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A Pooled Analysis of Advanced Colorectal Neoplasia Diagnoses following Colonoscopic Polypectomy

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Abstract

Background & Aims—Limited data exist regarding the actual risk of developing advanced adenomas and cancer following polypectomy or the factors that determine risk.

Methods—We pooled individual data from 8 prospective studies comprising 9167 men and women aged 22 to 80 with previously-resected colorectal adenomas to quantify their risk of developing subsequent advanced adenoma or cancer as well as identify factors associated with development of advanced colorectal neoplasms during surveillance.

Results—During a median follow-up of 47.2 months, advanced colorectal neoplasia was diagnosed in 1082 (11.8%) of the patients, 58 of whom (0.6%) had invasive cancer. Risk of a metachronous advanced adenoma was higher among patients with 5 or more baseline adenomas (24.1%; SE=2.2) and those with an adenoma 20 mm in size or greater (19.3%; SE=1.5). Risk

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factor patterns were similar for advanced adenomas and invasive cancer. In multivariate analyses, older age ($P<0.0001$ for trend) and male sex (odds ratio [OR], 1.40; 95% confidence interval [CI] 1.19–1.65) were significantly associated with increased risk of metachronous advanced neoplasia, as were the number and size of prior adenomas ($P<0.0001$ for trend), the presence of villous features (OR, 1.28; 95% CI 1.07–1.52), and proximal location (OR, 1.68; 95% CI 1.43–1.98). High-grade dysplasia was not independently associated with metachronous advanced neoplasia after adjustment for other adenoma characteristics.

Conclusions—Occurrence of advanced colorectal neoplasia is common following polypectomy. Factors that are most strongly associated with risk of advanced neoplasia are patient age and the number and size of prior adenomas.

In the United States, colorectal cancer is the third most common cancer in both men and women and the second leading cause of cancer death, accounting for nearly 150,000 new cases and 50,000 deaths annually¹. Colonoscopy screening with removal of adenomas is an effective strategy for reducing colorectal cancer incidence and mortality,^{2, 3} and it is one of several accepted screening modalities in the United States⁴. Among individuals who have one or more adenomas removed at colonoscopy, 20 to 50% will be found to have a metachronous lesion when undergoing follow-up (surveillance) colonoscopy within three to five years^{5, 6, 7, 8, 9}. As many as 20% of patients diagnosed with neoplasms during surveillance have advanced adenomas, defined as those with a diameter 10 mm or larger, having greater than 25% villous features, or having high-grade dysplasia^{5, 6, 7, 9, 10}, and a small, though not negligible, proportion are newly diagnosed with invasive colorectal cancer^{7, 11, 12, 13, 14, 15, 16}.

Professional groups have developed guidelines for surveillance colonoscopy intervals after polypectomy^{3, 17} with the goal of more efficient detection of early cancers or advanced adenomas, the latter carrying a presumed higher risk of progressing to invasive cancer. These guidelines use the characteristics of neoplasia at the most recent colonoscopy to classify patients as either higher or lower risk. Knowledge of the relation between patient characteristics or features of the baseline adenoma with risk of metachronous neoplasms, however, is based on a small body of scientific evidence¹⁸. Relatively few reports, including one meta analysis¹⁹, have addressed this issue, and none has been large enough to provide precise estimates of risk of advanced adenomas or invasive cancer. To clarify these issues, we pooled data from eight prospective studies to estimate absolute risks of metachronous advanced adenoma, colorectal cancer, and their combination (advanced colorectal neoplasia) and to identify patient characteristics and adenoma features that are independently associated with risk of these outcomes.

Materials and Methods

Study Population

The pooled analyses used patient-level data from eight North American studies^{6, 7, 10, 12, 20, 21, 22, 23} of patients with sporadic colorectal adenoma (Table 1). Six studies were randomized controlled trials^{6, 7, 12, 20, 21, 22}, and in two of these^{7, 20} a modest degree of efficacy of the intervention was demonstrated on the primary endpoint. Eligibility criteria for the chemoprevention trials were generally similar. However, study populations in the non-intervention studies^{10, 23} included average-risk individuals with a first-time diagnosis of adenomatous polyps. We aimed to include studies that met the following criteria: 1) 800 or more study participants; 2) study protocol requiring complete baseline colonoscopy with removal of one or more adenomas and removal of all visualized lesions; 3) a specified schedule of surveillance follow-up colonoscopies; and 4) availability of end-point data regarding the number, size, and histopathology of adenomas and colorectal

cancers detected in follow-up examinations. To our knowledge, we included all studies meeting these criteria that had reported findings by June 2005. Of the 10,021 men and women who were enrolled in the individual studies, we excluded patients who had a colorectal cancer present at baseline (n=27) and those who did not have a follow-up colonoscopy performed after the first six months of study (n=827), since these likely were individuals who were not under typical post-polypectomy surveillance. Thus, data for 9167 (91.5%) patients remained for inclusion in our pooled analyses.

