Colorectal Adenomas

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SINCE THE LAST REVIEW OF COLORECTAL ADENOMAS IN THE JOURNAL,¹ A wealth of new data has emerged that is improving our understanding of their clinical significance. In the past 10 years, several large studies, performed predominantly in the United States, have evaluated persons at average risk for colorectal adenomas. The new evidence that these studies have provided regarding the biology of adenomas, their prevalence and incidence, the relevance of risk profiles, and controversies in screening and surveillance is germane to clinical decisions and identifies potential targets for the improved management of these important premalignant lesions.

ADENOMAS AND SESSILE SERRATED POLyps

In 2016, it is estimated that 134,000 persons in the United States will be found to have colorectal cancer and that 49,000 will die from it.² Approximately 15% of persons with colon cancer are younger than 50 years of age.³ Adenomas of the colon are estimated to be present in 20 to 53% of the U.S. population older than 50 years of age, with a prevalence of 3.4 to 7.6% for advanced histopathological features and 0.2 to 0.6% for adenocarcinomas.³⁻¹⁰ Adults in the United States have a lifetime risk of approximately 5% for adenocarcinoma.³⁻¹⁰ Adenomas are categorized as either conventional adenomas or sessile serrated polyps and are recognized as precursors in the majority of cases of colorectal cancer.¹⁰ In persons younger than 60 years of age, slightly more than half of adenomas are located in the distal colon; in persons 60 years of age or older, a slightly higher percentage of adenomas are found in the proximal colon.⁴ Adenomas may be flat, sessile, subpedunculated (having a very short stalk, or peduncle), or pedunculated.¹⁰⁻¹¹

Sequencing studies have traced the evolution of most conventional adenomas and sessile serrated polyps into carcinomas through one of two major pathways: the chromosomal instability pathway or the microsatellite instability pathway. In both pathways, approximately 25 genes that are commonly affected by somatic mutations become the major drivers of most cancers. These genes include APC and TP53, the most commonly mutated tumor-suppressor genes, and KRAS, PI3KCA, BRAF, and NRAS, the most commonly mutated oncogenes. Approximately 85% of colorectal cancers are thought to evolve from conventional adenomas through a median of approximately 60 mutations per tumor that go beyond the genes that are major drivers; this process is referred to as the adenoma-to-carcinoma sequence. A minority of colorectal cancers (approximately 15%) develop through an alternative hypermutation pathway, with a median of 700 subtle mutations that are implicated in altering protein products and that result in high-frequency microsatellite instability. Molecular alterations include hypermethylation of CpG islands that leads to the CpG island methylator phenotype (CIMP), which, in association with BRAF mutations and dysfunction owing to hypermethylation of the MLH1 DNA
mismatch-repair gene, results in microsatellite instability, rendering the epithelial cells premalignant. This sequence of events is termed the serrated neoplasia pathway.\(^{10,12-15}\) That an extensive succession of multiple somatic mutations confers a growth advantage on a mutant cell is a putative model of cancer that implicates chance as well as causality.\(^{16}\)

Sessile serrated polyps are heterogeneous lesions that differ from conventional adenomas.\(^ {10,17-20}\) They are characterized by exaggerated, saw-toothed, luminal serrations with dilatation, branching, and distortion in the bases of the colonic crypts and are usually found in the proximal colon. The most serious subtypes are sessile serrated polyps and traditional serrated adenomas, although the most common type is a benign hyperplastic polyp.\(^ {10,20}\) The microscopic features are subject to interpretation, and the degree of variability of classification among pathologists is high.\(^ {21}\) The lesions are recognized endoscopically as flat and oblong; often they are covered with mucus and are thus difficult to see (Fig. 1).

The factors that increase the risk of malignant features in sessile serrated polyps are similar to those in conventional adenomas. These factors include a large size of the polyp and, in the patient, older age, a history of smoking, a family history of cancer, and nonuse of nonsteroidal antiinflammatory drugs (NSAIDs). There is a slightly higher rate of sessile serrated polyps, as well as some evidence of more aggressive biologic features, among women than among men.\(^ {13,17,20}\)

Studies of end-stage colon cancer have shown that malignant conditions that are identified within the first 5 years after colonoscopy are twice as likely to be characterized by CIMP and microsatellite instability as those identified after 5 years.\(^ {17,19}\) In prevalence studies, sessile serrated polyps are reported in 1 to 18% of patients (average, approximately 6 to 12%).\(^ {15,17,18,22}\) Their true prevalence has not been established, and more study is needed to determine their prevalence, relevance, and natural history.

