517 (35.6)		
Proximal only	377/2517 (15.0)		
Distal and proximal	519/2517 (20.6)		

* Plus–minus values are means ±SD. NA denotes not applicable.
† Chi-square tests were used for the comparison of categorical variables between groups; Student's t-test was used for the comparison of mean age.
‡ Data on age were missing for 10 patients in the adenoma cohort.
§ Data on sex were missing for 2 patients in the adenoma cohort.
¶ Race was self-reported. The proportion of blacks in the NPS patient population was consistent with the U.S. Census estimate of blacks at similar ages (9%).[11]
‖ Of the 2602 patients with adenomas, 85 (3.3%) had polyps that were originally classified as adenomatous at the clinical centers but were reclassified as nonadenomatous by NPS pathological review, so the total number of patients with adenomas in this calculation is 2517.
** Advanced adenoma was defined by a diameter of 1.0 cm or more, tubulovillous or villous histologic appearance, or high-grade dysplasia. Of the 1442 patients with advanced adenomas, 895 (62%) had only tubular adenomas that were 1.0 cm or larger.
†† Location of the adenomas was defined as proximal for lesions in the cecum, ascending colon, hepatic flexure, and transverse colon and as distal for lesions in the splenic flexure, descending colon, sigmoid colon, or rectum.

STATISTICAL ANALYSIS

Person-years at risk were calculated for each patient from the date of the initial colonoscopy until death or the last date of follow-up (December 31, 2003), according to NDI records and categorized by age (within 5-year groups), sex, race, calendar year, and calendar year of enrollment in the study. These data on person-years at risk were used in conjunction with the incidence-based mortality from colorectal cancer in the general population, according to SEER9 data, to determine the number of deaths from colorectal cancer that would be expected in the adenoma cohort if the cohort had the same rate of death as that among members of the general population with similar age, sex, race, and calendar-year characteristics and with adjustment for the same exclusions.[23]

The observed number of deaths was assumed to follow a Poisson distribution. The standardized incidence-based mortality ratio was derived as the ratio of observed to expected deaths from colorectal cancer, and the exact 95% confidence interval was calculated. A two-sided P value of 0.05 or less was considered to indicate statistical significance. The percent reduction was calculated as the complement of the standardized mortality ratio multiplied by 100. The results are presented for the entire follow-up time, for the first 10 years (0 to 9.9 years), and for 10 or more years of follow-up. The standardized mortality ratio for all causes of death was also calculated.

Fisher's exact test was used to compare the observed mortality in the adenoma and nonadenoma cohorts in the first 10 years of follow-up. The net cumulative mortality curves specific for colorectal cancer were derived as the complement of the Kaplan–Meier cumulative survival curve. SAS software, version 9.2 (SAS Institute), was used for analyses.

The accuracy of the NDI match to the NPS co-

Table 2. Characteristics of the 12 Patients with Adenomas Who Died of Colorectal Cancer, According to Interval from Baseline Colonoscopy to Death.*

Patient No.	Sex	Race†	At Baseline Colonoscopy							At Time of Death	
			Age	Year Enrolled	Adenomas	Most Advanced Histologic Type	Largest Adenoma	Location of Adenoma	First-Degree Relatives with Colorectal Cancer	Age	Interval from Baseline Colonoscopy to Death
			yr		*no.*		*cm*		*no.*		*yr*
1	M	Black	50	1989	2	Tubular	0.6	Splenic flexure, ascending	0	56	6
2	M	Other	49	1982	1	Tubular‡	1.0	Sigmoid	0	56	7
3	M	White	50	1981	1	Tubulovillous	1.5	Sigmoid	0	59	9
4	F	Other	56	1988	1	Tubular	0.2	Sigmoid	0	65	9
5	F	White	66	1982	1	Tubular	0.6	Descending	2	76	10
6	F	White	34	1982	1	Villous	1.0	Rectum	0	44	10
7	F	White	75	1989	2	Tubular	1.0	Sigmoid, ascending	0	86	11
8	M	White	58	1987	6	Tubular	2.0	Splenic flexure (1), ascending (5)	1	70	12
9	F	Other	62	1982	1	Villous	1.2	Sigmoid	0	75	13
10	M	White	50	1982	2	Tubular	2.0	Sigmoid	0	67	17
11	F	White	52	1981	1	Tubular	0.5	Sigmoid	0	72	20
12	M	White	63	1981	1	Tubular	0.8	Hepatic flexure	0	85	22

* For patients with deaths matched to the National Death Index (NDI) who died during the period from 1980 through 1998, the deaths from colorectal cancer were those with cause of death coded by NDI-Plus as 1530–1539, 1540, 1541, or 1590, based on codes from the *International Classification of Diseases, 8th Revision* and *9th Revision* (ICD-8 and ICD-9); if they died during the period from 1999 through 2003, the cause of death was coded as C18.0-C18.9, C19.0-C19.9, C20.0-C20.9, or C26.0, based on codes from the *International Classification of Diseases, 10th Revision* (ICD-10). Five cases of colorectal cancer were diagnosed in the patients with adenomas during active surveillance[5]; none of these patients died of colorectal cancer.

