

## Incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of colon adenomas: a meta-analysis and systematic review

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**Background:** Current guidelines stratify patients with a personal history of adenomas as low risk (ie, 1-2 small [ $<10$  mm] adenomas at index colonoscopy) or high risk ( $\geq 3$  small adenomas or advanced adenoma at index colonoscopy) for recurrent advanced adenomas. Guidelines recommend longer intervals between surveillance colonoscopies for low-risk patients, but physicians frequently perform surveillance colonoscopy at shorter intervals for these patients.

**Objective:** Our purpose was to perform a meta-analysis about the incidence of advanced adenomas at 3-year surveillance colonoscopy among high- and low-risk patients.

**Methods:** Computer searches of MEDLINE, PREMEDLINE, and EMBASE were performed to identify appropriate studies. Study selection criteria were (1) study design—prospective or registry-based study, (2) study population—patients with a personal history of adenomas, and (3) intervention—completion of surveillance colonoscopy at an interval of  $\geq 2$  years. Data were extracted on (1) incidence of advanced adenomas at surveillance colonoscopy, (2) interval between colonoscopies, and (3) risk factors associated with recurrent adenomas. After the validity of study design was assessed and independent, duplicate data extraction was performed from selected trials, summary relative risks (RR) for the incidence of advanced adenomas at 3-year colonoscopy were calculated.

**Results:** Fifteen studies met study selection criteria, but only 5 studies stratified surveillance colonoscopy results according to findings at the index colonoscopy. Patients with  $\geq 3$  adenomas at index colonoscopy were more likely to have recurrent advanced adenomas than were patients with 1 to 2 adenomas: RR 2.52, 95% CI 1.07-5.97. Patients with adenomas with high-grade dysplasia at index colonoscopy were also at increased risk for recurrent advanced adenomas: RR 1.84, 95% CI 1.06-3.19. In the individual studies, increasing size of adenomas and increasing number of adenomas at index colonoscopy were the most commonly reported risk factors associated with recurrent advanced adenomas. No studies stratified surveillance colonoscopy results according to the definitions of low risk and high risk used in current guidelines.

**Conclusion:** Few published studies stratify the incidence of advanced adenomas at surveillance colonoscopy according to index colonoscopy findings. In the future, large prospective studies or studies using pooled data from existing randomized controlled trial databases or polyp registries should be used to better define which patients are at low risk for advanced adenoma recurrence. (*Gastrointest Endosc* 2006;64:614-26.)

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States.<sup>1</sup> This malignancy is the end result of a complex multistep process in which the adenoma is an intermediate stage.<sup>2</sup> Interruption of this adenoma-carcinoma sequence with colonoscopy and polypectomy reduces the incidence of CRC by as much as

90%.<sup>3</sup> After polypectomy, periodic surveillance with colonoscopy is necessary to identify recurrent adenomas. This postpolypectomy surveillance is the most common reason for performing colonoscopy. The Clinical Outcome Research Initiative database reports that nearly 25% of all colonoscopies are performed for this indication,<sup>4</sup> and surveillance accounts for more than 50% of colonoscopies in some practices.<sup>5</sup> Extending the interval between surveillance colonoscopies could reduce procedure-related costs and risks and improve the allocation of limited endoscopic resources.

Several recent studies suggest that index colonoscopy findings stratify patients with adenomas as low risk or high risk for recurrent advanced adenomas (ie, adenoma  $\geq 10$  mm, villous adenoma, adenoma with high-grade dysplasia, or invasive cancer) at surveillance colonoscopy.<sup>3,6-8</sup> Citing this literature, current guidelines from the American Gastroenterological Association<sup>9</sup> and the American College of Gastroenterology<sup>10</sup> (the multisociety guidelines) state that patients with 1 or 2 small ( $< 10$  mm) adenomas at index colonoscopy are at low risk for recurrent advanced adenomas and should have surveillance colonoscopy at a 5-year interval. Alternatively, patients with an advanced adenoma or  $\geq 3$  small adenomas are at high risk for recurrent advanced adenomas and should have surveillance colonoscopy at a 3-year interval. However, the American Cancer Society (ACS) guideline<sup>11</sup> states that patients with 1 small adenoma at index colonoscopy are at low risk and should have surveillance colonoscopy at a 3- to 6-year interval. Patients with an advanced adenoma or  $\geq 2$  small adenomas should have surveillance colonoscopy within 3 years.

Many endoscopists currently use the most liberal interpretation of the ACS guideline. In a nationally representative survey of endoscopists, more than 50% of respondents recommended a 3-year surveillance interval for patients with 1 small adenoma on index colonoscopy.<sup>12</sup> Extending this interval to 5 years, as recommended by the multisociety guidelines, could decrease procedure-associated complications, decrease costs, and protect limited endoscopic resources.<sup>13</sup> Notably, more than 80% of respondents in the above survey stated that published evidence is very influential in their practice.<sup>12</sup> Thus, reviewing and synthesizing the literature may facilitate adherence to recommendations for longer surveillance intervals.

No previous study has performed a systematic review or meta-analysis about the incidence of recurrent advanced adenomas at surveillance colonoscopy or the risk factors for recurrence. In this study, we systematically reviewed studies reporting the incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of adenomas. Risk factors associated with recurrent advanced adenomas were also systematically reviewed. A meta-analysis was performed to quantify the relative risk of advanced adenomas at 3-year surveillance colonoscopy on the basis of the risk factors used in current guidelines (number, size, histologic diagnosis, and degree of dysplasia). Through this review, we hoped to (1) identify limitations in the current literature, (2) identify data that support or refute current guidelines, and (3) identify areas for future research.

## METHODS

### Search strategy for identification of studies

Three electronic databases (MEDLINE, PREMEDLINE, and EMBASE) were searched from January 1980 to January

## Capsule Summary

### What is already known on this topic

- Guidelines recommend longer intervals between surveillance colonoscopies for low-risk patients (1-2 small adenomas at index colonoscopy) than for those at high risk ( $> 3$  small adenomas or advanced adenoma at index procedure).
- Physicians frequently perform surveillance colonoscopy at shorter intervals than recommended.