Study Endpoints

We considered as endpoints all colorectal neoplasms that were diagnosed during an interval beginning six months after the baseline examination and ending on the date of the last protocol-specified colonoscopic examination. We excluded neoplasms found at colonoscopies conducted in the first six months following the baseline colonoscopy, since these examinations appeared to have been done primarily to address problems identified during the baseline colonoscopy and were not performed as surveillance procedures. In the course of each of the parent studies, staff reviewed the endoscopy and pathology reports to abstract data on number, size, and location of all neoplasms. For our analyses, we categorized anatomic location of lesions as proximal (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure), or distal (descending colon, sigmoid colon, and rectum). Histological features of colorectal neoplasms were determined from pathology reports generated by either an independent study pathologist or a community pathologist, depending on the individual study protocol (see Table 1). Definitions for adenomas were: tubular (25% or less villous component), tubulovillous (26 to 75% villous component), or villous (greater than 75% villous component). We considered advanced adenomas to be those that had one or more of the following features: 10 mm in diameter or larger, presence of high-grade dysplasia, or greater than 25% villous features (also classified as tubulovillous or villous histology). *We further combined advanced adenomas and invasive cancer into an endpoint of “advanced colorectal neoplasia”. Villous histology was included in our definition of advanced adenomas, although this was not the case in each of the original studies¹⁰. We tested whether villous features, high-grade dysplasia, and adenoma size were predictive of each of the features used to define advanced adenomas. The associations were similar across each of the features used to define advanced metachronous adenoma, suggesting that the inclusion of villous histology in our definition of advanced adenoma did not significantly influence the observed associations.*

Risk Factor Data

The studies had used self-administered questionnaires to obtain data on sociodemographic variables (age, sex, and race), cigarette smoking, family history of colorectal cancer in first-degree relatives, and history of polyps or adenomas before the baseline examination. Cigarette smoking status was classified as never, former, or current. Patient weight and height had been measured or self-reported according to study protocol. We calculated body mass index (BMI) by dividing weight (kg) by the square of height (m). Weight, height, and cigarette smoking were not ascertained in the National Polyp Study¹⁰. History of adenomas or polyps diagnosed before the baseline examination had been assessed by self report; the Veterans Affairs Cooperative Study²³ and the National Polyp Study¹⁰ only included individuals whose first adenoma was diagnosed at the baseline examination.

Data on baseline adenoma characteristics (number, size, location, histology, and high-grade dysplasia) had been ascertained from review of clinical and pathology reports; there were 957 patients whose pathology reports did not specify the presence or absence of villous features; these were included in the tubular adenoma group since their association with outcomes of interest were similar. The Antioxidant Polyp Prevention Study²⁴ and the

Calcium Polyp Prevention Study²⁰ did not collect data regarding the presence or absence of high-grade dysplasia in baseline adenomas.

Statistical Analysis

We generated summary descriptive data for baseline characteristics and endpoints for each study and for the total population. For each baseline characteristic, we estimated the absolute risk of colorectal neoplasia during the stipulated follow-up period for each specific outcome: non-advanced adenoma(s), one or more advanced adenoma(s), and invasive cancer. We also compared the absolute risk of advanced adenoma and cancer among patients defined as being at higher or lower risk according to the most recent surveillance guidelines³. In this categorization, the low-risk group included patients with one or two small (less than 1 cm), tubular adenoma(s) with low-grade dysplasia; the high-risk group included patients with three or more adenomas, or any adenomas 1 cm or larger, or with greater than 25% villous features, or with high-grade dysplasia.

We estimated pooled adjusted odds ratios for the study endpoints using logistic regression models that controlled for study, age, sex, race, smoking status, BMI, family history of colorectal cancer, history of polyp or adenoma prior to the baseline examination, and the baseline adenoma characteristics. There were too few cancers diagnosed in the study population to permit a full multivariate analysis of this outcome separately. Heterogeneity between study-specific risk estimates was assessed for each exposure variable separately by conducting a log likelihood ratio test²⁵ comparing the multivariate model presented in the tables with a multivariate model including additional interaction terms between each study indicator variable and the exposure variable of interest. Heterogeneity was assumed to be present when the likelihood ratio test yielded a P -value <0.05 . Given the lack of evidence of heterogeneity based on this criterion ($P=0.09$ for high-grade dysplasia and >0.30 for all other variables), pooled odds ratios (OR) and 95% confidence intervals (CI) computed from all individual data in unordered polytomous logistic regression models are presented for two principal outcomes, non-advanced and advanced neoplasms (advanced adenomas and invasive cancer).

