Adenomatous Polyps of the Colon

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

A 52-year-old man with no personal or family history of colon cancer, colonic polyps, or inflammatory bowel disease underwent a screening colonoscopy that showed no abnormalities except for a 1.5-cm pedunculated polyp at the hepatic flexure that was removed by means of a snare with cautery. The polyp was a tubulovillous adenoma without high-grade dysplasia. How should his care be managed?

**The Clinical Problem**

In 2006, it is estimated that there will be more than 145,500 new cases of colorectal cancer and 55,000 deaths from this disease in the United States, making colorectal cancer the second most common cause of death from cancer. Colonic adenomas, the precursors of almost all sporadic colorectal cancers, are found in up to 40% of persons by 60 years of age. The adenoma–carcinoma sequence — the progression from normal colonic mucosa to small tubular adenomas to larger adenomas and those with more advanced histologic features (villous features, high-grade dysplasia, or both) to cancer — is a central tenet of our understanding and management of colonic adenomas. Although not all colonic polyps are adenomas (hyperplastic polyps account for about half of small, rectosigmoid polyps) and more than 90% of adenomas do not progress to cancer, it is currently not possible to reliably identify those that will progress. Thus, colonic polyps identified at colonoscopy should be removed if it is technically feasible to do so. Complete removal of a colonic adenoma eliminates the risk of cancer from that adenoma, but the finding of a colonic adenoma may indicate an increased risk of metachronous adenomas and colorectal cancer for both the patient and his or her first-degree relatives (i.e., parents, siblings, and children).

Colonic adenomas are typically asymptomatic and are most commonly found by means of endoscopic or radiologic imaging studies performed because of unrelated symptoms or for colorectal cancer screening. Since at least 25% of men and 15% of women who undergo colonoscopic screening by experienced endoscopists are found to have one or more adenomas, the cumulative burden of subsequent surveillance colonoscopy on the health care system is substantial. In 1999, it was estimated that one quarter of the 4.4 million colonoscopies performed in the United States were for polyp surveillance, and there has been a marked increase in endoscopic screening since that time.

**Strategies and Evidence**

**Colonoscopic Polypectomy and Surveillance**

Colonoscopic surveillance is recommended for patients with adenomas because the risks of new (metachronous) adenomas and colorectal cancer among these patients...
Advanced adenomas are also predictive of an increased risk of colorectal cancer. In one study, the finding of one or more advanced adenomas at rigid sigmoidoscopy was associated with a rate of metachronous proximal colon cancer (i.e., above the reach of the sigmoidoscope) that was about 5 times higher than that in the general population; in contrast, the finding of only small, rectosigmoid tubular adenomas was not associated with an increased future risk of colon cancer. Other characteristics of the baseline adenoma (e.g., a location proximal to the splenic flexure) or of the patient (e.g., male sex, older age, or a first-degree relative with colorectal cancer) have also been reported in some studies to be predictive of metachronous adenomas or colorectal cancer.

Limited observational data suggest that adenomas that are smaller than 1 cm do not grow much during a 2-to-3-year period, whereas larger polyps have a greater tendency to grow and progress to cancer. In one study, polyps 1 cm or larger that were detected by means of a barium enema progressed to cancer at a rate of about 1% per year. Small adenomas can, however, have advanced histologic features, including foci of invasive cancer. Thus, the usual practice is to remove all polyps endoscopically if it is technically possible to do so. The current recommendations regarding intervals between colonoscopies are stratified on the basis of the number, size, and histologic features of the adenomas found at colonoscopy (Table 1).

The success of colonoscopic polypectomy and surveillance depends on the identification and complete removal of the adenoma or adenomas (see video, available with the full text of this article at www.nejm.org). It is thought that most colorectal cancers that occur within 5 years after colonoscopic polypectomy develop because of failure to identify or completely remove high-risk neoplasms (advanced adenomas or cancers) at the time of the initial colonoscopy. The adequacy of a polypectomy is assessed according to the endoscopic appearance of the polypectomy site and by a review of the pathological specimen to determine whether its margins are free of neoplastic tissue. This determination is sometimes difficult, particularly with large, sessile lesions that were removed in pieces. Endoscopy repeated within a few months is warranted if there is doubt about the adequacy of the initial polypectomy.