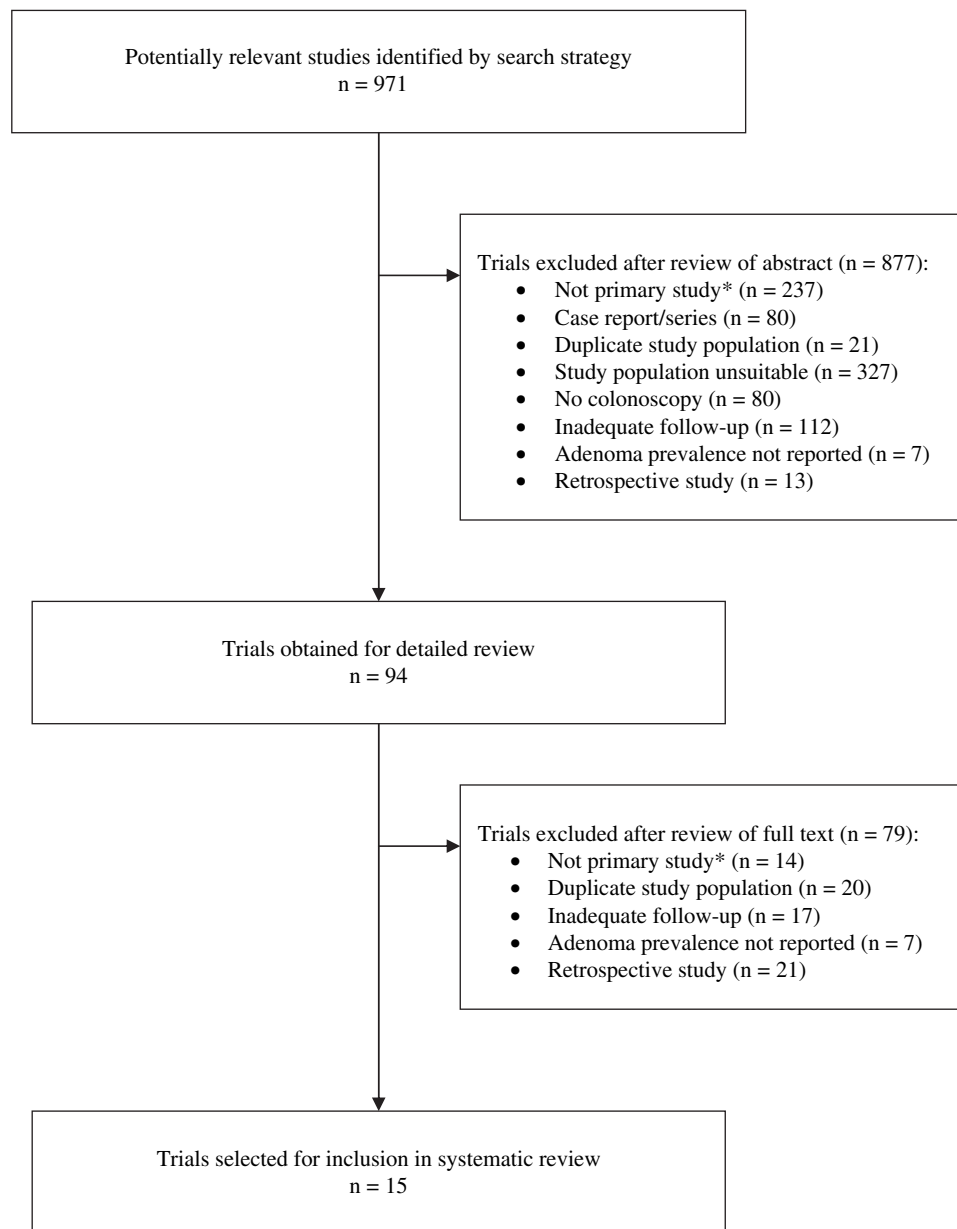
### What this study adds to our knowledge

- In a meta-analysis of 5 studies stratifying surveillance colonoscopy results according to findings at index colonoscopy, the increasing size and number of adenomas at index colonoscopy were the most commonly reported risk factors associated with recurrent advanced adenomas.

2003 to identify potentially relevant articles published in the English language. The following terms were used for the primary search: (1a) MESH terms *colonoscopy*, *adenoma*, *colonic polyps*, *intestinal polyps*, *colonic neoplasms*, *colorectal neoplasms*, *rectal neoplasms*, and *neoplasm recurrence*, *local* (MEDLINE and PREMEDLINE) or (1b) MESH terms *colonoscopy*, *adenoma*, *polyp*, *adenomatous polyp*, *colon polyp*, *intestine polyp*, *colon tumor*, *colorectal tumor*, *rectum tumor*, and *recurrent disease* (EMBASE) and (2) in conjunction with the key words *colonoscop*\$, *adenoma*\$, *polyp*\$, *metachronous*, *prevalence*, *incidence*, *recur*\$, *follow-up*, *risk factor*\$, *surveillance*, *interval*\$, *screening*, *rescreening*, and *registry*. In addition, a recursive search of the reference sections of selected studies, review articles, and practice guidelines was performed manually to identify other potentially relevant articles. Experts in the field were also individually contacted to identify unpublished data on this topic.

### Study selection criteria

Abstracts of articles from the literature search were individually evaluated for possible inclusion in this study. Complete texts were obtained for articles that were potentially relevant. Studies meeting the following criteria were included: (1) English language, (2) full-manuscript publication, (3) publication year 1980 to 2003, (4) study design: prospective cohort, prospective randomized controlled trial (RCT) or prospective polyp registry data, (5) study population: patients with a personal history of adenomas, (6) intervention: surveillance colonoscopy conducted at an interval of  $\geq 2$  years, and (7) results: incidence of recurrent advanced adenomas at surveillance colonoscopy reported. Data were also included from chemoprevention trials that (1) showed no difference between the chemoprevention agent and placebo or (2) showed significant



\* Review article, practice guideline, cost-effectiveness analysis, editorial, commentary, or letter

**Figure 1.** Flowchart outlining search process used to identify articles for inclusion in systematic review.

results but permitted extraction of data from the placebo arm of the trial. Studies enrolling patients with a personal history of hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), CRC, or inflammatory bowel disease (IBD) were excluded.

### Data extraction and analysis

Eligible articles were independently reviewed by the investigators (S. S., P. S.). Agreement between the investigators was >95% for selection of articles to include in this review. Disagreement was resolved by consensus. Data were extracted on (1) patient demographics, (2) incidence of nonadvanced and advanced adenomas at index colono-

scopy, (3) incidence of nonadvanced and advanced adenomas at surveillance colonoscopy, and (4) risk factors for the development of advanced adenomas at surveillance colonoscopy. Data were extracted independently by the primary investigators, and disagreement on data extraction was resolved by consensus. These data are presented in tabular form.