**Clinical Significance of Adenoma Size**

Size has long been recognized as one of the most important markers of the potential of the adenoma to contain cancer.\(^ {10,14,23}\) Large clinical studies involving patients with colonic adenomas have consistently confirmed the relationship of size to the likelihood of cancer.\(^ {6,8}\) Size is used to classify adenomas into three classes: diminutive (1 to 5 mm in diameter), small (6 to 9 mm), and large (≥10 mm). By definition, adenomas are considered advanced on the basis of size alone if they are 10 mm or more in diameter, and adenomas that are smaller than 1 cm in diameter are considered to be advanced if they contain at least 25% villous features, high-grade dysplasia, or carcinoma. Adenomas with 25 to 75% villous features are considered to be tubulovillous, and those with villous architecture of more than 75% are classified as villous adenomas (Fig. 2).\(^ {10}\)

In a study involving 13,992 participants who underwent screening colonoscopy, 5891 nontumor polyps were removed; of these, 3469 (59.0%) were adenomatous and 920 (15.6%) were advanced. Diminutive polyps made up 64% of all polyps, of which 1.1% were advanced adenomas, and included one cancer. Small polyps made up...
20% of all polyps, of which 1.3% were advanced adenomas, and included two cancers. Large polyps accounted for the remaining 16% of all polyps, of which 13.2% were adenomas; all these polyps were considered to be advanced because of their size, and one third had additional advanced histopathological features, including 25 cancers.8 Thus, polyps that were less than 1 cm in diameter represented 84% of all colon polyps removed and 15% of all advanced adenomas; they accounted for 3 of the 74 cancers found in the 13,992 people in the final study group (0.02% of participants). As polyp size increased to 10 mm or more, the risk of advanced histopathological features and cancer increased proportionally. In this study and three others,7,24,25 27 to 47% of all the subcentimeter polyps that were removed were nonadenomatous.

Radiologists conducting examinations with diagnostic computed tomographic (CT) colonography do not customarily report lesions that are less than 6 mm in diameter and consider lesions that are between 6 and 9 mm in diameter to be sufficiently benign such that either colonoscopy with immediate removal or follow-up CT colonography in 3 years is a reasonable option.25-27 In a study of combined CT colonography and colonoscopy involving 6283 patients, advanced adenomas of 6 to 9 mm in diameter, with no cancers, were reported in 0.2% of patients.26 Follow-up testing with use of CT colonography offers a unique opportunity for the study of the volumetric growth rates and natural history of these small and predominantly benign adenomas.28

The evidence that more than 99% of diminutive and small lesions are benign has led investigators to consider alternatives to submitting all polyps for histopathological analysis. These strategies include resecting and discarding diminutive polyps or making an endoscopic diagnosis of “unlikely to become cancerous” and leaving them in place;29,30 using data on polyps larger than 9 mm as a surrogate marker for advanced adenomas to the exclusion of subcentimeter polyps, which have advanced histopathological features in less than 3%;48 and recommending wider use of noninvasive screening approaches, particularly for persons in whom the risk of
advanced pathologic features is considered low.\textsuperscript{32,33} The approach of documenting diminutive polyps with a high-resolution photograph, followed by a resect-and-discard or diagnose-and-leave strategy, deserves further study.\textsuperscript{29,30}

### PATHOLOGICAL FEATURES AND THEIR EFFECT ON SURVEILLANCE

Histopathological examination of colon polyps defines their neoplastic nature and potential and is the best measure of their degree of severity; diminutive and small adenomas are considered to be advanced if they contain at least 25\% villous features, high-grade dysplasia, or carcinoma.\textsuperscript{10,14,23} Since as many as 1 in 10 of diminutive-to-small lesions contain advanced histopathological features, they make up the largest group of advanced adenomas (70 to 83\%), even though they are the smallest in size and contain the fewest cancers.\textsuperscript{7,8,25} When adenocarcinoma is found in an adenoma, the pathological examination emphasizes the distance between the cancer and the margins of the polyp, the size of the lesion, the degree of differentiation of the tumor, and the degree of lymphatic and vascular invasion.\textsuperscript{10,14,23} Guidelines for surveillance after the removal of adenomas recommend a follow-up colonoscopy at 3 years if any index adenoma (adenoma observed during the initial examination) is advanced, defined as 10 mm or more in diameter, if 25\% or more of an adenoma of any size has villous features or high-grade dysplasia, or if 3 to 10 adenomas of any size are present (Table 1).\textsuperscript{34}

