

THE ADVANCED ADENOMA AS THE PRIMARY TARGET OF SCREENING

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The adenoma-carcinoma sequence is now well established as the major pathway for the development of colorectal cancer.³⁸ The natural history of this sequence is believed to evolve over a period of 10 to 20 years on average except in hereditary nonpolyposis colorectal cancer, where an accelerated course may occur.³⁶ As a result of screening and surveillance studies conducted over the last quarter century there is a better understanding of the pathologic stages of this neoplastic progression. Screening provides an opportunity to intervene in this process to detect cancer and precursor lesions. Fecal occult blood testing has been shown to reduce colorectal cancer mortality primarily by detecting cancers at an earlier curable stage (Table 1).^{12, 15, 21, 22} Screening, however, also provides an opportunity for the detection of adenomas with the potential for preventing colorectal cancer.⁴⁰ Adenomas, rather than cancer, are the far more common neoplastic outcomes in screening trials (Table 2).^{3, 12, 18} Because of the understanding of the adenoma-carcinoma sequence there is the opportunity to prevent not only death from colorectal cancer but also the development of colorectal cancer and the associated treatment costs.^{11, 17, 20, 25, 31, 37}

The adenoma should be the major target of screening because detection and removal of adenomas provide an opportunity to prevent colorectal cancer. Furthermore, the adenoma should also be the end point for evaluating new screening technology and chemoprevention agents, and for evaluating nutrition interventions. The advanced adenoma, however,

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Table 1. MORTALITY REDUCTION FROM RANDOMIZED CONTROLLED TRIALS OF THE FECAL OCCULT BLOOD TEST

Author	Year Published	Location	Number Enrolled	Screening Interval	Duration of Follow-up (y)	Mortality Reduction (%)
Mandel et al ^{21, 22}	1993 1999	Minnesota	46,551	Annual* Biennial*	13 18	33 21
Hardcastle et al ¹²	1996	United Kingdom	152,850	Biennial	7.8	15
Kronborg et al ¹⁵	1996	Denmark	61,933	Biennial	10	18

*Rehydrated slides primarily used.

rather than any adenoma, is the more valid surrogate biologic indicator of future colorectal cancer risk, as is discussed next.

THE ADENOMA-CARCINOMA SEQUENCE

The relationship of colorectal cancer to a premalignant neoplastic lesion was demonstrated in cross-sectional studies by Lockhart-Mummery and Dukes¹⁹ at St. Marks Hospital in the United Kingdom and reported in the 1920s. This relationship was further delineated by Muto et al,²⁴ and later termed the *polyp-cancer sequence* by Morson.²³ This concept was challenged by Castelman and Krikstein⁸ because they failed to find adenomatous tissue associated with many colorectal cancers. It was subsequently observed that the reason for this was that as cancers advanced pathologically they destroyed the adenoma and no residual adenomatous tissue would be found in the specimen. A prospective study was conducted by Stryker et al³⁴ at the Mayo Clinic that clearly showed longitudinally the evolution of adenomas into colorectal cancer. Patients (N = 226) who had large (> 1 cm) polyps detected on barium enema but refused polyp removal by laparotomy with accompanying multiple colotomies were

Table 2. PREVALENCE OF ADENOMAS AND COLORECTAL CANCER IN SCREENING PROGRAMS: FECAL OCCULT BLOOD TEST, FLEXIBLE SIGMOIDOSCOPY, AND COLONOSCOPY

Study	Author	Number Screened	Adenomas N (%)	Colorectal Cancers N (%)
U.K.FOBT ¹²	Hardcastle et al	44,838	357 (0.8)	104 (0.2)
U.K.Once Offered Flexible Sigmoidoscopy ³	Atkin et al	40,675	4881* (12)	138 (0.3)
Veterans Administration Screening Colonoscopy Trial ¹⁸	Lieberman et al	3,196	1090 (35)	30 (1)

*Number derived from published percentage.

followed for up to 20 years. Colonoscopy had not yet been introduced. The incidence of colorectal cancer increased in direct relationship to time of follow-up with a cumulative incidence of colorectal cancer at the same site as the index polyp of 2.5% at 5 years, 8% at 10 years, and 24% at 20 years. The cumulative incidence at any site within the colon was 4% at 5 years, 14% at 10 years, and 35% at 20 years.