For the studies that stratified patients as high risk or low risk according to index colonoscopy findings, data were extracted on the incidence of recurrent adenomas at surveillance colonoscopy. None of these studies used the multisociety definition of low risk and high risk. Furthermore, the published studies did not allow for data

to be reanalyzed according to the multisociety definition. Thus, individual investigators were contacted and asked to reanalyze existing data on the basis of the multisociety definition, but this request could only be fulfilled for the National Polyp Study data.<sup>3</sup>

As a measure of association, the relative risk (RR) and 95% CIs of having an advanced adenoma at surveillance colonoscopy were calculated for each adenoma characteristic (number, size, histologic diagnosis, and degree of dysplasia) used to differentiate high-risk from low-risk patients in the current guidelines. Pooled RRs and 95% CIs were calculated by use of a random-effects meta-analysis method.<sup>14</sup> A test for heterogeneity across studies was also performed. A *P* value < .10 indicates statistically significant heterogeneity across studies, implying that combining the different studies to obtain a summary measure may be inappropriate.

## RESULTS

### Characteristics of selected studies

Nine hundred seventy-one references were identified by the search strategy outlined above (Fig. 1). Fifteen studies<sup>3,6-8, 15-26</sup> satisfied the primary selection criteria for this review (Table 1). These studies varied widely in design, inclusion criteria, and definition of advanced adenoma. Five studies<sup>3,6-8,17</sup> stratified surveillance colonoscopy findings by features at index colonoscopy (Tables 2-6), and RRs could be calculated for 4 of these studies.<sup>3,6,8,17</sup> Fourteen studies<sup>3,6,8,17-26</sup> reported risk factors associated with the development of recurrent adenomas (Table 7). In total, 6 risk factors were reported for recurrence of any adenoma and 5 risk factors were reported for recurrence of advanced adenomas.

### Characteristics of the individual studies in the meta-analysis

Bonithon-Kopp et al<sup>16,17</sup> presented data from the European Fiber-Calcium Intervention Trial, in which patients underwent index and 3-year surveillance colonoscopy. Data could be extracted for the following risk factors for advanced adenoma recurrence: number, size, histologic diagnosis, and degree of dysplasia. The RR was statistically significant for number of adenomas only: RR 3.26 (95% CI 1.81-5.89) (Table 2).

Martinez et al<sup>6</sup> presented data from the wheat bran fiber (WBF) trial. The WBF trial was an adenoma prevention trial that showed no significant difference between placebo and experimental arms. Sixty-nine percent (889/1287) of patients had a 1-year clearing colonoscopy (partly to identify polyps missed by the index colonoscopy) followed by a 3-year surveillance colonoscopy. The remaining patients had a surveillance colonoscopy 3 years after the index colonoscopy only. Data extraction could not be performed for the 3-year follow-up group alone. Data could

be extracted for the following risk factors for advanced adenoma recurrence: number, size, and histologic diagnosis. The RR was statistically significant for size only: RR 1.77 (95% CI 1.30-2.41) (Table 3).

Noshirwani et al<sup>7</sup> presented data from the Cleveland Clinic Foundation Adenoma Registry. An unspecified portion of patients in this study had follow-up at <3 years (mean follow-up interval 18 months, range 10-42 months), although follow-up interval was not found to be a significant risk factor for adenoma recurrence. The incidence of advanced adenomas at surveillance colonoscopy was 3.0% to 3.8% for low-risk patients (1 or 2 small adenomas at index colonoscopy) and 8.3% to 34.5% for high-risk patients (at least 1 large adenoma at index colonoscopy) (Table 4). However, no data could be extracted from the published article about the number of patients in each category, and the primary investigators could not provide these data. Therefore, RRs could not be calculated for our analysis, and this study was not used in the calculation of the pooled RR.

Van Stolk et al<sup>8</sup> presented data from the Polyp Prevention Study, an RCT that showed no difference between placebo and antioxidant vitamins on adenoma recurrence. Patients had 1-year clearing colonoscopy (to identify polyps missed by the baseline colonoscopy) followed by a 4-year surveillance colonoscopy, although only results from the 4-year surveillance colonoscopy were explicitly reported. Investigators reported no significant difference in results when findings from the 1-year clearing colonoscopy were included. Data could be extracted for the following risk factors for advanced adenoma recurrence: number, size, histologic diagnosis, and degree of dysplasia. None of the RRs for these factors were statistically significant (Table 5).

Winawer et al<sup>3</sup> randomized patients with newly diagnosed adenomas to either 1-year and 3-year surveillance colonoscopy or to 3-year surveillance colonoscopy alone. On the basis of personal communication with the National Polyp Study investigators, data were reanalyzed for patients from the 3-year surveillance colonoscopy arm of the trial on the basis of the multisociety definition of low risk and high risk.<sup>9,10</sup> The incidence of advanced adenomas at 3-year surveillance colonoscopy was 1.4% in the low-risk patients versus 5.4% in the high-risk patients: RR 3.87 (95% CI 1.09-13.66) (Table 6).

### Risk of advanced adenomas at surveillance colonoscopy according to index colonoscopy findings

**Number and size.** Four trials<sup>3,7,8,17</sup> provided adequate data to determine the incidence of recurrent advanced adenomas at surveillance colonoscopy on the basis of (1) number of adenomas at index colonoscopy ( $\geq 3$  vs 1-2) and (2) size of the largest adenoma at index colonoscopy ( $\geq 1$  cm [large] vs <1 cm [small]) (Figs. 2 and 3). For  $\geq 3$  adenomas versus 1 to 2 adenomas, the