Surveillance studies from a pooled analysis of data from 9167 patients and from follow-up studies of the incidence of advanced adenomas provide data that may be summarized as follows. First, after an advanced adenoma is found at baseline, the overall incidence of advanced ade-
nomas within 4 years averages 11%. Second, the rate of advanced adenomas is highest at 24% for index adenomas (those ≥20 mm in diameter), is next highest at 19% if there are five or more index adenomas of any size at baseline, and becomes progressively lower with less advanced neoplasia at baseline. Third, the rates of discovery of cancer at the time of a follow-up surveillance colonoscopy range from 0.3 to 0.9%, with an average of 0.6% — slightly higher than the rate at the initial screening. Fourth, after a negative surveillance examination, subsequent examinations yield progressively fewer advanced adenomas.35-38

These results can be compared with those of a study involving 17,525 patients who underwent colonoscopy and were then reexamined 1 to 5 years and 5 to 10 years later.31 Among the 15,719 patients who had negative findings on an initial uncompromised colonoscopy (defined as a complete examination with an adequate bowel preparation and no lesions found) and who were reexamined after 1 to 5 years and 5 to 10 years, the reported incidence of large polyps (which are surrogate markers for advanced adenomas) was 3.1% among the patients examined within 1 to 5 years and 3.7% among those examined within 5 to 10 years. Overall, 501 large polyps (>9 mm in diameter) were identified (incidence, 3.2%), as well as one established cancer (incidence, 0.006%). Among the 1806 patients (10.3%) who had a compromised initial colonoscopy, primarily because of inadequate bowel preparation or an incomplete examination, and underwent a repeat colonoscopy within 1 year, 117 patients (6.5%) had polyps that were larger than 9 mm in diameter and 2 (0.11%) had an established cancer.31 The authors concluded that repeated colonoscopy within 10 years after an uncompromised baseline examination is of little benefit to patients. Other follow-up studies that have been conducted after negative initial colonoscopic examinations have yielded similar favorable results.6,19,39-41

**FACTORS AFFECTING RISK**

**AGE**

Older age remains closely correlated with the incidence of both adenomas and colorectal cancer.6,10,19,27,42-44 Although the number of patients older than 50 years of age in whom colorectal cancer is diagnosed began to decline 30 years ago, the rate of decline has accelerated in the past few years; a decrease of 2.8% per year from 2003 to 2012 was noted in both men and women in almost all major racial and ethnic groups.2,3 Meanwhile, the percentage of patients with newly diagnosed colorectal cancer who are younger than 50 years of age has increased to 15%.45,46 A study involving 3558 persons from 20 to 89 years of age who underwent consecutive autopsies between 1985 and 2004 showed that the prevalence of adenomas in this deceased population was 1.72% in the third decade of life and increased to 3.59% in the fifth decade. The rate then increased sharply after 50 years of age, which conforms to the customary assumption that the rise in the prevalence of adenomas and carcinomas increases dramatically after 50 years of age.47

In screening studies that have evaluated persons who were 40 to 49 years of age, 2.0 to 5.6% are found to have an advanced adenoma or large polyp. The largest such study reported an incidence of large polyps of at least 5% among men who were white, black, or Hispanic and among black women.4,48 There is no consensus that persons in this age range who are at average risk should be screened. However, clinicians are advised to recognize the rising prevalence of colorectal cancer in this age group and to be prepared to pursue any suspicious symptoms, as well as to be aware of the possibility of a hereditary disorder.15,49

**SEX, RACE, AND ETHNIC BACKGROUND**

On the basis of data representing 327,785 adults who were 40 years of age or older and who had an average risk of colorectal cancer, the risk factors for advanced adenomas can be defined more clearly.4 Age remains critical, since the risk of large polyps and advanced adenomas increases progressively with age among both men and women, beginning to accelerate at 50 years of age. Blacks have a higher risk of advanced adenomas than whites from 50 to 65 years of age, and Hispanics have a lower risk than non-Hispanics from 50 to 80 years of age. The prevalence of large polyps among white men who are 50 to 54 years old was 6.2%, and it was similar among black men of the same age, black women and Hispanic men who were 55 to 59 years of age, white women who were 65 to 69 years of
age, and Hispanic women who were 70 to 74 years of age. Related studies have shown similar results.\textsuperscript{19,27,43} Age, sex, race, and ethnic background clearly define the sharpest boundaries among persons in different classifications and provide demarcations for the assignment of risk.

