The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 28, 2014 VOL. 371 NO. 9

Long-Term Colorectal-Cancer Mortality after Adenoma Removal

Magnus Løberg, M.D., Mette Kalager, M.D., Ph.D., Øyvind Holme, M.D., Geir Hoff, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Michael Bretthauer, M.D., Ph.D.

ABSTRACT

BACKGROUND

Although colonoscopic surveillance of patients after removal of adenomas is widely promoted, little is known about colorectal-cancer mortality among these patients.

METHODS

Using the linkage of the Cancer Registry and the Cause of Death Registry of Norway, we estimated colorectal-cancer mortality among patients who had undergone removal of colorectal adenomas during the period from 1993 through 2007. Patients were followed through 2011. We calculated standardized incidence-based mortality ratios (SMRs) using rates for the Norwegian population at large for comparison. Norwegian guidelines recommended colonoscopy after 10 years for patients with high-risk adenomas (adenomas with high-grade dysplasia, a villous component, or a size ≥10 mm) and after 5 years for patients with three or more adenomas; no surveillance was recommended for patients with low-risk adenomas. Polyp size and exact number were not available in the registry. We defined high-risk adenomas as multiple adenomas and adenomas with a villous component or high-grade dysplasia.

RESULTS

We identified 40,826 patients who had had colorectal adenomas removed. During a median follow-up of 7.7 years (maximum, 19.0), 1273 patients were given a diagnosis of colorectal cancer. A total of 398 deaths from colorectal cancer were expected and 383 were observed, for an SMR of 0.96 (95% confidence interval [CI], 0.87 to 1.06) among patients who had had adenomas removed. Colorectal-cancer mortality was increased among patients with high-risk adenomas (expected deaths, 209; observed deaths, 242; SMR, 1.16; 95% CI, 1.02 to 1.31), but it was reduced among patients with low-risk adenomas (expected deaths, 189; observed deaths, 141; SMR, 0.75; 95% CI, 0.63 to 0.88).

CONCLUSIONS

After a median of 7.7 years of follow-up, colorectal-cancer mortality was lower among patients who had had low-risk adenomas removed and moderately higher among those who had had high-risk adenomas removed, as compared with the general population. (Funded by the Norwegian Cancer Society and others.)

From the Department of Health Management and Health Economics, University of Oslo, Oslo (M.L., M.K., G.H., H.-O.A., M.B.), Department of Transplantation Medicine, Oslo University Hospital, Oslo (M.L., M.B.), Cancer Registry of Norway, Oslo (G.H.), Department of Research and Development, Telemark Hospital, Skien (M.K., G.H.), and Department of Medicine, Sørlandet Hospital Kristiansand, Kristiansand (Ø.H., M.B.) — all in Norway; the Department of Epidemiology, Harvard School of Public Health, Boston (M.L., M.K., Ø.H., H.-O.A., M.B.); and the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm (H.-O.A.). Address reprint requests to Dr. Løberg at the Department of Health Management and Health Economics, University of Oslo, 0317 Oslo, Norway, or at magnus.loberg@medisin.uio.no.

Drs. Løberg and Kalager contributed equally to this article.

N Engl J Med 2014;371:799-807.
DOI: 10.1056/NEJMoa1315870

Screening programs for colorectal cancer are currently implemented in many Western populations[1,2] because randomized trials have documented an association between screening and a sustained reduction in colorectal-cancer mortality.[3] The benefit is most likely due to early detection of cancer, endoscopic removal of adenomas, and surveillance of patients who are considered to be at high risk for the development of new neoplastic lesions.[4,5] However, precise quantification of the risk of death from cancer after adenoma removal has been hampered by the scarceness of large, population-based studies with long follow-up periods.