**TABLE 1. Study characteristics**

Study	Year	Design	Setting	Age (y)	% Male	Inclusion criteria
Baron et al <sup>15</sup>	1999	RCT	Multicenter	61.0 ± 9.1	70.2	Age < 80 y; Adenoma removed within 3 mo recruitment
Bonithon-Kopp et al <sup>16</sup>	2000	RCT	Multicenter	59.1	63.6	Age 35-75 y; At least 2 adenomas or 1 adenoma > 0.5 cm in diameter; No debilitating or life-threatening disease
Cordero et al <sup>18</sup>	2001	Prospective cohort	Single-center	59.4 ± 11.9	66.7	Advanced adenoma, multiple polyps, or family history of CRC; No more than 1 polyp < 1 cm in diameter
Fornasarig et al <sup>19</sup>	1998	Prospective cohort	Single-center	58.2	64.4	Any patient referred for colonoscopy
Fossi et al <sup>20</sup>	2001	Prospective cohort	Single-center	NA	NA	At least 1 adenoma at index colonoscopy
Hixson et al <sup>21</sup>	1994	Prospective cohort	Single-center	67.0 ± 10.0	98.3	Colonoscopy for any clinical indication
Jorgensen et al <sup>22</sup>	1995	Prospective cohort	Single-center	51.2	56.8	First diagnosis of adenoma; Referred for colorectal symptoms (74%) or occult blood positivity (26%)
Lund et al <sup>23</sup>	2001	RCT	Single-center	NA	NA	At least 1 adenoma at index colonoscopy
Martinez et al <sup>6</sup>	2001	Analysis of RCT data	Multicenter	66.2	66.8	Age 40-80 y; Removal of adenoma ≥ 3 mm within 3 mo of enrollment; Had complete clearing colonoscopy; Adequate nutritional status; Normal renal/liver function
Noshirwani et al <sup>7</sup>	2000	Registry	Single-center	NA	73.3	Adenoma removed at colonoscopy; Surveillance colonoscopy within 10-42 mo
Nusko et al <sup>24</sup>	2002	Registry	Single-center	NA	NA	First diagnosis of adenoma
Paspatis et al <sup>25</sup>	1995	Prospective cohort	Single-center	59.2	52.5	First diagnosis of adenoma
Schatzkin et al <sup>26</sup>	2000	RCT	Multicenter	61.0	64.5	Age ≥ 35 y; Adenoma removed within 6 mo of randomization
Van Stolk et al <sup>8</sup>	1998	Analysis of RCT data	Multicenter	60.0	77.0	Age < 80 y; First diagnosis of adenoma within 3 mo of enrollment; Had complete clearing colonoscopy; In good general health
Winawer et al <sup>3</sup>	1993	RCT	Multicenter	51.8	70.0	First diagnosis of adenoma; Had complete clearing colonoscopy

NA, Not available; CIS, carcinoma in situ.

\*Seventy-nine of 133 patients who had 3-year colonoscopies also had 6-month colonoscopies.

†Trial provided no further detail.

‡Patients aged > 75 y at time of follow-up were not included in the final data analysis.

Exclusion criteria	Definition of advanced adenoma	Definition of adenoma recurrence	No.	Surveillance intervals	% Follow-up
CRC, FAP; Malabsorption syndrome; Any condition worsened by supplemental calcium	None	Any adenoma detected after 1-y colonoscopy	466	0, 13 ± 0.2 mo, 50 ± 0.2 mo	91
CRC, FAP, IBD; History of colon resection; Malabsorption syndrome or other contraindication to calcium or fiber	≥ 1 cm in diameter; Villous histologic features; Moderate or severe dysplasia	Any adenoma detected >1 y after index colonoscopy	665	0, 3 y	83
CRC, FAP, IBD; Lynch syndrome	≥ 1 cm in diameter; Villous histologic features; High-grade dysplasia	Any adenoma detected at 3-year colonoscopy	223	6 mo, 3 y*	60
Age >75 y; CRC, FAP, IBD; Concomitant general diseases; Incomplete colonoscopy at any point during study; Previous intestinal neoplasms; Villous adenoma of rectum; Adenomas requiring surgical or piecemeal removal	High-grade dysplasia	Any adenoma detected at 3-year colonoscopy or adenoma <0.5 cm in diameter detected at 1-y colonoscopy	164	1, 3 y	95
CRC, IBD; Prior colonoscopy; History of colon polyps	None	Any adenoma detected at 3-y colonoscopy	172	0, 3 y	78
None	None	Any adenoma detected in segment of colon that did not previously have adenoma	90	0, 2.02 ± 0.28 y	64
CRC, FAP; History of colorectal neoplasia; Large sessile or villous adenoma	>1 cm in diameter; Villous histologic features; Severe dysplasia; CRC	Any adenoma detected at follow-up colonoscopy	673	0, 2, 4 y	64
None	> 2 cm in diameter; Severe dysplasia; ≥ 3 adenomas; ≥ 2 first-degree relatives with CRC	Any adenoma detected at follow-up colonoscopy	255	1, 2, 5 y	78 <sup>‡</sup>
FAP, IBD; Invasive cancer of any type within 5 y; History of colon resection ≥20 cm ≥ 3 first-degree relatives with CRC; Severe metabolic disorder or chronic disease	> 1 cm in diameter; Tubulovillous or villous histologic features; CRC	Adenoma detected at any time after randomization	1429	0, 1, 3 y (mean 36.8 ± 16.0 mo)	90
CRC, FAP; Ulcerative colitis	≥ 1 cm in diameter; Tubulovillous or villous histologic features; High-grade dysplasia/ CIS/CRC	Any adenoma detected at follow-up colonoscopy	697	10-42 mo (mean 18 mo)	—
CRC, FAP, HNPCC, IBD	>1 cm in diameter; High-grade dysplasia CRC	Any adenoma detected at follow-up colonoscopy	1159	0, 2 ± 1 y (> 1 index adenoma) or 4 ± 1 y (single index adenoma)	—
Noncompliance with surveillance colonoscopy; CRC	None	Any adenoma detected at second follow-up colonoscopy	40	0, 3-6, 24 mo	100
CRC, FAP, or IBD; History of bowel resection; Surgical adenoma resection; Obesity; Taking lipid-lowering medication; Dietary restriction or medical condition preventing adherence with protocol	≥ 1 cm in diameter; ≥ 25% villous component; High-grade dysplasia; CRC	Any adenoma detected after 1-y colonoscopy or ≥2 y after randomization	2079	0, 1, 4 y	77
CRC, FAP; Malabsorption syndromes; Any condition potentially worsened by vitamins C or E	≥ 1 cm in diameter; Villous histologic features; Severe or worse atypia	Any adenoma detected at 4-y colonoscopy	479	0, 1, 4.2 ± 0.3 y	87
Family or personal history of FAP or IBD; History of polypectomy or CRC; Nonadenomatous polyps; Sessile adenoma with base > 3 cm in diameter	>1 cm in diameter; High-grade dysplasia; CRC	Any adenoma detected at follow-up colonoscopy	1418	1, 3 y (mean 1.15 and 3.15-3.18 y)	78