The further elucidation of the adenoma-carcinoma sequence occurred following the introduction of colonoscopy in the early 1970s. In 1973, Wolff and Shinya⁴² demonstrated that colonoscopic polypectomy was feasible. Shortly after that, the National Polyp Study was organized to study many aspects of the adenoma-carcinoma sequence and follow-up surveillance intervals after polypectomy.⁴¹

Within the framework of the National Polyp Study, Winawer et al⁴⁰ reported a striking reduction in the incidence of colorectal cancer by removal of adenomatous polyps, providing further validity to the concept of the adenoma-carcinoma sequence (Fig. 1). Colonoscopy and polypectomy also provided an opportunity for studying the pathologic stages of this sequence. The acquired somatic DNA mutations that were shown to accumulate in polyps during the adenoma-carcinoma progression further clarified the natural history of colorectal neoplasia.⁹ The progression

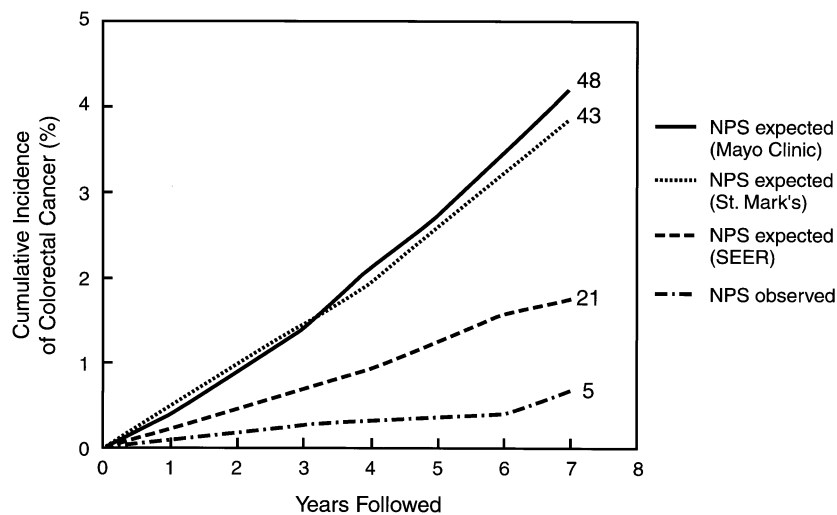


Figure 1. The observed and expected cumulative incidence of colorectal cancer in the National Polyp Study is presented with the scale denoted on the left vertical axis. The numbers of colorectal cancers expected and observed are shown on the curves. The expected rates are based on a comparison with the general population (SEER) and with two historical cohorts in which patients with rectosigmoid adenoma were ascertained but the colon was not cleared of additional polyps. Patients were followed up over time for the occurrence of colorectal cancer. (Adapted from Winawer SJ, Stewart ET, Zauber AG, et al: A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. *N Engl J Med* 329:1977–1981, © 1993 Massachusetts Medical Society. All rights reserved.)

of mutations is concordant with the concept of adenoma growth from small to larger polyps with subsequent risk of development of high-grade dysplasia.

Recently, the possibility of nonpolypoid or flat lesions giving rise to subsequent colorectal carcinoma has been raised as an alternative pathway to colorectal carcinogenesis. In particular it has been suggested that flat adenomas have a higher percentage with high-grade dysplasia than polypoid lesions of similar size.^{16,28} O'Brien et al,²⁶ however, reclassified as flat or polypoid all nonpedunculated adenomas detected at the initial colonoscopy in the National Polyp Study. Flat adenomas did not have an increased risk of high-grade dysplasia. In addition, patients with flat adenomas did not have an increased risk of subsequent advanced adenomas.

