

## Guidelines for Surveillance Intervals after Polypectomy: Coping with the Evidence

Economically advanced countries are having trouble coping with the consequences of advancing technology. They are asking how much health care is the right amount. The factors influencing how often to do surveillance colonoscopy after polypectomy encapsulate many elements of this debate. Patients are afraid of harboring undetected cancer, and physicians are afraid of missing an opportunity to prevent cancer. The resources devoted to surveillance colonoscopy may limit access to health care for other valid indications (1–3) and leave less to spend on disease prevention, prenatal care, or elementary school education. Finally, the evidence provides little guidance on optimal surveillance frequency.

The surveillance guidelines are aimed at people who are at increased risk for advanced colorectal neoplasia (cancer and advanced adenomas) because of previously removed colorectal cancer or adenomas. On the basis of a person's findings at index colonoscopy, current guidelines stratify the risk for subsequent advanced neoplasia. They recommend colonoscopy 3 years after removal of an advanced adenoma (defined as size  $\geq 1$  cm or having villous histology or high-grade dysplasia) or 3 or more adenomas of any size and 5 to 10 years after removal of 1 or 2 nonadvanced (small tubular) adenomas (4).

These guidelines rest on a small body of evidence. Two clinical trials have compared different postpolypectomy surveillance intervals. The National Polyp Study (5), which compared 1-year and 3-year surveillance intervals, found no difference in risk for a subsequent large adenoma. The Funen Adenoma Follow-up Study (6), which compared 2-year and 4-year surveillance intervals, also found no difference in risk for new adenomas at 4 years (5.2% vs. 8.6%, which was not statistically significant). These 2 trials suggest that polyp surveillance before 3 years has little value. Case-control studies of screening sigmoidoscopy suggest that protection against cancer persists for at least 10 years and perhaps longer (7, 8). The most clinically relevant study measured cancer rates in 1618 persons who had rigid sigmoidoscopic removal of rectosigmoid adenomas but did not have the proximal colon examined for synchronous neoplasia (9). Among the 842 persons with an advanced rectosigmoid adenoma at baseline, the 14-year standardized incidence ratio for any colorectal cancer was 3.6 (95% CI, 2.4 to 5.0) overall and 6.6 (CI, 3.3 to 11.8) for patients with multiple rectosigmoid adenomas. The standardized incidence ratio in the remaining 776 persons, who had small rectosigmoid tubular adenomas, was 0.5 (CI, 0.1 to 1.3). Such is the slender body of evidence supporting current guidelines.

The key question is whether baseline colonoscopic findings, as defined by the guidelines, predict recurrent

advanced neoplasia. Lieberman and colleagues (10) recently reported the 5.5-year risk for advanced neoplasia in a cohort of 1171 veterans who underwent colonoscopy at baseline. The risk for advanced neoplasia was 2.4% in patients with no baseline adenomas, 4.6% in those with 1 or 2 small tubular adenomas, 11.9% in those with 3 or more small tubular adenomas, 15.5% in those with 1 large tubular adenoma, and 16% to 17% in those with villous adenomas or high-grade dysplasia. In this all-veteran population, more advanced adenomas at baseline predicted advanced neoplasia at follow-up, providing support for the surveillance guidelines. The next logical step is to ask about guideline performance in a more representative study population.

In this issue, Laiyemo and colleagues (11) use data from the PPT (Polyp Prevention Trial) to assess the clinical utility of the recommended surveillance intervals. The PPT was a 4-year randomized trial that demonstrated that diet did not affect adenoma recurrence rates. Among the entire cohort of 1905 patients, the overall risk for an advanced adenoma at 4 years was 6%. Among the 715 patients with baseline high-risk adenomas as defined by the guidelines (1 advanced adenoma or  $\geq 3$  adenomas of any size), the 4-year risk for an advanced adenoma was 9%. The remaining 1190 patients, all of whom had low-risk adenomas at baseline, had a 5% risk. The 4-year risk for advanced adenomas was higher for persons with an advanced adenoma at baseline (9% vs. 5% for nonadvanced), a villous polyp (12% vs. 5% for nonvillous), a large adenoma (8% vs. 6% for a small adenoma), or a high-grade dysplastic polyp (10% vs. 6% for low-grade dysplasia). All of these risk differences were statistically significant.