The adenoma “miss rate,” which can vary by...
a factor of 2 to 3 among examiners, is about 6 to 12% for adenomas that are 1 cm or larger and up to 25% for smaller adenomas.11-13 Thus, missed adenomas or cancers may contribute to the occurrence of colorectal cancer despite colonoscopic surveillance and may underlie many instances of “metachronous” neoplasia reported during surveillance. In this issue of the Journal, Barclay and colleagues14 note an important relationship between adenoma detection rates and the withdrawal time of the colonoscope. They report that endoscopists with an average withdrawal time that was longer than 6 minutes had significantly higher rates of adenoma detection than those with a shorter average withdrawal time. To be most effective, colonoscopy should be performed by well-trained, certified endoscopists who meticulously examine the entire colon during withdrawal of the instrument.

Recommendations regarding the appropriate interval for colonoscopic surveillance are based on the estimated 5 to 15 years required for the minority of adenomas that progress to cancer to do so,15 the results of limited data from controlled trials of surveillance intervals, and the recognized associations between certain findings at the initial colonoscopy and the subsequent risk of the development of advanced adenomas and cancer. Until the mid-1990s, patients with colonic adenomas were routinely advised to undergo colonoscopic surveillance every year. The National Polyp Study,16 a randomized trial that compared the findings of follow-up colonoscopic surveillance at 1 and 3 years with those of follow-up colonoscopy at 3 years alone, showed that the detection of advanced adenomas was low (3.3%) and was the same in the two groups. This study indicates that surveillance intervals that are shorter than 3 years are not required for most patients with adenomas. A smaller trial in Denmark17 comparing surveillance intervals of 2 and 4 years showed a nonsignificant difference in the rate of detection of advanced adenomas or colorectal cancer between groups at 4 years (5.2% and 8.6%, respectively). Patients with more than 10 adenomas, those with a large, sessile adenoma that was removed piecemeal, and those suspected of having a familial colon cancer syndrome are generally excluded from these controlled trials and require earlier follow-up.

Although controlled trials have not compared surveillance intervals that are longer than 3 to 4 years, the low rate of colorectal cancer (<0.5%) after 5 to 6 years of follow-up in patients with only one or two small, tubular adenomas on initial colonoscopy18-20 suggests that a follow-up interval of 5 or more years is safe for these patients.

Nutritional Management and Chemoprevention

The mortality from colon cancer varies by a factor of more than 20 among countries,21 and the rate of colon cancer increases substantially among persons who emigrate from low-risk to high-risk countries within only one to two generations. These observations strongly suggest a role of environmental factors in the pathogenesis of colorectal adenomas and cancer. Case–control and cohort studies suggest that obesity, physical inactivity, excessive alcohol intake, smoking, and a diet that is high in fat or low in fruits, vegetables, or fiber are associated with an increased risk of adenomas and colorectal cancer.22 Although avoiding obesity, engaging in regular exercise, and consuming a healthful diet are prudent, randomized intervention trials suggest that modest dietary changes (10% lower fat, 25 to 75% higher fiber, and 50% more fruits and vegetables) in adults over a period of 3 to 8 years do not significantly reduce the risk of adenoma or colorectal cancer.23-25

Trials of calcium and nonsteroidal antiinflammatory drugs (NSAIDs) in patients with previous adenomas have shown that these agents appear to have modest efficacy in reducing the risk of metachronous adenomas. One trial26 showed that supplemental calcium carbonate (1200 mg of elemental calcium per day) reduced the rate of me-