Previous studies were performed in populations undergoing intensive surveillance,[5,6] were small,[5-8] or had limited follow-up.[6,9] Therefore, the generalizability of these findings remains uncertain. Nevertheless, professional organizations and national authorities recommend surveillance colonoscopy for patients with low-risk adenomas and for patients with high-risk adenomas, every 5 or 10 years for the former and every 3 or 5 years for the latter.[10-12] The workload of surveillance colonoscopy is rapidly increasing. In the United States, polyp surveillance accounts for more than 20% of all colonoscopies performed in patients 50 years of age or older.[13] Taking advantage of nationwide data in the Cancer Registry of Norway on patients who have had colorectal adenomas removed, we evaluated colorectal-cancer mortality in a large, population-based cohort with virtually complete follow-up for death from colorectal cancer.

Methods

Data Sources

Norway has a public health care system with universal coverage. Each resident is assigned a unique national identification number, which is linked to information on sex and date of birth. We used data on adenomas from the Cancer Registry, which was established in 1952 and is considered close to 100% complete.[14,15] The registry classifies morphologic and topographic features of all lesions according to the third edition of the *International Classification of Diseases for Oncology* (ICD-O-3).[16] Reporting of cancer and cancer precursors, including colorectal adenomas, is mandatory for Norwegian health care providers. However, completeness of adenoma reporting was uncertain before 1993, when coding practices changed substantially. Adenomas reported to the Cancer Registry more than 4 months apart are recorded as separate occurrences. At each notification, the histopathological characteristics of all adenomas are pooled, and the most severe characteristics (growth pattern [villous, tubulovillous, or tubulous] and dysplasia [high-grade or low-grade]) are registered. The number of adenomas removed is recorded as single or multiple.

Norwegian guidelines for surveillance of patients with adenomas — which was in place throughout the study period[17] — recommended colonoscopy after 10 years for patients younger than 75 years of age with high-risk adenomas (those with high-grade dysplasia, a villous growth pattern, or a size of ≥10 mm in diameter) and after 5 years for patients with three or more adenomas. Surveillance was not recommended for patients with low-risk adenomas or for patients older than 74 years of age. Almost all colonoscopies are performed at public hospitals, and adherence to guidelines is high.[18] From 2006 to 2012, adenoma surveillance accounted for approximately 9% of all colonoscopies performed in Norway.[19]

Study Population

For the adenoma cohort, we retrieved data from the Cancer Registry for all patients who were 40 years of age or older and had had at least one colorectal adenoma removed between 1993 and 2007 that could be classified by ICD-O-3 topography codes 180 through 189, 199, or 209 and morphology codes 8140, 8210, 8211, 8261, or 8263. We defined adenoma location as either distal (rectum or sigmoid colon) or proximal (more proximal than the sigmoid colon). We could not define adenomas as high-risk or low-risk entirely on the basis of guidelines because we lacked information about polyp size and the exact number of polyps (polyp number in the registry is categorized as one or more than one). Thus, we classified multiple adenomas and adenomas with a villous growth pattern or high-grade dysplasia as high-risk adenomas. We excluded 22 patients with familial adenomatous polyposis who were identified by linkage to the National Polyposis Registry. Using the national registration number, we linked data for all patients to the nationwide registries of cancer, population, and cause of death to obtain information on cancer incidence, date of emigration in the case of patients who

emigrated, and date and cause of death until December 31, 2011. The board of directors at the Cancer Registry approved the study.

REVIEW OF PATHOLOGY REPORTS

The size and number of adenomas are reported to the Cancer Registry. But neither this information nor the procedure (colonoscopy or flexible sigmoidoscopy) used to detect and remove the adenomas has been entered into the electronic database. To better characterize the study cohort, we undertook a manual review of original pathology reports in a random sample of 457 patients from our cohort and successfully retrieved information for 442 (97%) of these patients (Tables S1 and S7 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

STUDY END POINTS

Colorectal-cancer mortality was our primary end point. We compared the observed mortality in the adenoma cohort with rates in the general population. We retrieved annual information from Statistics Norway on the population according to age and sex.[20] Data on all patients in whom colorectal cancer was diagnosed were retrieved from the Cancer Registry, including age at the time of diagnosis, date of diagnosis, cancer location, and date and cause of death. Since the observed colorectal-cancer mortality among patients who had had adenomas was limited to those in whom a diagnosis was made after first removal of adenomas, the expected mortality included only deaths from colorectal cancer among patients in the general population who received a diagnosis during our study period.[21] For transparency, we also estimated colorectal-cancer incidence and all-cause mortality in the adenoma cohort as compared with the general population (see the Supplementary Appendix). However, the interpretation of incidence is problematic because incidence estimates are subject to lead-time bias and possibly overdiagnosis bias due to colonoscopic surveillance in the adenoma cohort (see the Supplementary Appendix). Therefore, we focused on colorectal-cancer mortality, which is not affected by such biases.