**BODY-MASS INDEX, LIFESTYLE, DIET, AND MEDICATIONS**

The search for additional markers of risk has involved evaluation of risk factors including the medical history of first-degree relatives with colorectal cancer, personal history of smoking and alcohol consumption, presence of obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], $\geq 30$), quantity of red meat in the diet, and previous detection of polyps, as well as protective factors including the consumption of fruits and vegetables, regular physical exercise, use of hormone-replacement therapy, current or past regular use of NSAIDs (at least two times per week for $\geq 1$ year), and favorable prior screening examinations.\textsuperscript{40} A study involving 4143 patients who were scheduled for an initial colonoscopy validated a risk-assessment score that was based on age, sex, family history, smoking history, and waist circumference and that was used to assign some patients to undergo less invasive tests, such as flexible sigmoidoscopy and fecal occult-blood testing.\textsuperscript{51}

Among attempts to identify medications that can prevent or forestall colon cancer, the most promising has been the regular use of aspirin, which inhibits cyclooxygenase-2 and induces apoptosis in adenomatous tissue. However, this effect has required long-term use of aspirin, for 10 years or longer, and the side effect of gastrointestinal bleeding has had a dampening effect on its implementation.\textsuperscript{52} In 2015, the U.S. Preventive Services Task Force published a draft recommendation statement that aspirin therapy is a viable approach to the prevention of colorectal cancer, as well as cardiovascular disease. These guidelines apply to persons who have no increased risk of bleeding, have a life expectancy of at least 10 years, and are willing to take a low-dose aspirin (81 mg) once a day. The greatest benefit is expected in persons 50 to 59 years of age (a grade B recommendation) and in persons 60 to 69 years of age (a grade C recommendation).\textsuperscript{53,54} The American Cancer Society recognizes this apparent advantage as well.\textsuperscript{3} Reviews have noted that the effect of estrogen and progesteron, calcium, vitamin D, folate, and statins in preventing adenomas is limited to nonexistent.\textsuperscript{35-57}

**GUIDELINES AND SCREENING**

Screening for adenomas and early-stage colorectal cancer is endorsed by the U.S. Preventive Services Task Force, the American Cancer Society, the American College of Physicians, and other authoritative organizations.\textsuperscript{2,3,58,59} The decline in mortality from colorectal cancer since 1975 has been attributed primarily to three factors: screening (responsible for 53% of the decline); improved lifestyle, including better diet and exercise, use of hormone-replacement therapy and NSAIDs, and less smoking and alcohol consumption (responsible for 35%); and better treatment (responsible for 12%).\textsuperscript{2,3} Guidelines in the United States recommend that screening for colon adenomas and carcinomas be initiated at the age of 50 years for men and women who are at average risk, with follow-up at specified intervals according to whether the initial screening identifies an absence of neoplasia, advanced neoplasia, or cancer (Table 2). Screening methods include the fecal occult-blood test, stool DNA test, sigmoidoscopy, barium enema with the use of air contrast, CT colonography, and optical colonoscopy. In the U.S. population, 59% of persons 50 years of age or older are current with recommended screening, which indicates a modest rise since 2000 that is due exclusively to colonoscopy testing.