† Race was self-reported.

‡ The diagnosis was made on the basis of pathological classification at a clinical center. Diagnoses for the other 11 patients were made on the basis of NPS pathological review.

hort was determined by evaluating the sensitivity and specificity of the match in the group of 1418 patients with adenomatous polyps who were enrolled and followed directly in the randomized trial of surveillance intervals.[9] Deaths were closely monitored among these patients from 1980 through 1990. Analysis of these deaths served as an assessment of the completeness of the overall cohort match to the NDI for all deaths.[24]

RESULTS

MORTALITY IN THE ADENOMA COHORT

The characteristics of the 2602 patients with adenomatous polyps are shown in Table 1. In the randomized adenoma cohort, 81% of patients underwent one or more surveillance colonoscopies.[9] There were 37,073 person-years at risk in the adenoma cohort. The median follow-up period was 15.8 years, with a maximum of 23 years. On the basis of the NDI match, there were 1246 deaths among the 2602 patients (48%). All-cause mortality was lower in the adenoma cohort than in the general population, matched by age, sex, race, and calendar year on the basis of SEER data (standardized mortality ratio, 0.85; 95% confidence interval [CI], 0.81 to 0.90). The NDI match for the 1418 patients in the randomized, controlled trial had 97.5% sensitivity, 99.7% specificity, and 99.4% overall accuracy in classifying deaths.

There were 12 deaths from colorectal cancer in the adenoma cohort (Table 2), as compared with 25.4 expected deaths from the disease in the general population (standardized incidence-based mortality ratio, 0.47; 95% CI, 0.26 to 0.80) (Table 3), corresponding to an estimated 53% reduction

Table 3. Deaths from Colorectal Cancer in the Adenoma Cohort, as Compared with Incidence-Based Mortality from Colorectal Cancer in the General Population.*

	Adenoma Cohort			General Population			
Follow-up Time	No.	Person-Years at Risk	Observed Deaths	Expected Deaths	SMR (95% CI)	Reduction	P Value
			no.	*no.*		%	
All	2602	37,073	12	25.4	0.47 (0.26–0.80)	53	0.008
<10 yr	2602	22,903	4	9.1	0.44 (0.14–1.06)	56	0.09
≥10 yr	2031	14,170	8	16.3	0.49 (0.23–0.93)	51	0.04

* Data on the general population are from the Surveillance, Epidemiology, and End Results registries of nine areas (SEER9). The standardized mortality ratio (SMR) and percent reduction in mortality are for the adenoma cohort as compared with the general population.

in mortality from colorectal cancer. The reduction in mortality for the first 10 years of follow-up (0 to 9.9 years) was similar to that for 10 or more years of follow-up (Table 3). The cumulative mortality rate in the adenoma cohort at 20 years was 0.8%, as compared with an estimated 1.5% in the general population (on the basis of SEER9 data) (Fig. 2).

Sensitivity analyses of 2-year and 5-year cancer sojourn times showed a reduction in mortality from colorectal cancer of 56% (P=0.003) and 44% (P=0.04), respectively, for the entire 23 years of follow-up. The 51% reduction in mortality for the follow-up period of 10 or more years was not affected by varying the sojourn time.

MORTALITY IN THE NONADENOMA COHORT

Of the 773 patients in the NPS with nonadenomatous polyps, 278 (36%) had hyperplastic polyps; there were no serrated polyps with adenomatous change or dysplasia in this cohort. These patients were followed for a total of 12,090 person-years, with a median follow-up period of 16.5 years. Patients with nonadenomatous polyps were similar to those with adenomatous polyps with respect to race and number of first-degree relatives with colorectal cancer. However, they were younger than the adenoma cohort (57 years vs. 62 years, P<0.001) and more likely to be women (40% vs. 34%, P=0.002) and accordingly at lower risk for colorectal cancer (Table 1). There was one death from colorectal cancer at 7.7 years. In the first 10 years after the initial colonoscopy, the observed mortality for colorectal cancer in the adenoma cohort was similar to that in the nonadenoma cohort (0.19% and 0.15%, respectively; relative risk for the adenoma cohort, 1.2; 95% CI, 0.1 to 10.6; P=1.0) (Table 4).