STATISTICAL ANALYSIS

We calculated person-years at risk from the date of adenoma removal until death (and until diagnosis of colorectal cancer for incidence). For patients who had adenomas removed at different times, person-years at risk were calculated separately for the periods after the first adenoma removal and the second adenoma removal. To explore the effect of adenoma removal followed by recommended surveillance, we also calculated person-years continuously from the first adenoma removal until the data were censored. The results were not materially altered as compared with our primary analytic approach (data not shown). All time-to-event data were censored at the time of emigration, in the case of patients who emigrated, or at the end of follow-up (December 31, 2011). We estimated person-years at risk for the general population, stratified according to sex, 5-year age group, and calendar year, and used the number of events and person-years to calculate overall and site-specific colorectal-cancer mortality, as well as all-cause mortality and colorectal-cancer incidence (see the Supplementary Appendix).

We calculated standardized mortality ratios (SMRs) as observed deaths in the cohort divided by the expected number of deaths that would occur if the cohort had the same risk as the general population, with the risk in the general population calculated as the strata-specific mortality rates multiplied by the time at risk. We calculated 95% confidence intervals for the SMRs under the assumption that occurrence of the events followed a Poisson distribution. SMRs were calculated according to sex, age group, calendar period, and adenoma site and characteristics.

We constructed cumulative curves for colorectal-cancer mortality among patients for whom the first adenoma was classified as either low-risk or high-risk, and we treated death from other causes as a competing risk.[22] Cumulative curves were compared with the use of Gray's test.[23] To separate out the effects of explanatory variables (age and sex; number of adenoma occurrences and period of adenoma removal; and adenoma location, number of adenomas, grade of dysplasia, and growth pattern), we used Cox proportional-hazard models to estimate hazard ratios and 95% confidence intervals. We fitted multivariate models using forward selection, which required P values of less than 0.05, according to the Wald test, for inclusion of variables in the multivariate model. For all Cox models, we plotted scaled Schoenfeld residuals against follow-up time and found no violation of the proportional-hazards assumption.

Table 1. Characteristics of the Patients Who Had Undergone Adenoma Removal.

Variable	Patients	Adenoma Occurrences
	no. (%)	
Total	40,826	45,755
Sex		
Female	20,088 (49.2)	
Male	20,738 (50.8)	
Age at first adenoma removal		
40–49 yr	3,789 (9.3)	
50–59 yr	9,327 (22.9)	
60–69 yr	11,409 (28.0)	
70–79 yr	10,901 (26.7)	
≥80 yr	5,400 (13.2)	
Period of first adenoma removal		
1993–1999	14,169 (34.7)	
2000–2007	26,657 (65.3)	
Duration of follow-up		
0–4 yr	6,914 (16.9)	
5–9 yr	17,956 (44.0)	
10–14 yr	11,256 (27.6)	
15–19 yr	4,700 (11.5)	
No. of adenoma occurrences*		
1	36,296 (88.9)	36,296 (79.3)
≥2	4,530 (11.1)	9,459 (20.7)
Adenoma location		
Distal		21,667 (47.4)
Proximal		6,264 (13.7)
Multiple or unspecified		17,824 (39.0)
Adenoma characteristics†		
Low-risk		23,449 (51.3)
High-risk		22,306 (48.8)
≥2 Adenomas		10,408 (22.8)
Villous or tubulovillous growth pattern		13,153 (28.8)
High-grade dysplasia		6,983 (15.3)

* Reports of colorectal adenomas sent to the Cancer Registry within a 4-month period were treated as a single occurrence, and those reported more than 4 months apart were recorded as separate occurrences.