We also conducted random-effects modeling using a two-stage method in which study-specific ORs and 95% CIs were first estimated, followed by estimation of summary ORs, weighted by the inverse of their variance²⁶. These results were not materially different from those of the fixed effects models presented. We considered the likelihood that differential follow-up time across studies might confound the observed associations. However, inclusion of a variable for follow-up time in the multivariate models did not appreciably alter the results. Tests for trend were conducted in separate analyses in which the exposure variable was modeled as an ordinal variable with values corresponding to the categorization level of that variable in the original analyses.

If a study, by design, had not collected information for a specific variable, we excluded it from the analyses that pertained to that factor (for example, the National Polyp Study data were not included in analyses of risk associated with BMI and smoking). In the case of data that were missing/unknown for other reasons, we first created a missing data indicator variable for missing responses and then compared the model results to those where the missing data observations were dropped from the analyses. The overall results were not appreciably different between models using these two approaches, and we present here the results from the models that included the missing data indicator variable.

Results

The study population of 9167 patients was predominantly male (71.2%) and Caucasian (89.1%), with a mean age of 62.0 years (Table 2). The median follow-up for the entire group was 47.2 months (range of medians among studies 36.9 to 59.0), and 46.7% of patients had at least one neoplasm diagnosed during this period (Table 3). Advanced adenomas were found during follow-up in 1024 patients (11.2% of the total population), and 58 (0.6%) had invasive colorectal cancer.

The proportions of patients diagnosed during follow-up with advanced adenoma or invasive cancer increased with age, male sex, and history of polyps or adenoma prior to the baseline examination (Table 4). Risk varied only slightly according to race, family history of colorectal cancer, smoking history, or BMI. Both advanced adenoma and invasive cancer occurred more often in patients with baseline adenomas that were larger, more numerous, were located proximally, had villous features, or had high-grade dysplasia. Risk of a metachronous advanced adenoma approached 20% in patients who had four or more baseline adenomas, or whose largest baseline adenoma was 20 mm in size or greater (Table 4). Risk of invasive cancer was 1.2% in patients who had larger (20 mm or greater) baseline adenomas and 1.3% in those who had prior lesions with high-grade dysplasia. Analyses that assessed risk according to surveillance guidelines' risk stratification categories³ showed a moderate degree of discrimination. Compared to patients who could be categorized as low-risk, those deemed high-risk were more often diagnosed with both advanced adenoma (15.5% vs. 6.9%) and colorectal cancer (0.8% vs. 0.5%). There was essentially no difference in the occurrence of non-advanced neoplasms.

In light of the similar risk factor patterns for advanced adenoma and invasive cancer (Table 4), we combined these two outcomes into a category of advanced colorectal neoplasms for subsequent analyses. Results of the multivariate models (Tables 5) indicate that after adjustment for other variables, older age was strongly associated with risk of advanced neoplasms (P -trend<0.0001). The odds of advanced neoplasms was modestly higher in men (OR, 1.40; 95% CI, 1.19–1.65) and in patients who reported a history of previous polyps (OR, 1.76; 95% CI, 1.48–2.09); it was not clearly associated with race, family history of colorectal cancer, current cigarette smoking, or obesity (defined as BMI of 30 kg/m² or greater). Adenoma number was strongly and independently associated with the odds of both advanced and non-advanced metachronous neoplasms (P -trend <0.0001). Patients with larger adenomas were also more likely to develop advanced neoplasms. Relative to patients with a baseline adenoma less than 5 mm, the adjusted odds for advanced neoplasms for those with an adenoma 10 to 19 mm was 2.27 (95% CI, 1.84–2.78), and for those with at least one 20 mm or larger it was 2.99 (95% CI, 2.24–4.00). Presence of any proximal adenoma at baseline was significantly associated with metachronous advanced neoplasms (adjusted OR, 1.68; 95% CI, 1.43–1.98). The strong association observed in the unadjusted statistical model between baseline villous histology and metachronous advanced neoplasia was attenuated in the multivariate analysis, and the association with baseline high-grade dysplasia essentially disappeared once adenoma size, histology, and location were included in the multivariate model. Study-specific analyses for baseline adenoma characteristics and advanced neoplasms showed consistent results across studies (Figure 1), a finding that supports the lack of statistically significant heterogeneity between study-specific risk estimates. Including in our multivariate models a variable for treatment assignment for those studies that entailed an intervention did not materially alter any of our results

Discussion

This pooled analysis of post-polypectomy patients showed that after a median of four years of follow-up surveillance, roughly one in ten patients was diagnosed with an advanced colorectal neoplasm, and approximately one in 150 was diagnosed with colorectal cancer. Development of metachronous advanced colorectal neoplasia was associated with the number, size, location, and histological features of prior adenomas, as well as with the age and sex of patients. Of these factors, patient age and adenoma size and number had the strongest association with risk.