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<th>Table 1. U.S. Consensus Guidelines for Colonoscopic Surveillance after Polypectomy.</th>
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<td><strong>Colonoscopic Findings</strong></td>
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<tr>
<td>Small, rectal, hyperplastic polyps</td>
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<td>1 or 2 Low-risk adenomas;‡</td>
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<td>3–10 Low-risk adenomas or any high-risk adenoma§</td>
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<td>&gt;10 Adenomas</td>
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<td>Inadequately removed adenomas</td>
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* More intensive surveillance is indicated when the patient’s family history is suggestive of hereditary nonpolyposis colorectal cancer, an adenomatous syndrome, or a hyperplastic polyposis syndrome.4,10
† Other screening options include fecal occult-blood testing every year, sigmoidoscopy every 5 years, both, or barium enema every 5 years.
‡ Low-risk adenomas are tubular adenomas that are smaller than 1 cm.
§ High-risk adenomas are large (<1 cm) or histologically advanced adenomas (tubulovillous or villous adenomas and those with high-grade dysplasia).
tachronous adenomas by 20%. Enthusiasm for calcium chemoprevention was tempered, however, by the report on the Women’s Health Initiative trial. This trial assessed the effects of supplemental calcium (1000 mg of elemental calcium) and vitamin D (400 IU) on the risk of colon cancer in more than 36,000 women at average risk for this disease. Although this trial was limited by a relatively low adherence rate (only about 70% of subjects took 50% or more of the study medication through the end of the study) and a high rate of use of nonstudy calcium supplements (almost 70% of all subjects took supplemental calcium), it did not show a protective effect of calcium and vitamin D supplementation on the incidence of colorectal cancer.

Data on NSAIDs are also mixed. Two recent articles reported that metachronous adenoma rates decreased by 35 to 45% among patients who received the selective cyclooxygenase 2 (COX-2) inhibitor celecoxib, but this benefit was outweighed by a rate of serious cardiovascular events that was 1.3 to 3.4 times that among patients who did not receive this drug. Aspirin also prevents metachronous adenomas, but concerns remain about the risks of bleeding and ulcers associated with aspirin, and there is uncertainty about the optimal dose. One trial showed that among patients who received aspirin at a dose of 325 mg per day, there was a 35% reduction in the rate of metachronous adenomas after 13 months, whereas another trial showed significant reductions in the rate of metachronous adenomas (20% for any adenoma and 40% for advanced adenomas) after 3 years at a dose of 80 mg per day but no effect at a dose of 325 mg per day. Chemoprevention of colorectal adenomas or cancer with the use of calcium or aspirin is not routinely recommended, but it may be considered in selected populations (e.g., patients at low risk for complications of these agents and those who would benefit from these agents for other reasons such as a cardiovascular benefit with aspirin and osteoporosis prevention with calcium).

GUIDELINES

Winawer et al. recently reported consensus recommendations for colonoscopic surveillance that have been endorsed by the American Cancer Society and the professional gastroenterology societies in the United States. The recommendations (Table 1) are based on the colonoscopic findings, with an interval between colonoscopies that ranges from 5 to 10 years among patients with low-risk adenomas and an interval of 3 years among those with high-risk adenomas. More intensive surveillance is advised if a strong family history of multiple adenomas or colorectal cancer suggests a familial cancer syndrome.

The consensus guidelines emphasize the critical importance of adequate bowel cleansing and of high-quality colonoscopy and polypectomy, and they acknowledge that discontinuing surveillance but continuing average-risk screening may be appropriate for subgroups of patients with low-risk adenomas. In practice, colonoscopic surveillance is often performed at intervals that are shorter than those recommended. More than 50% of gastroenterologists and colorectal surgeons surveyed from 1999 to 2000 reported that they routinely recommend colonoscopy at more frequent intervals than those suggested by the published guidelines. Excessive colonoscopic surveillance is expensive and diverts substantial endoscopic capacity away from screening efforts that could have a greater effect in preventing colorectal cancer.

AREAS OF UNCERTAINTY

CONTROVERSIES REGARDING SURVEILLANCE AFTER POLYPECTOMY

If adenomas are the major precursors of colorectal cancer, colonoscopic removal of adenomas should substantially decrease the risk of this cancer. Only indirect evidence is available, however, to provide support for this idea. The National Polyp Study and the Italian Multicenter Study Group reported marked reductions in the incidence of colorectal cancer among patients who underwent colonoscopic surveillance after the removal of colonic adenomas; the rates among these patients were 66 to 76% lower than registry-based estimates of rates in the general population and 88 to 90% lower than those among historical controls with adenomas. However, in other cohorts of patients who have undergone colonoscopic surveillance after polypectomy, the rates of colorectal cancer have been two to four times higher than those in the National Polyp Study and the Italian Multicenter Study Group cohorts. These higher rates, which are closer to those in the general population, translate into substantially lower es-
microsatellite instability.