THE VALIDITY OF THE ADENOMA AS A SURROGATE MARKER OF COLORECTAL CANCER RISK

Adenomas have a prevalence of 30% to 50% in autopsy studies in Western countries, increase as a function of age, and are more common in men than women.³⁸ A very small percentage, perhaps as few as 1%, grow to a size of 1 cm or more and some transform into cancer. The presence of a single small rectosigmoid adenoma, particularly with tubular pathology and no high-grade dysplasia, does not seem to confer an increased risk of colon cancer according to a study reported by Atkin et al.⁴ On the other hand multiple adenomas, regardless of size, have been reported to be associated with an increased risk of advanced adenomas or colorectal cancer in many studies.^{6, 30, 35, 41}

THE VALIDITY OF THE ADVANCED ADENOMA AS A SURROGATE MARKER OF COLORECTAL CANCER RISK

The advanced adenoma is a more valid surrogate biologic marker for colorectal cancer risk than are smaller adenomas because it is the advanced adenoma that has the greater potential to develop into a cancer. In studies by Atkin et al⁴ and Bertario et al⁶ advanced adenomas seem to confer an increased risk of subsequent colorectal cancer. Furthermore, in the National Polyp Study cohort, the colorectal cancer incidence reduction reported by Winawer et al^{40, 41} was associated with removal of adenomas in a cohort in which advanced adenomas constituted 56% of the adenomas at baseline.

From a pathologic point of view the advanced adenoma bridges benign and malignant states and includes villous features; high-grade dysplasia; and early invasive cancer (malignant polyps). Perhaps the most important feature of the advanced adenoma is size of 1 cm or greater. O'Brien et al²⁷ demonstrated a direct correlation between size and high-grade dysplasia in the National Polyp Study. The precise definition of advanced

adenoma has not been established and varies among studies. It is reasonable to cast a wide net at the present time and consider including in this category any adenoma that is 1 cm in size or larger; or has significant villous features (> 25%); or high-grade dysplasia or invasive cancer.

USE OF ADENOMAS AS SURROGATE MARKERS IN CLINICAL TRIALS

Although the adenoma endpoint has been used in the past, various studies have increasingly used the advanced adenomas as a more valid endpoint in intervention studies. In the National Polyp Study, a high proportion of patients had adenomas at follow-up surveillance colonoscopies after clearing the colon of all identifiable polyps. The proportion of patients who had advanced adenomas at follow-up, however, was small; 3.3% at the 3-year follow-up and 6% at the 6-year follow-up.^{41, 43} The authors believe that the endpoint of the advanced adenoma found at surveillance provides a more accurate outcome by which to measure the intervention effect of colonoscopic polypectomy. It is not clear what the significance is of finding small adenomas at surveillance after polypectomy. These adenomas found at follow-up very likely represent new adenomas and missed synchronous adenomas. Two tandem colonoscopy studies, one by Hixson et al¹³ and another by Rex et al²⁹ demonstrated a 20% to 25% miss rate for adenomas less than 1 cm in size (Table 3).

Dietary and chemoprevention intervention studies have used all adenomas, adenoma burden, and advanced adenomas as endpoints in randomized controlled trials (Table 4). Adenoma burden is a reflection of both size and numbers. The Wheat Bran Fiber Trial by Alberts et al² used adenomas at follow-up as the major outcome to assess the effect of high and low wheat bran fiber diets in 1429 patients with adenomas. The dietary intervention had no effect on adenomas at follow-up. The Calcium Polyp Prevention Study also used adenomas at follow-up as the major outcome of the effect of calcium supplements in 913 adenoma patients and found that calcium provided a 19% reduction in adenomas at follow-up compared with placebo.⁵ The Polyp Prevention Trial study by Schatzkin et al³⁰ used both adenomas and the advanced adenoma to assess the effect of a low-fat, high-fiber diet rich in fruits and vegetables compared with a usual diet in 1905 adenoma patients. This diet had no effect on the percentage of patients with adenomas during the follow-up period. Steinbach

Table 3. COLONOSCOPY MISS RATE FOR ADENOMAS AND ADVANCED ADENOMAS AS DETERMINED BY TANDEM COLONOSCOPIES

Author	% Miss Rate for Adenomas	% Miss Rate for Advanced Adenomas
Hixson et al ¹³	15	0
Rex et al ²⁹	24	6

Table 4. NUTRITION AND CHEMOPREVENTION ENDPOINTS IN RANDOMIZED CONTROLLED TRIALS

Author	Intervention	End point	Effect
Alberts et al ²	Fiber	Adenomas	None
Schatzkin et al ³⁰	Low fat-high fiber	Advanced Adenomas	None
Baron et al ⁵	Calcium	Adenomas	19% reduction
Steinbach et al ³²	Celecoxib	Adenoma burden	30% reduction

et al³² used adenoma burden in a study of the effect of celecoxib in comparison with placebo in 77 familial adenomatous polyposis patients and found a 30% reduction in adenoma burden with celecoxib.