Prior reports have indicated that risk of metachronous advanced adenoma and cancer is increased with adenoma multiplicity^{9, 10, 27, 28, 29, 30, 31}, villous features^{9, 29, 31, 32}, high-grade dysplasia^{9, 27, 29, 31, 33, 34}, and adenoma size^{5, 9, 28, 29, 30, 31, 34, 35}. The presence of proximal adenomas has also been associated with a higher likelihood of metachronous advanced colorectal neoplasia in some studies^{5, 27, 32}. However, reports from individual studies have been based on relatively small numbers of patients with metachronous advanced neoplasms and the estimates of risk have been imprecise. A report from one meta-analysis¹⁹ also indicated that prior adenoma number and high-grade dysplasia were predictive of subsequent advanced adenoma, but the investigators did not use subject-level data, and their conclusions were based on only four studies for adenoma number and two studies for high-grade dysplasia.

The large number of patients and endpoints in our pooling study allowed us to generate more precise risk estimates than have previously been reported and to perform multivariate analyses to assess independent contribution of various factors to risk of advanced neoplasia. In our data, both patient age and number of prior adenomas were strong predictors of risk; the proportion of patients who developed advanced neoplasia increased almost linearly with increases in these factors. Our multivariate analyses confirmed the independent importance of these two factors, as well as prior adenoma size and proximal location, in determining risk. We found that once other factors were accounted for, the presence of villous histology in a prior adenoma was only modestly associated with subsequent advanced neoplasia. We observed no independent association between family history and subsequent advanced colorectal neoplasia among post-polypectomy patients, unlike the stronger associations typically seen for family history in epidemiological studies of colorectal cancer incidence³⁶. Further, there were no clear associations between metachronous advanced neoplasia and current cigarette smoking or obesity; thus, these factors seem unlikely to add much information in assessing risk.

In our univariate analyses, high-grade dysplasia was clearly associated with risk; however, this association was largely explicable by other factors (e.g., prior adenoma size, location, and villous features). We are uncertain why our results in this regard differ from those in some^{9, 29, 34, 35}, though not all^{27, 33}, prior reports of an increased risk of metachronous advanced neoplasms associated with high-grade dysplasia. The apparent discordance in results may reflect differences in the extent to which other risk factors were taken into account in the various reports. Other possible explanations include differences in study populations or in the definition of high-grade dysplasia, which in our data was derived from reports produced by pathologists who were based in both academic and community hospital settings. Lastly, in our data only three percent of patients who had small, tubular adenomas also had high-grade dysplasia; the small number of these patients did not permit us to assess whether an isolated finding of high-grade dysplasia might be associated with increased risk.

Our pooled analyses were based on patients who were followed prospectively for four years on average, according to well-defined protocols, and with relatively few losses to follow-up,

thereby lessening the likelihood that differential follow-up intensity could bias the associations we observed. However, eligibility criteria for all the studies included in our analyses required an adequate colonic preparation and a full examination to the cecum; thus we were unable to assess the potential effects of variations in the quality of baseline colonoscopy examinations. Colonoscopy quality may be an important factor in routine clinical practice, and missed and incompletely excised lesions are thought to be likely explanations for some of the advanced adenomas and cancers found during surveillance^{11, 15, 16, 32, 37, 38}. Missing data for some variables also posed a challenge in our analyses; although we used two different methods to address this issue, we cannot exclude the possibility of bias resulting from these approaches³⁹.

The goal of surveillance is to minimize (not eliminate) the risk of interval cancer. Current risk stratification guidelines³ are based on small individual studies. Our pooled data represent the largest cohort of patients who have had systematic surveillance colonoscopy. These data show relatively good discrimination between low and high-risk groups (6.9 vs. 15.5%) using current risk-stratification guidelines. Thus, our results strengthen the concept of risk stratification and should lead to improved physician adherence to these guidelines. Enhanced adherence would have an improved impact on saving resources from inappropriate intensive surveillance in the lower risk group, which constitutes approximately 75% of those under surveillance⁴⁰. Nevertheless, the guidelines are not perfect; 7.4% of patients in our analyses who would be categorized as low-risk by the guidelines developed an advanced adenoma or invasive cancer during follow-up. Our data warrant consideration of additional risk factors, such as proximal location, sex, and age in the next iteration of the surveillance guidelines. Lastly, a formal prediction modeling analysis would be helpful in determining which combination of factors would maximally distinguish risk of recurrent advanced adenomas and cancers.