Exploratory analyses revealed 2 interesting predictors of advanced adenoma. First, patients with proximal adenomas had a higher risk than those with distal adenomas (9% vs. 5%). Patients with 2 nonadvanced adenomas were at higher risk (9%) if at least 1 was proximal, compared with a single adenoma anywhere or 2 distal adenomas. Second, patients with 3 or more nonadvanced adenomas had the same 6% risk for advanced adenoma as the entire cohort.

The most important contribution of Laiyemo and colleagues' study is that the surveillance guidelines' stratification into high-risk and low-risk adenoma does not discriminate well between those destined to have a subsequent advanced adenoma and those who will have no adenoma or a nonadvanced adenoma. These rates at 4 years are 9% and 5%, a statistically significant difference that may not be important to clinicians or patients.

A model that included all baseline adenoma characteristics reinforced the challenges faced in trying to predict a recurrence with an advanced adenoma. Only older age,

higher body mass index, proximal location, and villous histology were associated with increased risk, whereas use of nonsteroidal anti-inflammatory drugs reduced risk. These factors provided a moderate amount of discrimination (c-statistic of 0.71, meaning that the model has a 71% probability of identifying a person in whom an advanced adenoma will recur as being at higher risk than someone who will not develop an advanced adenoma). A c-statistic of 0.50 means no discrimination. This finding raises concern about whether adenoma recurrence can be predicted with sufficient accuracy to satisfy clinicians and patients.

What prevalence of advanced adenoma is low enough to warrant a longer surveillance interval? This key question has no satisfactory answer. The prevalence threshold should depend on the natural history of the advanced adenoma. Although the advanced adenoma is the driver of polyp surveillance policy, we know far too little about its natural history. The sparse, limited literature suggests that most adenomas will not progress to cancer (12, 13). In a longitudinal study of 226 patients with large polyps that were identified and followed by serial barium enemas, the rate of progression to cancer was about 1% per year (14). We need higher-quality natural history data; surveillance studies using computed tomography of the colon may improve our understanding of the relationship between the size of a polyp when first detected and its subsequent rates of growth and malignant transformation.

Does Laiyemo and colleagues' study provide promising hints for better guidelines? Our answer is a cautious yes. The exploratory findings suggest that proximal location may be a useful predictor. In addition, although persons with 3 or more adenomas of any size at baseline currently qualify for surveillance at 3 years, the 4-year risk for advanced adenoma is just 6% if none are advanced. Both findings provide direction for further tailoring of the surveillance guidelines, but they require validation on independent patient samples.

In exploratory analyses, older age, higher body mass index, and nonsteroidal anti-inflammatory drug use were associated with subsequent risk for advanced adenoma, which suggests that guideline developers should consider clinical factors (such as cigarette smoking, waist circumference, and measures of insulin resistance), as well as polyp characteristics. We suggest that genetic mutations in polyps—or lack of them—may have prognostic value. In Laiyemo and colleagues' study, a villous polyp at baseline was the only independent endoscopic predictor of recurrence. Villous polyps are more likely to express mutations of both Ki-ras and p53, 2 mutations in the adenoma-to-carcinoma sequence (15–17).

If we can identify and validate additional prognostic factors, how can we best use them to tailor colonoscopic surveillance? We will need a clinical prediction rule that considers all independent predictors, calculates an absolute risk for recurrence, and—we hope—identifies a large subgroup with a less than 1% to 2% probability of recurrence

with an advanced adenoma. This requires a large cohort study, with collection of all relevant demographic, clinical, endoscopic, histologic, and genetic factors at baseline and complete colonoscopic follow-up. Such a study would be costly and logistically challenging, but the immense societal costs of surveillance colonoscopy should give it high priority for public funding.

Until we improve our ability to predict high-risk recurrent adenomas, how should Laiyemo and colleagues' findings affect current management of persons with adenomatous polyps? We should be partially reassured that the guidelines do discriminate somewhat, albeit far from perfectly. We also should think about how to respond to patients who believe that even a 5% risk for a recurrent advanced adenoma is too high to wait longer for surveillance colonoscopy. We need to provide them with better data about the probability of malignant transformation at the recommended surveillance interval. Until these quantitative issues are addressed, our decision making should start with published recurrence rates (10, 11) and then be tailored further by taking into account individual patient features, such as age, nonsteroidal anti-inflammatory drug use, life expectancy, comorbid conditions, and preferences.