**TABLE 2. Adenoma incidence at surveillance colonoscopy according to index colonoscopy features**

	3-y Follow-up (n = 552)		
	Baseline	Advanced adenoma*	RR (95% CI)
Bonithon-Kopp et al <sup>17</sup>	1-2 adenomas (n = 469)	5.5% (n = 26)	3.26 (1.81-5.89)
	≥3 adenomas (n = 83)	18.1% (n = 15)	
	Small adenoma (<1 cm) (n = 243)	7.8% (n = 19)	0.91 (0.50-1.64)
	Large adenoma (≥1 cm) (n = 309)	7.1% (n = 22)	
	Tubular histologic features (n = 455)	6.8% (n = 31)	1.51 (0.77-2.98)
	Villous histologic features (n = 97)	10.3% (n = 10)	
	Mild dysplasia (n = 308)	5.5% (n = 17)	1.78 (0.98-3.24)
	Moderate/severe dysplasia (n = 244)	9.8% (n = 24)	

\*Advanced adenoma defined as adenoma ≥ 1 cm, adenoma with villous histologic features, or adenoma with moderate or severe dysplasia. Unable to extract data about incidence of nonadvanced adenomas at surveillance colonoscopy. Unable to extract data about the incidence of advanced adenomas among patients with ≥ 3 small adenomas at index colonoscopy.

**TABLE 3. Adenoma incidence at surveillance colonoscopy according to index colonoscopy features**

	Baseline	3-y Follow-up (n = 1287)		RR (95% CI) <sup>†</sup>
		Nonadvanced adenoma	Advanced adenoma*	
Martinez et al <sup>6</sup>	1-2 adenomas (n = 1026)	33.0% (n = 339)	11.1% (n = 114)	1.10 (0.76-1.59)
	≥3 adenomas (n = 261)	53.6% (n = 140)	12.3% (n = 32)	
	Small adenoma (<1 cm) (n = 938)	36.7% (n = 344)	9.4% (n = 88)	1.77 (1.30-2.41)
	Large adenoma (≥1 cm) (n = 349)	38.7% (n = 135)	16.6% (n = 58)	
	Tubular histologic features (n = 842)	36.9% (n = 311)	10.9% (n = 92)	1.22 (0.88-1.68)
	Villous histologic features (n = 376)	37.8% (n = 142)	13.3% (n = 50)	

\*Advanced adenoma defined as adenoma ≥ 1 cm, villous histologic features, or colon cancer. Sixty-nine percent (889/1287) of patients had 1-year clearance colonoscopy and 3-year surveillance colonoscopy. Authors state no statistically significant difference between patients who underwent 1- and 3-year follow-up colonoscopy and patients who only underwent 3-year follow-up colonoscopy.

<sup>†</sup>RR of advanced adenoma.

pooled RR was 2.52 (95% CI 1.07-5.97), and the pooled absolute risk difference was 5% (95% CI 1%-10%). For patients with large versus small adenomas, the pooled RR was 1.39 (95% CI 0.86-2.26), and the pooled absolute risk difference was 2% (95% CI -2% to 6%). For both pooled RRs, the test of heterogeneity was significant ( $P < .001$  for number of adenomas and  $P < .05$  for size of adenoma), indicating that the individual studies demonstrated significant differences in the RR of recurrent advanced adenomas.

**Histologic diagnosis.** Three trials<sup>7,8,17</sup> provided adequate data to determine the incidence of recurrent advanced adenomas at surveillance colonoscopy on the basis of adenoma histologic features (tubulovillous/villous vs tubular) (Fig. 4). For patients with a villous adenoma

versus no villous component, the pooled RR was 1.26 (95% CI 0.95-1.66), and the pooled absolute risk difference was 2% (95% CI -1% to 4%). The test of heterogeneity for the pooled RR was not significant ( $P > .2$ ), indicating that the individual studies did not demonstrate significant differences in the RR of recurrent advanced adenomas.

**Dysplasia.** Two trials<sup>8,17</sup> provided adequate data to determine the incidence of recurrent advanced adenomas on the basis of the degree of dysplasia at index colonoscopy (high-grade vs no high-grade dysplasia) (Fig. 5). The RRs for patients with an adenoma with high-grade dysplasia were 1.78 and 2.17 in these 2 studies, although neither RR was statistically significant. The pooled RR was 1.84 (95% CI 1.06-3.19). The absolute risk difference

was 4% for each trial, and the pooled absolute risk difference was also 4% (95% CI 0%-8%). The test of heterogeneity for the pooled RR was not significant ( $P > .2$ ), indicating that the individual studies did not demonstrate significant differences in the RR of recurrent advanced adenomas.

### Risk factors for recurrent adenomas at surveillance colonoscopy

Nine studies<sup>3,6-8,17,18,21,22,24</sup> reported a total of 5 risk factors that were associated with advanced adenomas at surveillance colonoscopy: (1) number of adenomas, (2) size of largest adenoma, (3) incomplete index colonoscopy, (4) concurrent proximal and distal adenomas, and (5) parental history of CRC. Four studies identified increasing number of adenomas at index colonoscopy as a risk factor for recurrent advanced adenoma. Three studies found that having  $\geq 3$  adenomas was significant,<sup>3,17,22</sup> and 1 reported the number of adenomas to be a risk factor but provided no further detail.<sup>7</sup> Nusko et al<sup>24</sup> found the number of adenomas to be a risk factor for advanced adenomas in patients with only tubular adenomas at index colonoscopy. Adenoma  $\geq 10$  mm in diameter in male patients and parental history of CRC were also significant risk factors in this study. Two other studies also reported adenoma  $\geq 10$  mm in diameter to be a significant risk factor.<sup>6,7</sup> Finally, individual studies reported incomplete initial colonoscopy<sup>22</sup> and the presence of concurrent proximal and distal adenomas at index colonoscopy<sup>6</sup> to be risk factors for advanced adenoma recurrence.

For any recurrent adenoma at surveillance colonoscopy, 14 studies<sup>3,6-8,17-26</sup> reported a total of 6 risk factors: (1) number of adenomas, (2) size of largest adenoma, (3) patient age, (4) tubulovillous/villous features or severe dysplasia, (5) advanced adenoma, and (6) adenoma in the proximal colon (Table 7).