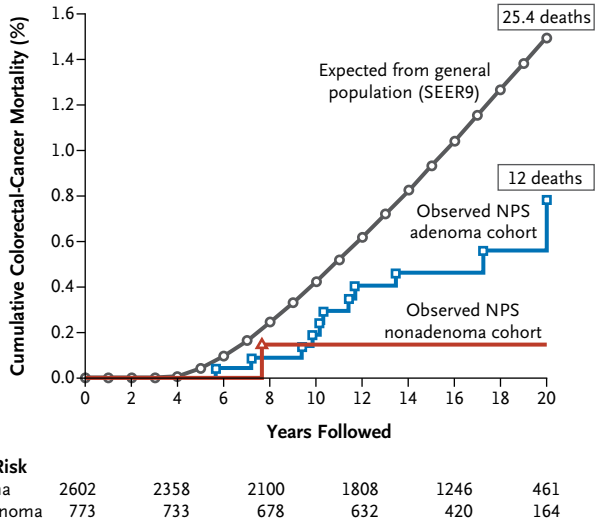

Figure 2. Cumulative Mortality from Colorectal Cancer in the General Population, as Compared with the Adenoma and Nonadenoma Cohorts.

We censored the curves at 20 years; the 12th death in the adenoma cohort was at 22 years and was included in the analysis. The numbers of deaths from colorectal cancer are given at the end of the curves for the general population (25.4 expected deaths) and the adenoma cohort (12 observed deaths). Expected deaths are based on data from Surveillance, Epidemiology, and End Results registries in nine areas (SEER9).

DISCUSSION

We previously found that polypectomy reduced the incidence of colorectal cancer in the NPS cohort.[5] The present study suggests that adenoma removal significantly reduced the risk of death from colorectal cancer, as compared with that in the general population, and in the first 10 years after polypectomy, reduced the risk to a level similar to that in

Table 4. Comparison of Adenoma and Nonadenoma Cohorts in the First 10 Years after Initial Colonoscopy.*

Cohort	No. of Patients	Person-Years at Risk	Observed Deaths	Relative Risk (95% CI)	P Value†
Adenoma	2602	22,903	4	1.2 (0.1–10.6)	1.00
Nonadenoma	773	7,178	1	1.0	

* The mean follow-up time within the first 10 years was 9 years for both the adenoma and nonadenoma cohorts.
† Fisher's exact test was used to compare the observed mortality in the two cohorts.

an internal concurrent control group of patients with no adenomas.

Our comparison of observed deaths in the adenoma cohort with expected deaths in the general population, based on SEER data that were specific for age, sex, race, and calendar year, may have underestimated the reduction in mortality that may be achieved with colonoscopic polypectomy in screening populations. Because all the patients in the adenoma cohort had adenomas, including 57.3% with advanced adenomas, they represented a higher-risk group than the general population.[25-27]

The comparison of mortality in the adenoma cohort with that in a concurrent control group of patients in the NPS who did not have adenomatous polyps supported the results of the comparison with estimated mortality in the general population.[6] The patients without adenomas were similar to those with adenomas, except for the findings at initial colonoscopy. The group without a precursor adenoma would be expected to have low mortality from colorectal cancer, and several studies have also shown that patients with no polyps or with nonadenomatous polyps have low rates of colorectal neoplasia after colonoscopy.[28-31]

A cohort of patients with adenomas in whom polypectomy was not performed would, of course, be a more meaningful comparison group for the patients in the NPS with adenomas, all of whom underwent polypectomy, but such a comparison group would not be an option on either ethical or clinical grounds because of the known potential for adenomas to progress to carcinoma. We addressed this comparison using a microsimulation model of the mortality effect had the adenomas not been removed and the natural history of the adenoma–carcinoma sequence had proceeded without intervention. This model, the MISCAN-Colon model of the Cancer Intervention and Surveillance Modeling Network (CISNET) (http://cisnet.cancer.gov/colorectal), showed an even larger reduction in mortality from polypectomy than the comparison with the SEER incidence-based mortality rates (see the Supplementary Appendix).