† High-risk characteristics were the presence of two or more adenomas, high-grade dysplasia, or villous architecture.

Statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Gray's test was performed with the use of R software, version 3.0.2 (R Development Core Team). Stata software, version 13.1 (StataCorp), was used for all other analyses.

RESULTS

CHARACTERISTICS OF THE ADENOMA COHORT

The adenoma cohort consisted of 40,826 patients. The total follow-up time was 334,154 person-years, and the median follow-up time was 7.7 years (maximum, 19.0). A total of 20,423 patients (50.0%) were included before 2002 and were followed for 10 years or more. Characteristics of the adenoma cohort are shown in Table 1.

According to our review of the pathology reports for 442 patients, the median diameter of the adenomas was 9 mm (Tables S1 and S7 in the Supplementary Appendix), and the diameter did not differ significantly according to age, sex, or adenoma location. Adenomas with high-grade dysplasia were larger than adenomas with low-grade dysplasia (median, 15 mm vs. 7 mm; P<0.001), and adenomas with a villous growth pattern were larger than adenomas with a tubular growth pattern (median, 15 mm vs. 6 mm; P<0.001). The median diameter decreased with the calendar period, from 10 mm in the 1990s to 7 mm in the 2000s (P=0.002). Of the 442 patients, 220 (49.8%) had adenomas that were classified as high-risk on the basis of the criteria used in this study (i.e., adenomas with a villous growth pattern or high-grade dysplasia or the presence of two or more adenomas) and 269 (60.9%) had adenomas that were classified as high-risk with the use of more detailed criteria enumerated in the guidelines, which include polyp size and the exact number of polyps. Among the 220 patients with adenomas that were classified as high-risk on the basis of the study criteria, the review of pathology reports revealed that 8.2% had adenomas that were low-risk according to the more detailed guideline criteria. Among the 222 patients with adenomas that were classified as low-risk on the basis of the study criteria, 30.2% had adenomas that were high-risk when the more detailed criteria were applied (Table S1 in the Supplementary Appendix).

COLORECTAL-CANCER MORTALITY

During the follow-up period, a total of 1273 patients in the adenoma cohort (387 per 100,000 person-years) were given a diagnosis of colorectal cancer. Of these, 383 patients (115 per 100,000 person-years) died of colorectal cancer (of 13,436

observed deaths from any cause) (Table 2, and Table S5 in the Supplementary Appendix). Colorectal-cancer mortality in the adenoma cohort was similar to that in the general population (Table 2 and Fig. 1). In men, adenoma removal was associated with a risk reduction of 14% (95% confidence interval [CI], 0 to 26); no significant risk reduction was observed in women. Colorectal-cancer mortality among patients who had had low-risk adenomas was reduced by 25% (95% CI, 12 to 37), as compared with the general population, whereas the risk among patients who had had high-risk adenomas was increased by 16% (95% CI, 2 to 31) (Fig. 1). After a median of 7.7 years of follow-up, there were 33 more deaths from colorectal cancer among patients who had had high-risk adenomas and 48 fewer deaths from colorectal cancer among patients who had had low-risk adenomas, as compared with the general population. As shown in Figure 2, cumulative colorectal-cancer mortality was significantly higher among patients who had had high-risk adenomas than among those who had had low-risk adenomas. Patients who received a diagnosis of colorectal cancer before 2000 had a higher risk of death than did those who received a diagnosis after 2000 (Table S6 in the Supplementary Appendix). Among patients who had had adenomas removed before 2002 and thus had 10 years or more of follow-up, the SMR for colorectal cancer was 1.10 (95% CI, 0.98 to 1.23). The risk of death from any cause among patients who had had adenomas, as compared with the general population, was increased by 20% (95% CI, 18 to 22) (Table S5 in the Supplementary Appendix).