## DISCUSSION

Adherence to guideline recommendations can reduce costs and procedure-related risks and facilitate more appropriate use of limited endoscopic resources.<sup>13</sup> However, many endoscopists do not follow multisociety guideline recommendations, although most physicians (83%) state that published data are very influential in their practice.<sup>12</sup> Our study reviewed the published data and found that no studies reported the incidence of advanced adenomas at surveillance colonoscopy according to the multisociety low-risk/high-risk definitions. Only 5 studies stratified surveillance colonoscopy results according to index colonoscopy findings. In these studies,  $\geq 3$  adenomas (RR 2.52, 95% CI 1.07-5.97) and adenomas with high-grade dysplasia (RR 1.84, 95% CI 1.06-3.19) were significantly associated with recurrent advanced

**TABLE 4. Adenoma incidence at surveillance colonoscopy according to index colonoscopy features**

	Baseline	Advanced adenoma*
Noshirwani et al <sup>7</sup>	1 small adenoma	3.0%
	2 small adenomas	3.8%
	3 small adenomas	8.5%
	> 3 small adenomas	15.3%
	Large adenoma (with 1 adenoma total)	8.3%
	Large adenoma (with 2 adenomas total)	10.3%
	Large adenoma (with 3 adenomas total)	21.3%
	Large adenoma (with >3 adenomas total)	34.5%

Surveillance colonoscopy interval ranged from 10 to 42 months (n = 697).

\*Advanced adenoma defined as adenoma > 1 cm, villous adenoma, adenoma with high-grade dysplasia or carcinoma in situ, or invasive colon cancer. Unable to extract data about incidence of nonadvanced adenomas or number of patients in each category.

adenomas. Adenomas  $\geq 1$  cm (RR 1.39, 95% CI 0.86-2.26) and villous adenomas (RR 1.26, 95% CI 0.95-1.66) demonstrated trends for increased risk of recurrent advanced adenomas.

Unfortunately, we could not calculate a summary RR for recurrent advanced adenomas by use of the multisociety definition of high-risk and low-risk patients because most investigators could not provide a reanalysis of their results. We did obtain a reanalysis of National Polyp Study (NPS) data with patients stratified as low risk or high risk for recurrent advanced adenomas on the basis of multisociety guideline definitions. These data demonstrated that the incidence of advanced adenomas at 3-year surveillance colonoscopy in low-risk patients was only 1.4%. NPS data have also shown that patients with  $\leq 2$  adenomas at index colonoscopy and age < 60 years are at low risk for recurrent advanced adenomas 6 years after index colonoscopy ( $\leq 4\%$ ).<sup>27</sup> Furthermore, data from Atkin et al<sup>28</sup> suggest that such patients are at low risk for colorectal cancer. In the future, it will be important to validate the multisociety prognostic scheme in a population other than the NPS cohort, perhaps by pooling data from RCTs or from polyp registries.<sup>29</sup>

Given these results from the published literature, it is possible that endoscopists sometimes deviate from guideline recommendations because the data supporting such recommendations are moderate. Yet, it is likely that other factors also influence the practice decisions of endoscopists. Potentially important factors include fear of missed

**TABLE 5. Adenoma incidence at surveillance colonoscopy according to index colonoscopy features**

	Baseline	4-y Follow-up (n = 477)	
		Advanced adenoma*	RR (95% CI) <sup>†</sup>
Van Stolk et al <sup>8</sup>	1-2 adenomas (n = 393)	3.3% (n = 13)	1.80 (0.66-4.91)
	≥3 adenomas (n = 84)	6.0% (n = 5)	
	Small adenoma (<1 cm) (n = 258)	4.3% (n = 11)	0.75 (0.30-1.90)
	Large adenoma (≥1 cm) (n = 219)	3.2% (n = 7)	
	Tubular histologic features (n = 256)	3.5% (n = 9)	1.17 (0.47-2.89)
	Villous histologic features (n = 219)	4.1% (n = 9)	
	Mild/moderate dysplasia (n = 451)	3.5% (n = 16)	2.17 (0.53-8.93)
	Severe dysplasia (n = 26)	7.7% (n = 2)	

\*Advanced adenoma defined as adenoma ≥ 1 cm, villous histologic features, severe atypia, or invasive colon cancer. Unable to extract specific data about recurrence of nonadvanced adenomas. Patients underwent a clearing colonoscopy at 1 year. Authors state no statistically significant difference in results when results from 1-year colonoscopy are included. Results shown above only include findings at 4-year colonoscopy.

<sup>†</sup>RR of advanced adenoma.

**TABLE 6. Adenoma incidence at surveillance colonoscopy according to index colonoscopy features**

	Baseline	3-y Follow-up (n = 938)		
		Nonadvanced adenoma	Advanced adenoma*	RR (95% CI) <sup>†</sup>
Winawer/Zauber et al <sup>3</sup>	1-2 adenomas (n = 741)	24.3% (n = 180)	1.3% (n = 10)	6.77 (3.18-14.43)
	≥3 adenomas (n = 197)	36.5% (n = 72)	9.1% (n = 18)	
	Small adenoma (<1 cm) (n = 582)	24.9% (n = 145)	1.9% (n = 11)	2.53 (1.20-5.33)
	Large adenoma (≥1 cm) (n = 356)	30.1% (n = 107)	4.8% (n = 17)	
	1-2 small tubular adenomas (n = 214) <sup>‡</sup>	26.2% (n = 56)	1.4% (n = 3)	3.87 (1.09-13.66)
	Advanced adenoma or ≥3 adenomas (n = 203) <sup>‡</sup>	32.1% (n = 65)	5.4% (n = 11)	

\*Advanced adenoma defined as adenoma > 1 cm, adenoma with high-grade dysplasia, or invasive colon cancer.

<sup>†</sup>RR of advanced adenoma.