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Data from controlled trials to guide decisions
about when surveillance should be discontinued
are also lacking. Since the risks associated with
cathartics, sedation, and colonoscopy are increased
among the elderly and patients with coexisting
disease, it would seem reasonable to discontinue
surveillance in patients with an estimated life expec-
tancy of less than 10 years. Similarly, the
benefit of continued surveillance after one or
more negative colonoscopies in patients who ini-
tially had an adenoma is uncertain.

Although the prevalence of adenomas and
colorectal cancer is higher among men than
among women and is higher among blacks than
among whites or Hispanic persons, the recom-
manded surveillance intervals do not vary accord-
ing to sex, race, or ethnic group. It is not known
whether other forms of imaging, such as com-
puted tomography, could replace surveillance
colonoscopy or whether stool analyses for blood
or mutations could complement it.

Although small, distal hyperplastic polyps are
not thought to progress to cancer, it has been
suggested that some large hyperplastic polyps
and related lesions (serrated adenomas) may do
so. These adenomas have a serrated luminal
border that is similar to that of hyperplastic
polyps, but they are also characterized by altered
patterns of proliferation and maturation. Recent
clinical and molecular analyses suggest that these
serrated polyps may be the precursors of a type
of sporadic colorectal cancer characterized by DNA
microsatellite instability. The natural history of
these large, hyperplastic polyps and serrated
adenomas is not well defined, and appropriate
surveillance intervals for patients with these les-
sions have not been established. Currently, follow-
up for such patients is often similar to that for
patients with nonserrated adenomas.

SURVEILLANCE FOR RELATIVES OF PATIENTS WITH ADENOMAS

First-degree relatives of patients with sporadic
colonic adenomas appear to have a modest in-
crease in the risk of colorectal cancer (by a factor
of 1.5 to 2), but data on which subgroups are at
highest risk are limited and inconsistent. The
National Polyp Study showed that the detection
of any adenoma in patients younger than 60 years
of age conferred an increased risk of colorectal
cancer (by a factor of 2.6) in their relatives as
compared with the risk among relatives of older
patients. Other studies found that the increased
risk was limited to relatives of patients with large
or histologically advanced adenomas, independent
of the patient’s age. Some have recommended
that the first-degree relatives of patients with
colonic adenomas that were detected before 60
years of age should begin colonoscopic screening
at 40 years of age or 10 years younger than the
age at diagnosis of the youngest person in the fam-
ily with an adenoma, but this recommenda-
tion has not been validated in controlled trials.
Clinicians should encourage patients with colonic
adenomas to tell their first-degree relatives about
their adenoma diagnosis and to advise their rela-
tives to talk with their own clinicians about
screening.

SUMMARY AND RECOMMENDATIONS

Colonic adenomas are the precursor lesions of
almost all colorectal cancers, but most adenomas
never progress to cancer; for those that do, pro-
gression is thought to take many years. In a pa-
tient found to have one or more adenomas on
colonoscopy, the usual practice is to remove all
adenomas completely, with confirmation based on
both endoscopic and pathological assessment.
Colonoscopic surveillance is recommended at
intervals that vary according to the number and types
of adenomas found and the presence or absence
of a family history of colorectal polyps and can-
cer, although some of these recommendations are
based on limited data. For the patient described in
the vignette, who had a large (greater than 1 cm),
histologically advanced (tubulovillous) adenoma,
initial colonoscopic surveillance would be recom-
manded in 3 years. He should be advised that
colonoscopic surveillance by an expert endosco-
pist, although not perfect, is the best way to de-
crease his subsequent risk of colon cancer. He
should encourage his first-degree relatives to dis-
cuss their family history and screening with their
clinicians. Chemoprevention with calcium or low-
dose aspirin could be considered for this patient,
but their use would not alter the colonoscopic surveillance intervals.

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REFERENCES