MULTIVARIATE ANALYSES

Table 3 shows the results of univariate and multivariate analyses of colorectal-cancer mortality among patients who had undergone removal of adenomas. In the multivariate analysis, mortality was 37% lower (95% CI, 22 to 49) among patients who underwent their first adenoma removal in the 2000s as compared with those who underwent removal in the 1990s. Multiple adenomas, high-grade dysplasia, and a villous growth pattern were predictors of a significant (31 to 45%) increase in mortality from colorectal cancer.

Table 2. Standardized Mortality Ratio for Deaths from Colorectal Cancer among Patients Who Had Adenomas Removed.

Variable	No. of Observed Deaths/No. of Expected Deaths	Standardized Mortality Ratio (95% CI)
Total deaths	383/398	0.96 (0.87–1.06)
Sex		
Female	210/198	1.06 (0.93–1.22)
Male	173/201	0.86 (0.74–1.00)
Age at first adenoma removal		
40–49 yr	9/6	1.48 (0.77–2.84)
50–59 yr	50/42	1.19 (0.91–1.58)
60–69 yr	93/106	0.88 (0.72–1.08)
70–79 yr	138/161	0.86 (0.73–1.01)
≥80 yr	93/84	1.11 (0.91–1.36)
Period of first adenoma removal		
1993–1999	229/196	1.17 (1.03–1.33)
2000–2007	154/202	0.76 (0.65–0.89)
Duration of follow-up		
0–4 yr	162/171	0.95 (0.81–1.11)
5–9 yr	139/145	0.96 (0.81–1.13)
10–14 yr	69/67	1.04 (0.82–1.31)
15–19 yr	13/16	0.82 (0.48–1.42)
No. of adenoma occurrences		
1	330/344	0.96 (0.86–1.07)
≥2	53/54	0.98 (0.75–1.28)
Adenoma location		
Distal	208/210	0.99 (0.87–1.14)
Proximal	51/59	0.87 (0.66–1.15)
Multiple or unspecified	124/130	0.95 (0.80–1.14)
Adenoma characteristics		
Low-risk	141/189	0.75 (0.63–0.88)
High-risk	242/209	1.16 (1.02–1.31)
No. of adenomas per occurrence		
1	267/301	0.89 (0.79–1.00)
≥2	116/97	1.19 (1.00–1.43)
Growth pattern		
Tubulous	226/274	0.83 (0.73–0.94)
Villous or tubulovillous	157/125	1.26 (1.08–1.47)
Grade of dysplasia		
Low	288/330	0.87 (0.78–0.98)
High	95/68	1.40 (1.15–1.72)

DISCUSSION

Our study revealed that patients who underwent the removal of low-risk adenomas had a reduced risk of death from colorectal cancer. This risk reduction was achieved at a time when surveillance colonoscopy was not recommended for these pa-

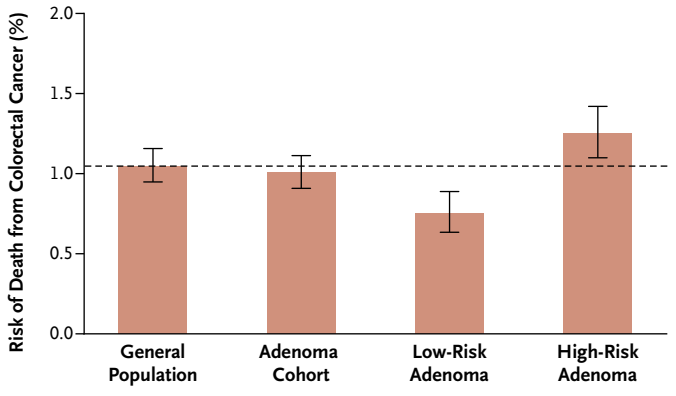
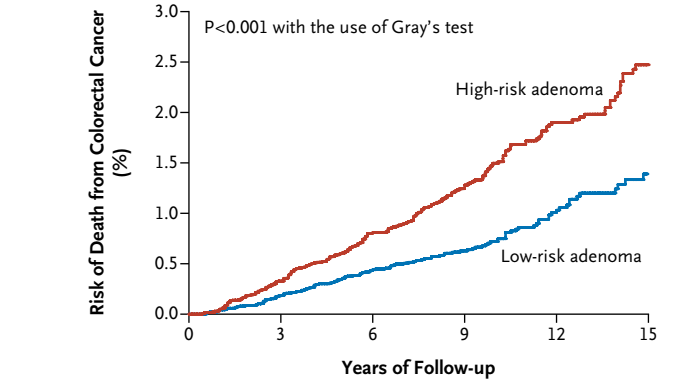


Figure 1. Colorectal-Cancer Mortality in a Cohort of Patients Who Underwent Removal of Adenomas and in the General Population.