<sup>‡</sup>This is previously unpublished data from the National Polyp Study, which conforms to high-risk and low-risk groups as defined by multisociety guidelines.

neoplastic lesions and lack of knowledge of guideline recommendations. With the existing data on polyp miss rates, it is reasonable to hypothesize that endoscopists may fear missing adenomas.<sup>30-32</sup> A recent study by Robertson et al<sup>33</sup> has suggested that the risk of CRC in patients undergoing colonoscopic surveillance is significant, with a reported incidence rate of 1.74 cancers per 1000 person-years. Available data from 9 of the 15 studies included in this review yielded a similar incidence rate of 1.94 cancers per 1000 person-years.<sup>3,6,8,15,17,18,22,23,26</sup> Among those patients in the study of Robertson et al who underwent a 1-year “clearing” colonoscopy, more than 50% (7/13) of identified cancers were found at this 1-year examina-

tion, with the remaining patients being identified with cancer at surveillance colonoscopy 3 years later. This finding raises questions about the technical quality of colonoscopy. The multisociety task force on CRC screening has recommended guidelines for performance of effective colonoscopy, including documentation of cecal landmarks and appropriate withdrawal technique.<sup>34</sup> When the quality of colonoscopy is suboptimal, endoscopists may recommend shorter surveillance intervals. Future studies could examine whether documentation of these performance measures decreases the miss rate of adenomas and improves adherence to recommended intervals between surveillance colonoscopies. Alternatively, endoscopists may

**TABLE 7. Risk factors at index colonoscopy associated with adenoma recurrence at surveillance colonoscopy**

Study	Any adenoma	Advanced adenoma	Statistical method
Bonithon-Kopp et al <sup>17</sup>	Number $\geq 3$ Proximal location	Number $\geq 3$	Multivariate analysis adjusting for "patient characteristics" and treatment group
Cordero et al <sup>18</sup>	None	None	Pearson $\chi^2$ test and Fisher exact test
Fornasarig et al <sup>19</sup>	Increasing size/number*	NA	Multivariate analysis adjusting for age and sex
Fossi et al <sup>20</sup>	> 1 cm in diameter Villous histologic features Severe dysplasia	NA	Multivariate analysis adjusting for age and sex
Hixson et al <sup>21</sup>	None	None	NA
Jorgensen et al <sup>22</sup>	Number $\geq 2$ Age > 60 y	Number $\geq 3$ Incomplete index colonoscopy	Cox regression
Lund et al <sup>23</sup>	Advanced adenoma <sup>†</sup>	NA	NA
Martinez et al <sup>6</sup>	Number $\geq 3$  > 1 cm in diameter Proximal adenoma	>1 cm in diameter  Concurrent proximal and distal adenomas	Multivariate analysis adjusting for age, sex, and index lesion characteristics
Noshirwani et al <sup>7</sup>	Number* <sup>‡</sup> $\geq 1$ cm in diameter <sup>§</sup>	Number* $\geq 1$ cm in diameter	Multivariate analysis adjusting for age, sex, baseline adenoma pathologic conditions, and time interval between colonoscopies
Nusko et al <sup>24</sup>	NA	Number* <sup>¶</sup>  > 1 cm in diameter in males <sup>¶</sup>  Parental history of CRC <sup>¶</sup>	Multivariate analysis
Paspatis et al <sup>25</sup>	Number* <sup>  </sup>	NA	Fisher exact test
Schatzkin et al <sup>26</sup>	Number* <sup>  </sup>  Age*	NA	NA
Van Stolk et al <sup>8</sup>	Number $\geq 3$ * Tubulovillous histologic features <sup>§</sup>	None	Multivariate analysis adjusting for baseline adenoma characteristics, age, sex, clinical center, and time interval between colonoscopies
Winawer et al <sup>3</sup>	Number $\geq 2$  $\geq 0.6$ cm in diameter  Age $\geq 60$ y	Number $\geq 3$	Multivariate analysis

\*Trial provided no further detail.

†Determined by use of 1- and 2-year flexible sigmoidoscopy and 2-year colonoscopy groups; unusual definition of advanced adenoma.

‡Associated with  $\geq 4$  recurrent adenomas.

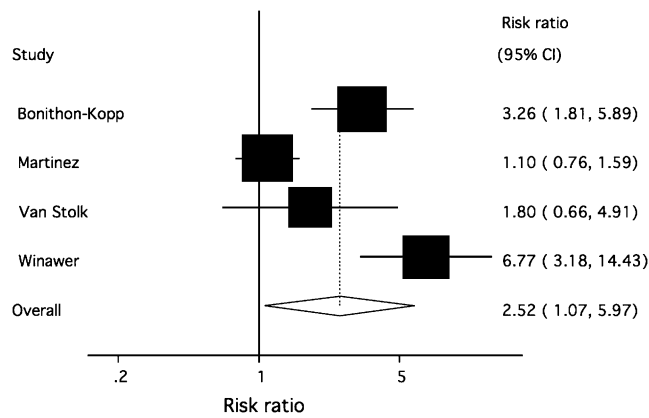
§For patients with tubular adenomas only at index colonoscopy.

||Associated with  $\geq 2$  recurrent adenomas.

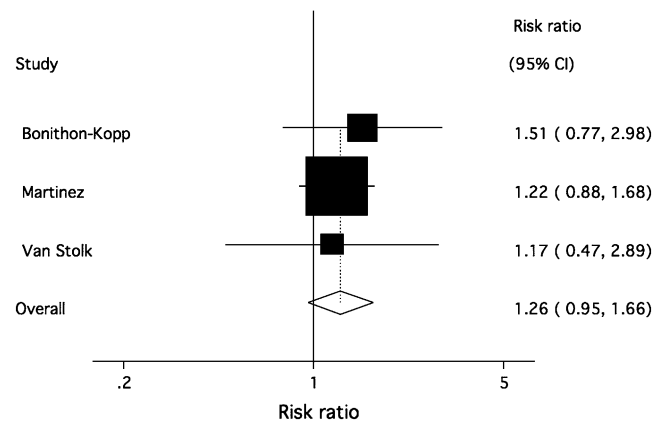
¶No further information about specific number of adenomas provide.

simply not know guideline recommendations. Recent survey data demonstrate that many gastroenterologists did not know the recommended surveillance interval for patients with 2 small adenomas (39%), 3 small adenomas (49%), and a large adenoma with high-grade dysplasia (47%).<sup>35</sup>

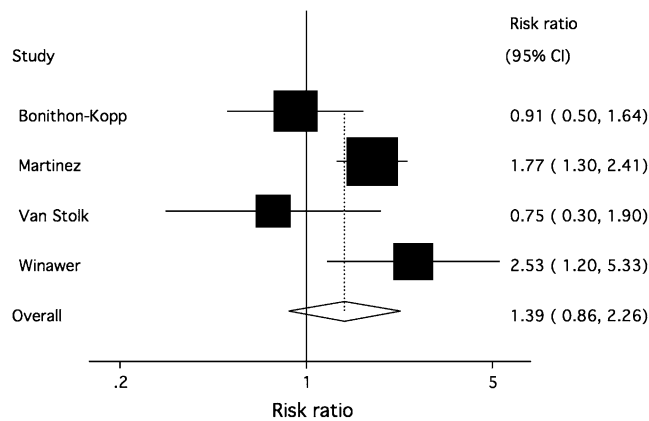
This systematic review and meta-analysis demonstrates the limitations of the current literature. First, none of the studies stratified high-risk and low-risk patients according to the definitions used in the multisociety or ACS guidelines, nor did they use consistent definitions of advanced adenomas. This may partly explain the wide variation