There are two types of high-sensitivity fecal occult-blood tests: guaiac-based and immunochromical (also called the fecal immunochemical test [FIT]). The guaiac-based test measures blood from any source, including dietary meat. FIT uses an antibody specific to human hemoglobin and can be calibrated quantitatively but is more expensive than the guaiac-based fecal occult-blood test and has not been standardized (e.g., the test measures nanograms of hemoglobin per milliliter of buffer, and the result is converted to micrograms of hemoglobin per gram of stool; different brands of the test may use different quantities of stool or buffer for testing; thus, a positive report may reflect a wide difference in the concentration of hemoglobin per gram of stool).\textsuperscript{60} Randomized trials with the use of the
guaiac-based fecal occult-blood test have shown its efficacy in detecting cancer and reducing mortality from colon cancer by 15 to 33% in the short term, but its use has not affected all-cause mortality in the long term.61,62

Multitarget stool DNA testing for mutant KRAS and for aberrant methylation in NDRG4 and BMP3 has been shown to have a 92% sensitivity for detecting colorectal cancer, but it is inferior (sensitivity, 42%) for detecting advanced adenomas. These results were compared with concurrent detection with use of the FIT, which had a sensitivity of 74% for colorectal cancer and 24% for advanced adenomas. However, the spec-
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The specificity of the FIT for nonadvanced or negative findings (96.4%) was superior to that of the stool DNA test (89.8%). The authors indicated that the role of stool DNA testing in screening for colorectal cancer requires that additional factors be assessed, including performance characteristics of alternative tests, testing intervals, complications, costs, acceptance by the patient of this type of stool test (e.g., DNA analysis), and adherence by the patient to the stool-collection and submission process. The FIT and stool DNA tests are moderately sensitive for cancer but much less sensitive than colonoscopy for precancerous adenomas (Table 3). Randomized trials of assessment by means of flexible sigmoidoscopy have shown reductions in the incidence of and mortality from colorectal cancer of the distal colon by 21% and 26%, respectively, but no evidence of such reductions in the proximal colon.

Screening with CT colonography evaluates the entire colon and is free from complications from bleeding or perforation. The disadvantages of this method include the inability to remove an identified polyp, which may require a second bowel preparation and procedure, and the detection of incidental extracolonic lesions, which may lead to unnecessary risks and costs. The procedure is equivalent to optical colonoscopy for the detection of polyps larger than 5 mm in diameter. In view of the low rate of advanced histopathological findings among polyps smaller than 10 mm in diameter, patients are often followed up with a further examination after 3 years. A decision analysis suggests that this approach may result in more cancers and deaths than would occur with immediate removal. Barium enema with the use of air contrast has been replaced for the most part with the more sensitive optical colonoscopy and CT colonography, but it remains an option when these tests are unavailable.

Optical colonoscopy makes possible the diagnosis of cancer and the removal of precancerous adenomas. Although randomized trials have not been conducted, observational and case-control studies strongly suggest that optical screening by means of colonoscopy can reduce the incidence of and mortality from distal and proximal colorectal cancers. These results are more robust for distal than proximal colorectal cancer, and this effect on incidence and mortality can last up to 15 years. Optical colonoscopy is associated with a 2 to 9% risk of an interval cancer (one that is detected between scheduled colonoscopies) and a risk of major complications. The rate of bleeding is 0.1 to 0.6% and the rate of perforation is 0.1 to 0.3%; these risks increase with age. The majority of cancers that are not detected during colonoscopy are in the proximal colon. The appearance of interval cancers is often due to the progression of adenomas or adenocarcinomas that were present at the most recent examination but were not detected or were incompletely removed, inadequate time devoted to the

Table 3. Rates of Detection of Advanced Adenomas and Colorectal Cancer by FIT and Stool DNA Testing, as Compared with Optical Colonoscopy.*

| Trial and Test        | Participants | Advanced Adenomas Detected | P Value | Cancers Detected | P Value |
|-----------------------|--------------|----------------------------|---------|-----------------|---------|
|                       | no.   | no. (%) |                     |         | no. (%) |         |
| Quintero et al.61     | 5,059  | 493 (9.7) | 27 (0.5) | <0.001 | 36 (0.3) | 0.09   |
| Optical colonoscopy   | 10,507 | 252 (2.4) | 65 (0.7) | <0.001 | 60 (0.6) | 0.13   |
| FIT                   | 9,989  | 180 (1.8) | 48 (0.5) | <0.001 | 48 (0.5) | 0.13   |
| Stool DNA 9,989       | 321 (3.2) | 48 (0.5) | 0.13   |