The graph shows the risk of death from colorectal cancer after a median follow-up of 7.7 years (maximum, 19) in the general population (dashed line) and in the cohort of patients with adenomas that were removed, which included patients who had high-risk adenomas and those who had low-risk adenomas. I bars indicate 95% confidence intervals.



No. at Risk

Low-risk adenoma	19,934	17,701	13,372	8230	4095	1615
High-risk adenoma	20,892	17,947	13,270	8080	4334	1916

Figure 2. Cumulative Risk of Death from Colorectal Cancer.

The curves show the cumulative risk of death from colorectal cancer after the removal of low-risk adenomas and after the removal of high-risk adenomas (defined by the presence of two or more adenomas or adenomas with high-grade dysplasia or villous growth pattern or a combination of those findings).

tients. Thus, any increase in the risk of death from colorectal cancer associated with low-risk adenomas may have been eliminated by the polypectomy. Patients who underwent the removal of high-risk adenomas had a 16% increase in the risk of death from colorectal cancer, an excess risk of 33 deaths from colorectal cancer in our cohort of 40,826 patients. Although this excess risk is not as high as previously suggested,[7,8,12] it could perhaps have been reduced with more surveillance. Our study cannot clarify the extent to which the increased risk after polypectomy reflects the underlying increase in the risk of death from colorectal cancer among these patients, but in any case, surveillance might not have been sufficient to lower this increased risk. This question can be answered only by performing comparative randomized trials with different surveillance intervals.

The strengths of our study include its large size, population-based design, and complete follow-up. Although negative colonoscopies (those that revealed no adenomas) could not be ascertained, such examinations cannot influence future colorectal-cancer incidence and mortality, because the benefit of colonoscopy is based entirely on polypectomy, not on the visualization of the colonic mucosa alone. All patients who underwent colonoscopies in which adenomas were detected and removed were reported to the Cancer Registry and are included in our cohort. Thus, the lack of information about colonoscopies that did not result in adenoma removal cannot bias our results. Potential limitations of our study are the lack of information about the indication for the endoscopy that entailed detection and removal of adenomas. Because standardized histopathological review of this large cohort was not feasible, we relied on Cancer Registry data. We also lack individual information about polyp size, the exact number of polyps, and the procedure used for adenoma removal. Our review of a random sample of pathology reports, however, gives an indication of the possible misclassification that resulted from our inability to apply standard criteria to classify low-risk and high-risk adenomas. As we have shown, 30.2% of patients in the low-risk group according to the study criteria would have been assigned to the high-risk group on the basis of the guideline criteria, and only 8.2% of patients in the high-risk group would have been assigned to the low-risk group.[24] Thus, our main results may overestimate the already decreased risk of death from colorectal cancer in the low-risk group and may underestimate the risk in the high-risk group (see the Supplementary Appendix). Furthermore, colonoscopy became

Table 3. Univariate and Multivariate Hazard Ratios for Death from Colorectal Cancer among Patients from Whom Adenomas Were Removed.*