Newer screening approaches have reported adenomas by both size and pathologic features to characterize performance and outcome based on the advanced adenoma. Two screening colonoscopy studies in average-risk people have recently been reported, one by Lieberman et al¹⁸ based on 3196 patients ascertained from 13 Veterans Administration clinics, and a second by Imperiale et al¹⁴ based on 1994 employees, retirees, and dependents of Eli Lilly who had screening colonoscopies. Both studies have reported findings of adenomas and cancer and have also categorized adenomas as advanced. In both studies approximately 10% of screened people had advanced neoplasia including early cancer and advanced adenomas. Studies of virtual colonoscopy by Fenlon et al¹⁰ have also broken down adenomas by size to demonstrate sensitivity for the larger more advanced adenomas. In a report from the National Polyp Study, Winawer et al³⁹ have reported the low sensitivity (48%) of the double-contrast barium enema for advanced adenomas in 862 paired double-contrast barium enema and colonoscopy surveillance examinations of 580 adenoma patients.

Screening studies using stool markers have also turned to the advanced adenomas as an important endpoint. The study by Ahlquist et al¹ demonstrated a high sensitivity for a panel of DNA mutations, not only for cancer but also for advanced adenomas in a small cohort. In 22 patients sensitivity of the stool assay panel of selected DNA alterations was 91% for cancer and 82% for adenomas greater than 1 cm with a specificity of 93%. Evaluation of new fecal occult blood tests has also used the advanced adenomas as the valid endpoint for performance measurements.³³

CONCLUDING COMMENTS

There is now a better understanding of the progressive pathologic stages of the adenoma-carcinoma sequence. A review of available evidence strongly suggests that the advanced adenoma is the most valid surrogate marker for present and future colorectal cancer risk. Based on this understanding the advanced adenoma should be used in the evaluation

of new screening technology, nutritional interventions, and chemoprevention agents. Prevention studies should demonstrate a high efficacy in reducing the number of these lesions. With the present insight into the evolution of colorectal cancer one should no longer be satisfied with detecting early curable colorectal cancer as the major goal. If attention is solely to detect cancer rather than advanced adenomas, then one may permit disease to unfold, some of which is incurable and some of which requires major treatment and causes significant morbidity. Use of the advanced adenoma as the measure of the effective outcome can provide the most benefit with the least harm. Directing efforts to earlier adenoma stages could expose people to larger risk of colonoscopy with less benefit.

There are many related issues. There is not as yet a well-established definition of the advanced adenoma based on evidence of colorectal cancer risk. In addition, pathologic characteristics do not provide a complete and accurate predictor of future risk. Molecular characteristics have to be delineated and added to the portrait, especially in studies that demonstrate a regression of the advanced adenoma.³² It is not known whether regression as measured by reduction in size or reversal of pathologic features is associated with improvement in molecular characteristics or a reduction in risk.

Another major issue relates to the technology required to identify advanced adenoma as the goal of screening. This can be achieved by screening colonoscopy. Widespread screening colonoscopy in the general population, however, may not be feasible at present given the available facilities and manpower resources. Identification of people in the population most likely to have advanced adenomas as candidates for colonoscopy is an attractive strategy that could use resources more efficiently and perhaps provide a good benefit-harms ratio. This two-staged approach could increase population participation, reduce complications, and provide benefit to those people having the more advanced neoplasia and who are more likely to benefit from an invasive and costly procedure. More sensitive and specific fecal markers could provide the first-stage screening in this approach.¹ Virtual colonoscopy is also a possible promising first-stage screening test but at present is costly and is not totally noninvasive.^{7,10} An alternative is to offer once-in-a-lifetime colonoscopy to the general population beginning at age 55, 60, or 65. The efficacy of these various approaches should be measured by their ability to identify people with advanced adenomas so that they can be removed and colorectal cancer prevented.

Any screening colonoscopy strategy requires strong evidence of benefit and harms, major public campaigns, a major expansion of facilities and manpower, and a dramatic shift of resources from unnecessary colonoscopies and less intense surveillance to more effort applied to screening. The approach of screening colonoscopy, however, whether in a single- or a two-stage approach, with the advanced adenoma as the major target, is so promising in its potential to eradicate colorectal cancer that it deserves a major research effort.

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