Although the NPS does not address the effectiveness of screening colonoscopy in the general population, our findings provide an indirect estimate of the effect of removing adenomas, which is the primary interventional measure in screening colonoscopy. Studies and commentaries have raised issues regarding the magnitude of the effect of colonoscopy on the incidence of and mortality from colorectal cancer.[32-38] A recent study from Germany showed a large effect of colonoscopy on the incidence of colorectal cancer.[39] In two Canadian studies,[32,34] the mortality reduction from colonoscopy in community practice was largest when the colonoscopy was performed by a gastroenterologist[34] and when the examination was complete.[32] The magnitude of the reduction in mortality among the patients in the NPS after polypectomy is probably due to high-quality colonoscopy performed by well-trained gastroenterologists.[40-45] These issues will be more precisely understood after completion of long-term randomized, controlled trials of screening colonoscopy in the general population that have recently been initiated in northern Europe (Nordic-European Initiative on Colorectal Cancer; ClinicalTrials.gov number, NCT00883792),[46] in Spain (ClinicalTrials.gov number, NCT00906997), and by the Veterans Administration in the United States (ClinicalTrials.gov number, NCT01239082); the incidence and mortality end points will not be available for at least 10 or more years.

This prospective study has some limitations. First, a small number of trained endoscopists performed the colonoscopies according to a study protocol that required examination to the cecum, adequate preparation, careful inspection of the colon, and removal of all identified polyps, features that are consistent with reports of high-quality performance.[40-42] Consequently, the NPS observations may not be generalizable to present community practice, for which reported incidence rates of colorectal cancer after polypectomy are higher than those reported in the NPS.[47,48]

Comparisons with mortality from colorectal cancer in the general population, based on the SEER data, were limited by our inability to adjust for differences between the NPS cohort and the general population in risk factors, behaviors, ac-

cess to health care, or quality of health care. All-cause mortality was lower for the patients enrolled in the NPS than for the general population; the difference may be attributable to better access to medical care (which included colonoscopy) in the NPS study and the fact that the study patients were in sufficiently good health (especially with respect to cardiovascular disease)[49] to have been referred for colonoscopy during the period from November 1980 through February 1990.

Our comparison of the two NPS cohorts (patients with and those without adenomas) was limited by the very small number of deaths from colorectal cancer, as reflected by the wide confidence intervals, indicating either a large decrease or a large increase in the relative risk of death from colorectal cancer for the patients with adenomas, as compared with those with only nonadenomas.

An additional limitation of the study is that it did not take account of potential changes in lifestyle over time. After detection and removal of an adenoma, patients may stop smoking, modify their diet, control their weight, increase their physical activity, and take multivitamins and nonsteroidal antiinflammatory drugs[15,50-53] to prevent recurrence of adenomas and prevent colorectal cancer.

Deaths that occurred during the study were ascertained with the use of data from the NDI. These data are based on information from death certificates, which do not include the site in the colorectum of the original cancer. Consequently, mortality rates associated with proximal and distal cancers could not be compared in this study.[24]

Finally, 81% of the patients in the randomized adenoma cohort underwent surveillance colonoscopies after polypectomy.[9] Consequently, the polypectomy effect for these patients would include the effect of surveillance colonoscopies as well.[54]

In conclusion, we previously reported a lower-than-expected incidence of colorectal cancer in patients after the removal of adenomatous polyps,[5] and this study shows that polypectomy results in reduced mortality from colorectal cancer. These combined findings indicate that adenomas identified and removed at colonoscopy include those that are clinically important, with the potential to progress to cancer and cause death. A demonstrated reduction in mortality with colonoscopic polypectomy is a critical prerequisite for continued recommendations of screening colonoscopy in clinical practice while we wait for the results of randomized, controlled trials of screening colonoscopy.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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