Variable	Univariate Hazard Ratio (95% CI)	P Value	Multivariate Hazard Ratio (95% CI)	P Value
Sex				
Female	1.00			
Male	0.86 (0.70–1.05)	0.14		
Age at first adenoma removal				
40–49 yr	1.00		1.00	
50–59 yr	2.41 (1.19–4.90)	0.02	2.43 (1.20–4.95)	0.01
60–69 yr	4.10 (2.07–8.14)	<0.001	3.85 (1.94–7.64)	<0.001
70–79 yr	8.34 (4.25–16.39)	<0.001	7.38 (3.75–14.51)	<0.001
≥80 yr	19.68 (9.89–39.15)	<0.001	17.74 (8.90–35.38)	<0.001
Period of first adenoma removal				
1993–1999	1.00		1.00	
2000–2007	0.62 (0.50–0.77)	<0.001	0.63 (0.51–0.78)	<0.001
No. of adenoma occurrences				
1	1.00			
≥2	0.74 (0.53–1.03)	0.08		
Adenoma location				
Distal	1.00			
Proximal	0.96 (0.71–1.30)	0.78		
Multiple or unspecified	0.99 (0.79–1.24)	0.94		
No. of adenomas per occurrence				
1	1.00		1.00	
≥2	1.48 (1.19–1.84)	<0.001	1.31 (1.05–1.63)	0.02
Growth pattern				
Tubulous	1.00		1.00	
Villous or tubulovillous	1.93 (1.57–2.36)	<0.001	1.40 (1.14–1.73)	0.002
Grade of dysplasia				
Low	1.00		1.00	
High	2.04 (1.62–2.58)	<0.001	1.45 (1.14–1.85)	0.002

* The risk for the reference category in each subgroup analysis is defined as 1.00. The multivariate regression model was fitted with the use of forward selection and the Wald test, which required a P value of less than 0.05 for inclusion of variables from the univariate models in the multivariate model. (The variables with only univariate hazard ratios, not multivariate hazard ratios, did not reach a P value of 0.05.)

the predominant endoscopic procedure during the 2000s, indicating that the results for patients who were included in the study during this period better reflect the risk of cancer among patients in whom adenomas are diagnosed today.

The median follow-up time in our study was 7.7 years, which might be too short to draw strong conclusions about the value of surveillance intervals up to 10 years. However, 20,423 patients (50.0% of the adenoma cohort) had adenomas removed before 2002 and could have had 10 years or more of follow-up. In this group, the SMR for colorectal cancer was 1.10 (95% CI, 0.98 to 1.23), which is slightly higher than the SMR for the whole cohort (0.96; 95% CI, 0.87 to 1.06). However, as in any longitudinal study, the downside of longer follow-up is that patients were included a long time ago, and the interventions then may

differ from the ones offered today. Thus, the comparison of two periods of adenoma removal is of value, because it might reveal that in the modern era of colonoscopic removal of adenomas, the risk of death from colorectal cancer is significantly smaller than in earlier periods.

The overarching goal of surveillance is the prevention of disease-specific death. Therefore, colorectal-cancer mortality was the primary end point in the present study. However, the absolute excess risk of death from any cause among patients who have undergone the removal of high-risk adenomas far outreaches the excess risk of death from colorectal cancer (33 deaths from colorectal cancer vs. 2222 deaths from any cause) (see Section 3 and Table S5 in the Supplementary Appendix). It is possible that adenomas are associated with an increased risk of death from any cause. Death from any type of cancer contributes to a large proportion of the excess mortality observed in the adenoma cohort (see Section 3 in the Supplementary Appendix). The increase in all-cause mortality in the adenoma cohort as compared with the general population may reflect selection bias. Patients in whom adenomas were removed may have had health problems that led to diagnostic evaluations resulting in adenoma detection. Screening colonoscopy and flexible sigmoidoscopy were not performed in Norway during the period of our study, and our cohort may therefore not be representative of patients with adenomas who live in countries where screening is common. Patients who undergo screening may be healthier than the patients in our cohort; thus, all-cause mortality in our study may differ from that in countries where screening is widespread.

Most previous studies of the risk of cancer after adenoma removal were based on colorectal-cancer incidence, with challenges and limitations similar to those for this study (see Section 2 in the Supplementary Appendix). Hence, the excess colorectal-cancer mortality and all-cause mortality among patients who have undergone the removal of adenomas have not been studied sufficiently. Our study extends recent findings from the National Polyp Study. We confirm that the risk of death from colorectal cancer after adenoma removal is similar to the risk of death from colorectal cancer in the general population. The National Polyp Study, with its small number of deaths from colorectal cancer (12, as compared with 383 in this study), was not able to elaborate on important distinctions in the study cohorts. We found that colorectal-cancer mortality was considerably higher among patients who underwent removal of high-risk adenomas than among those who underwent removal of low-risk adenomas.