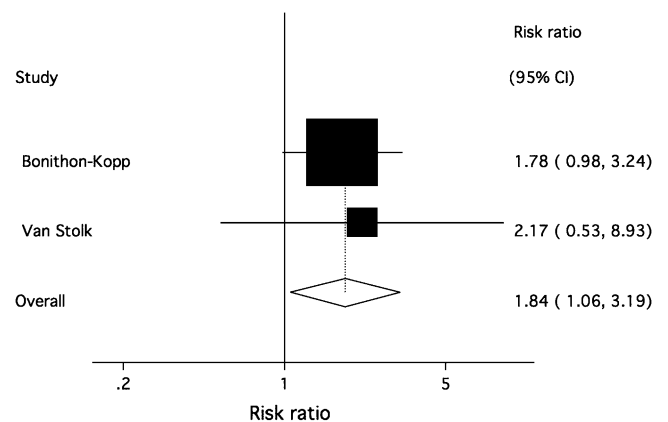
**Figure 2.** RR of advanced adenoma at 3-year surveillance colonoscopy (van Stolk et al had a 4-year surveillance colonoscopy) in patients with  $\geq 3$  versus 1 to 2 adenomas at index colonoscopy. The RRs are 3.26 (95% CI 1.81-5.89) for Bonithon-Kopp et al,<sup>17</sup> 1.10 (95% CI 0.76-1.59) for Martinez et al,<sup>6</sup> 1.80 (95% CI 0.66-4.91) for van Stolk et al,<sup>8</sup> and 6.77 (95% CI 3.18-14.43) for Winawer et al.<sup>3</sup>



**Figure 4.** RR of advanced adenoma at 3-year surveillance colonoscopy (van Stolk et al had a 4-year surveillance colonoscopy) in patients with tubulovillous/villous versus tubular adenomas at index colonoscopy. The RRs are 1.51 (95% CI 0.77-2.98) for Bonithon-Kopp et al,<sup>17</sup> 1.22 (95% CI 0.88-1.68) for Martinez et al,<sup>6</sup> and 1.17 (95% CI 0.47-2.89) for van Stolk et al.<sup>8</sup> Data could not be extracted for Winawer et al.<sup>3</sup>



**Figure 3.** RR of advanced adenoma at 3-year surveillance colonoscopy (van Stolk et al had a 4-year surveillance colonoscopy) in patients with large (>1 cm) versus small ( $\leq 1$  cm) adenomas at index colonoscopy. The RRs are 0.91 (95% CI 0.50-1.64) for Bonithon-Kopp et al,<sup>17</sup> 1.77 (95% CI 1.30-2.41) for Martinez et al,<sup>6</sup> 0.75 (95% CI 0.30-1.90) for van Stolk et al,<sup>8</sup> and 2.53 (95% CI 1.20-5.33) for Winawer et al.<sup>3</sup>



**Figure 5.** RR of advanced adenoma at 3-year surveillance colonoscopy (van Stolk et al had a 4-year surveillance colonoscopy) in patients with nonmild dysplasia versus mild dysplasia at index colonoscopy. The RRs are 1.78 (95% CI: 0.98-3.24) for Bonithon-Kopp et al<sup>17</sup> and 2.17 (95% CI 0.53-8.93) for van Stolk et al.<sup>8</sup> Data could not be extracted for Martinez et al<sup>6</sup> or Winawer et al.<sup>3</sup>

across studies in the incidence of advanced adenomas at surveillance colonoscopy. In the study by Martinez et al<sup>6</sup> nearly 12% of low-risk patients had recurrent advanced adenomas. These numbers contrast sharply with recurrence rates for advanced adenomas in low-risk patients in the studies by Bonithon-Kopp et al<sup>17</sup> (7.1%), van Stolk et al<sup>8</sup> (3.5%), and Winawer et al<sup>3</sup> (3.3%). Future studies should use consistent definitions of high risk and low risk to stratify their patients and use a consistent definition of advanced adenoma. Second, current studies rely on the advanced adenoma as the intermediate end point to define surveillance intervals. However, the natural history of the advanced adenoma is poorly understood, and

future research should attempt to quantify the proportion of advanced adenomas that develop into CRC and the period of time required for this transformation. Third, current studies also use variable definitions of risk factors (eg, increasing number of adenomas or increasing size of adenomas). Future research studies would be much easier to interpret if risk factors for recurrent advanced adenomas were more clearly defined (eg,  $\geq 3$  adenomas at index colonoscopy or adenoma  $\geq 10$  mm at index colonoscopy). Studies should also be powered to look more specifically at risk factors for advanced adenoma recurrence. The low incidence of recurrent advanced adenomas at surveillance colonoscopy makes it difficult to

perform multivariate logistic regression for more than a handful of risk factors and produces imprecise estimates because of lack of statistical power. Therefore, pooled analysis of existing databases may be helpful. Finally, we have very limited data about the incidence of recurrent advanced adenomas at 5-year surveillance colonoscopy in low-risk patients, and future studies should also address this topic.

In conclusion, published data provide limited support for multisociety guidelines, which state that low-risk patients with 1 or 2 small tubular adenomas at index colonoscopy do not need surveillance colonoscopy at 3-year intervals. Published data provide less support for ACS guidelines, which state that patients with 2 or more small adenomas should get surveillance colonoscopy at 3 years and patients with 1 small adenoma should get surveillance colonoscopy 3 to 6 years after the initial colonoscopy. In the future, large prospective studies or studies using pooled data from existing RCT databases or polyp registries should be used to better define which patients are at low risk for advanced adenoma recurrence. These data can then be used to make evidence-based recommendations for colon polyp surveillance intervals.

## DISCLOSURE

*The authors have no relevant disclosures to reveal.*

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Received November 16, 2005. Accepted June 19, 2006.

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Supported by NIDDK K23 Career Development Award K23DK060040-03. The opinions and assertions contained herein are the sole views of the authors and are not to be construed as official or as reflecting the views of the Department of Veterans Affairs.

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