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REFERENCES

1. 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. Gastroenterology 2008;134:1570-95.
2. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-7.
3. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348:1467-71.
4. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. [Erratum, N Engl J Med 1993;328:1365-71.]
5. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993; 329:1977-81.
6. Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. N Engl J Med 2011;364:476-80.
7. O'Brien MJ, Winawer SJ, Zauber AG, et al. The National Polyp Study: patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology 1990;98:371-9.
8. Winawer SJ, Zauber AG, O'Brien MJ, et al. The National Polyp Study: design, methods, and characteristics of patients with newly diagnosed polyps. Cancer 1992; 70:1236-45.
9. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. N Engl J Med 1993;328:901-6.
10. Winawer S, O'Brien M. Management of malignant polyps. In: Waye JD, Rex DK, Williams CB, eds. Colonoscopy: principles and practice. 2nd ed. Hoboken, NJ: Wiley-Blackwell, 2009:401-11.
11. Olson SH, Layne TM, Simon JA, et al. Studying cancer in minorities: a look at the numbers. Cancer 2011;117:2762-9.
12. Chu KC, Miller BA, Feuer EJ, Hankey BF. A method for partitioning cancer mortality trends by factors associated with diagnosis: an application to female breast cancer. J Clin Epidemiol 1994;47:1451-61.
13. Gyrd-Hansen D, Søgaard J, Kronborg O. Analysis of screening data: colorectal cancer. Int J Epidemiol 1997;26:1172-81.
14. Vogelaar I, van Ballegooijen M, Schrag D, et al. How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. Cancer 2006;107:1624-33.

15. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544-73.
16. Jouve JL, Remontet L, Dancourt V, et al. Estimation of screening test (Hemoccult) sensitivity in colorectal cancer mass screening. Br J Cancer 2001;84:1477-81.
17. Launoy G, Smith TC, Duffy SW, Bouvier V. Colorectal cancer mass-screening: estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. Int J Cancer 1997;73:220-4.
18. Prevost TC, Launoy G, Duffy SW, Chen HH. Estimating sensitivity and sojourn time in screening for colorectal cancer: a comparison of statistical approaches. Am J Epidemiol 1998;148:609-19.
19. Surveillance, Epidemiology, and End Results (SEER) Program home page (http://www.seer.cancer.gov).
20. National Center for Health Statistics home page (http://www.cdc.gov/nchs).
21. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol 2003;27:65-81.
22. National Death Index. Atlanta: Centers for Disease Control and Prevention, 2011 (http://www.cdc.gov/nchs/ndi.htm).
23. Breslow NE, Day NE. Statistical methods in cancer research. Lyon, France: International Agency for Research on Cancer, 1987.
24. Ederer F, Geisser MS, Mongin SJ, Church TR, Mandel JS. Colorectal cancer deaths as determined by expert committee and from death certificate: a comparison. J Clin Epidemiol 1999;52:447-52.
25. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. N Engl J Med 2000;343:162-8. [Erratum, N Engl J Med 2000;343:1204.]
26. 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.
27. Regula J, Rupinski M, Kraszewska E, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355:1863-72.
28. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133:1077-85.
29. 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.]
30. 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.
31. Brenner H, Haug U, Arndt V, Stegmaier C, Altenhofen L, Hoffmeister M. Low risk of colorectal cancer and advanced adenomas more than 10 years after negative colonoscopy. Gastroenterology 2010;138:870-6.
32. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
33. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? Ann Intern Med 2009;150:50-2.
34. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterology 2010;139:1128-37.
35. Sandler RS. Colonoscopy and colorectal cancer mortality: strong beliefs or strong facts? Am J Gastroenterol 2010;105:1633-5.
36. Neugut AI, Lebwohl B. Colonoscopy vs sigmoidoscopy screening: getting it right. JAMA 2010;304:461-2.
37. Jørgensen OD, Kronborg O, Fenger C, Rasmussen M. Influence of long-term colonoscopic surveillance on incidence of colorectal cancer and death from the disease in patients with precursors (adenomas). Acta Oncol 2007;46:355-60.
38. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol 2009;7:770-5.
39. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22-30.
40. Rex DK, Bond JH, Winawer S, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002;97:1296-308.
41. Rex DK, Petrini JL, Baron TH, et al. Quality indicators for colonoscopy. Am J Gastroenterol 2006;101:873-85.
42. Lieberman D. A call to action — measuring the quality of colonoscopy. N Engl J Med 2006;355:2588-9.
43. Atkin W, Rogers P, Cardwell C, et al. Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. Gastroenterology 2004;126:1247-56.
44. 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.
45. Rabeneck L, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. Clin Gastroenterol Hepatol 2010;8:275-9.
46. Bretthauer M. The capsule and colorectal-cancer screening — the crux of the matter. N Engl J Med 2009;361:300-1.
47. Robertson DJ, Greenberg E, Beach M, et al. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005;129:34-41.
48. Zauber AG, Winawer SJ. High-quality colonoscopies must be an integral part of screening and surveillance programs. Gastroenterology 2006;130:620-1.
49. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150:849-57.
50. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology 2008;134:21-8.
51. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603-13.
52. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741-50.
53. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
54. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology 2006;130:1872-85.