Because the evidence base is limited, prevailing and substantially varying guidelines for colonoscopic surveillance of patients after the removal of adenomas have been developed chiefly on the basis of consensus and circumstantial evidence. Our finding that the removal of low-risk adenomas reduces the risk of death from colorectal cancer over a period of 8 years to a level below the risk in the general population is consistent with the hypothesis that surveillance every 5 years[10] after removal of low-risk adenomas may confer little benefit over less intensive surveillance strategies. Furthermore, complications associated with colonoscopy are not trivial and might offset the benefit of surveillance.[12] Randomized trials testing the noninferiority of less intensive surveillance are needed to generate high-quality evidence that can guide recommendations about surveillance intervals after adenoma removal.

Supported by grants from the Norwegian Cancer Society (HS02-2009-0082, to Dr. Løberg), the U.S.–Norway Fulbright Foundation for Educational Exchange (to Drs. Løberg and Holme), and the Research Council of Norway (205143, 224845/F11, and 231920) and by a Distinguished Professor Award from the Karolinska Institutet (2368/10-221, to Dr. Adami).

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

REFERENCES

1. Bretthauer M, Kalager M. Colonoscopy as a triage screening test. N Engl J Med 2012;366:759-60.
2. Garborg K, Holme Ø, Løberg M, Kalager M, Adami HO, Bretthauer M. Current status of screening for colorectal cancer. Ann Oncol 2013;24:1963-72.
3. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013;369:1106-14.
4. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977-81.
5. 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.
6. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.
7. Atkin WS, Morson BC, Cuzick J. Long-

term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658-62.
8. 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.
9. Loeve F, van Ballegooijen M, Boer R, Kuipers EJ, Habbema JDF. Colorectal cancer risk in adenoma patients: a nationwide study. Int J Cancer 2004;111:147-51.
10. 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. Gastroenterology 2012;143:844-57.
11. Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: first edition — colonoscopic surveillance following adenoma removal. Endoscopy 2012;44:Suppl 3:SE151-SE163.
12. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842-51.
13. Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Utilization of colonoscopy in the United States: results from a national consortium. Gastrointest Endosc 2005;62:875-83.
14. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45:1218-31.
15. Tingulstad S, Halvorsen T, Norstein J, Hagen B, Skjeldestad FE. Completeness and accuracy of registration of ovarian cancer in the cancer registry of Norway. Int J Cancer 2002;98:907-11.
16. International classification of diseases for oncology, 3rd edition (ICD-O-3). Geneva: World Health Organization, 2000 (http://www.who.int/classifications/icd/adaptations/oncology/en).
17. Hoff G, Sauar J, Hofstad B, Vatn MH. The Norwegian guidelines for surveillance after polypectomy: 10-year intervals. Scand J Gastroenterol 1996;31:834-6.
18. Søreide K, Træland JH, Stokkeland PJ, Glomsaker T, Søreide JA, Kørner H. Adherence to national guidelines for surveillance after curative resection of nonmetastatic colon and rectum cancer: a survey among Norwegian gastrointestinal surgeons. Colorectal Dis 2012;14:320-4.
19. Gastronet — quality program. Oslo: Cancer Registry of Norway (http://www.kreftregisteret.no/no/Forskning/Prosjekter/Gastronet).
20. Population, by sex and age. Oslo: Statistics Norway (http://www.ssb.no/statistikkbanken/selecttable/hovedtabellHjem.asp?KortNavnWeb=folkemengde&CMSSubjectArea=befolkning&PLanguage=1&checked=true).
21. Kalager M, Zelen M, Langmark F, Adami H-O. Effect of screening mammography on breast-cancer mortality in Norway. N Engl J Med 2010;363:1203-10.
22. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695-706.
23. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
24. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604-8.