* The studies were selected on the basis of their large numbers of participants, their randomized, controlled designs, and the comparison of the results of FIT or stool DNA testing with those of optical colonoscopy. FIT was positive in the study by Quintero et al. at the level of 75 ng or more of hemoglobin per milliliter of buffer and in the study by Imperiale et al. at the level of more than 1000 ng of hemoglobin per milliliter of buffer. All P values were determined by means of Pearson’s chi-square analyses.
examination, or the presence of biologically aggressive tumors with a rapid growth rate.\textsuperscript{6,15,71} Multiple studies show a correlation among interval cancers, examinations lasting less than 6 to 8 minutes, and rates of detection of adenomas below 20\%.\textsuperscript{6,19,72,73,75} Although these shortcomings are being evaluated\textsuperscript{71,75,76} and should be correctable, it remains to be proven that the rate of interval cancers will fall.

An age of 76 years or older and the presence of serious coexisting conditions with a life expectancy of less than 10 years are considered to be contraindications to screening and surveillance.\textsuperscript{71,77,78} Persons between 76 and 85 years of age who have never undergone screening are exceptions if they are in satisfactory health. Although the risk of colorectal cancer continues with advancing age, the risks of complications of colonoscopy also increase with age. Screening is not appropriate after 85 years of age or at any stage at which risk exceeds benefit.

However, studies indicate that these guidelines are not closely observed. An analysis of Medicare claims data for 57,597 beneficiaries who were 66 years of age or older and who underwent at least one colonoscopy showed that nearly 25\% had an estimated life expectancy of less than 10 years.\textsuperscript{79} Similarly, evaluation of the care received by 3627 patients enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial and by 1455 patients in the Veterans Affairs health care system who underwent colonoscopic reexamination indicated nonadherence to guidelines among patients at low risk and underuse of colonoscopies among patients at high risk.\textsuperscript{80,81} These findings indicate that improvement in the selection of persons for surveillance and screening is eminently feasible.

CONCLUSIONS

Data reported during the previous decade are improving our understanding of the natural history and management of colonic adenomas and have identified strengths and exposed weaknesses in the general approach to their detection and removal. Colorectal cancers evolve by the malignant transformation of conventional adenomas and sessile serrated polyps or adenomas. Studies of the prevalence of adenomas have shown that they are identified in as many as 50\% of asymptomatic persons who undergo screening by means of colonoscopy or CT colonography; 3.4 to 7.6\% of these adenomas are advanced and 0.2 to 0.6\% are cancerous. The size of the adenoma correlates most closely with the likelihood of advanced pathologic findings and is significantly related to older age, male sex, and the predictability of metachronous advanced adenomas.

Multiple screening tests are available, but none is perfect. Colonoscopy is widely used for the detection and removal of adenomas and is effective in reducing the incidence of and mortality from proximal and distal colon cancer. Studies of the importance of sex, race, ethnic background, and age suggest that improved stratification and the definition of low-risk profiles could lead to wider use of less invasive screening techniques. Subcentimeter adenomas are the least serious type and could be a target in efforts to reduce the volume and costs of histopathological examinations.

Studies of the incidence of adenomas within 5 years after the removal of an advanced adenoma show that such adenomas are identified, on average, in 11\% of patients and cancer is identified in 0.6\%; these rates can be compared with rates of 3.1\% and 0.014\%, respectively, among persons 1 to 5 years after an uncompromised index colonoscopy with negative findings. These yields confirm that large adenomas and multiple adenomas are the most serious risk factors for the subsequent development of metachronous advanced adenomas. After an initial uncompromised colonoscopy with negative findings, the rates of detection of advanced adenomas are uniformly low, with correspondingly low rates of cancer.

Enhanced strategies are being used to reduce the rate of advanced adenomas and carcinomas in the interval between examinations, but proof of the success of these modifications is needed. Approaches to the prevention of adenomas with diet, lifestyle changes, and medications have been slow to evolve, since no clearly effective measures have been identified. Diets that are low in fat, regular physical exercise, maintenance of an appropriate body-mass index, and avoidance of smoking remain critical to everyone’s health. As we move into an era in which increased benefit will be required from health care–related expenditures, improvements in risk stratification, adenoma detection, surveillance intervals, and uptake of screening should hasten our journey on the pathway to prevention of colorectal cancer as a common disease.
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43. Brenner H, Chang-Claude J, Jansen L, I thank Dr. Emma Du for assistance with preparation of the figures and Mr. Clarence Sandbakken for research assistance.

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