*Thomas F. Imperiale, MD*  
Indiana University  
Indianapolis, IN 46202

*Harold C. Sox, MD*  
Editor

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Thomas F. Imperiale, MD, Indiana University, Regenstrief Institute, 1050 Wishard Boulevard, Indianapolis, IN 46202.

Current author addresses are available at [www.annals.org](http://www.annals.org).

*Ann Intern Med.* 2008;148:477-479.

## References

1. Boolchand V, Olds G, Singh J, Singh P, Chak A, Cooper GS. Colorectal screening after polypectomy: a national survey study of primary care physicians. *Ann Intern Med.* 2006;145:654-9. [PMID: 17088578]
2. Mysliwiec PA, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. *Ann Intern Med.* 2004;141:264-71. [PMID: 15313742]
3. Rex DK, Lieberman DA. Feasibility of colonoscopy screening: discussion of issues and recommendations regarding implementation [Editorial]. *Gastrointest Endosc.* 2001;54:662-7. [PMID: 11677497]
4. Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, et al. US Multi-Society Task Force on Colorectal Cancer. 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. [PMID: 16697750]
5. Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med.* 1993;328:901-6. [PMID: 8446136]

6. Jørgensen OD, Kronborg O, Fenger C. A randomized surveillance study of patients with pedunculated and small sessile tubular and tubulovillous adenomas. The Funen Adenoma Follow-up Study. *Scand J Gastroenterol.* 1995;30:686-92. [PMID: 7481533]
7. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst.* 1992;84:1572-5. [PMID: 1404450]
8. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med.* 1992;326:653-7. [PMID: 1736103]
9. 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. [PMID: 1736104]
10. Lieberman DA, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology.* 2007;133:1077-85. [PMID: 17698067]
11. Laiyemo AO, Murphy G, Albert PS, Sansbury LB, Wang Z, Cross AJ, et al. Postpolypectomy surveillance guidelines: predictive accuracy for advanced adenoma at 4 years. *Ann Intern Med.* 2008;148:419-26.
12. Eide TJ. Risk of colorectal cancer in adenoma-bearing individuals within a defined population. *Int J Cancer.* 1986;38:173-6. [PMID: 3733258]
13. Loeve F, Boer R, Zauber AG, Van Ballegooijen M, Van Oortmarssen GJ, Winawer SJ, et al. National Polyp Study data: evidence for regression of adenomas. *Int J Cancer.* 2004;111:633-9. [PMID: 15239144]
14. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology.* 1987;93:1009-13. [PMID: 3653628]
15. Barry EL, Baron JA, Grau MV, Wallace K, Haile RW. K-ras mutations in incident sporadic colorectal adenomas. *Cancer.* 2006;106:1036-40. [PMID: 16456810]
16. Einspahr JG, Martinez ME, Jiang R, Hsu CH, Rashid A, Bhattacharaya AK, et al. Associations of Ki-ras proto-oncogene mutation and p53 gene overexpression in sporadic colorectal adenomas with demographic and clinicopathologic characteristics. *Cancer Epidemiol Biomarkers Prev.* 2006;15:1443-50. [PMID: 16896030]
17. Maltzman T, Knoll K, Martinez ME, Byers T, Stevens BR, Marshall JR, et al. Ki-ras proto-oncogene mutations in sporadic colorectal adenomas: relationship to histologic and clinical characteristics. *Gastroenterology.* 2001;121:302-9. [PMID: 11487539]

#### INFORMATION FOR AUTHORS

The *Annals* Information for Authors section is available at [www.annals.org](http://www.annals.org). All manuscripts must be submitted electronically using the manuscript submission option under the Information for Authors/Reviewers item at [www.annals.org](http://www.annals.org).

**Current Author Addresses:** Dr. Imperiale: Indiana University, Regen-  
strief Institute, 1050 Wishard Boulevard, Indianapolis, IN 46202.  
Dr. Sox: American College of Physicians, 190 N. Independence Mall  
West, Philadelphia, PA 19106-1572.