Results of our pooled data show that occurrence of colorectal neoplasia is common following colonoscopic polypectomy. Several patient characteristics and features of the prior adenoma are associated with advanced colorectal neoplasia at surveillance colonoscopy, the most important of these being the number and size of prior adenomas and patient age. Although current guidelines help stratify patients into high and low-risk groups, it may be possible to further refine estimates of risk for prediction risk modeling; our analyses point to a promising set of characteristics that might be considered in these analyses.

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Figure 1. Study-Specific and Pooled Multivariate Odds Ratios of Advanced Colorectal Neoplasia (Advanced Adenoma and Cancer) for Baseline Adenoma Characteristics

Odds ratios (ORs) are adjusted for age, sex, race, smoking status, BMI, family history of colorectal cancer, history of polyp or adenoma prior to the baseline examination, and the baseline adenoma characteristics. ORs for number and size of adenomas represent an increase in risk per adenoma and per 10mm increment, respectively. The black squares and horizontal lines correspond to the study-specific multivariate ORs and 95% confidence intervals (CIs), respectively. The area of the black square reflects the study-specific weight (inverse of the variance). The pooled ORs are based on data from 8814 patients due to missing data on baseline adenoma size and number for 353 individuals. The diamond represents the pooled multivariate OR and 95% CIs. The solid line represents an OR of 1.0. The abbreviations for the studies are listed in Table 1.

Table 1

Description of Studies Included in the Pooled Analyses^a

	APPS	NPS	CPPS	PPT	WBF	VA	AFT	UDCA
Number enrolled	864	1418	930	2079	1429	3121/895 ^b	1121	1285
Study design	4-arm trial	2-arm endoscopy study	2-arm trial	2-arm trial	2-arm trial	2-arm endoscopy study	3-arm trial	2-arm trial
Entry criteria	Any recent adenoma	First adenoma found at screening	Any recent adenoma	Any recent adenoma	Any recent adenoma	First adenoma found at screening	Any recent adenoma	Any recent adenoma
Recruitment period	1984–88	1980–1990	1991–1998	1991–1998	1990–1998	1994–1997	1994–1998	1995–1999
Age range (years)	25–79	22–88	27–80	35–89	40–80	50–75	29–79	40–80
Number of centers	6	7	7	8	1	13	9	2
Follow-up colonoscopy schedule	Years 1 and 4	Years 1 and 3 or Year 3	Years 1 and 4	Years 1 and 4	Years 1 and 3 for 889 patients; only year 3 for 415 patients	Years 2 and 5 for patients with large adenomas; only year 5 for patients with small adenomas	Year 3	Year 3
Number (%) completed ^c	837 (96.9)	939 (81.0) ^d	913 (98.2)	2024 (97.4)	1304 (91.3)	871 (97.3)	1086 (96.9)	1193 (92.8)
Study Pathologist Review (%)	100	96	0 (baseline) 100 (follow-up)	99	0	100	0 (baseline) 100 (follow-up)	0 ^e

^a APPS, Antioxidant Polyp Prevention Study²¹; NPS, National Polyp Study⁸; CPPS, Calcium Polyp Prevention Study²⁰; WBF, Wheat Bran Fiber study;¹² VA, Veterans Affairs Cooperative Study²³; AFT, Aspirin Folate Trial⁷; UDCA, Ursodeoxycholic Acid study²².

^b 3121 includes participants with and without polyps; 895 is population with adenomas at baseline that were included in the pooling analyses.

^c Indicates number of participants who underwent one or more follow-up colonoscopies.

^d Percent based on patients who were on study long enough to be due for one or more surveillance colonoscopies.

^e Study pathologist review was included for missing data.

Table 2

Baseline Characteristics of Patients

	APPS ^a (N=837)	NPS (N=939)	CPPS (N=913)	PPT (N=2024)	WBF (N=1304)	VA (N=871)	AFT (N=1086)	UDCA (N=1193)	Total (N=9167)
Age, mean (SD), y	61.1±8.3	61.0±9.9	61.0±9.1	60.6±10.0	65.7±8.8	63.0±6.9	57.4±9.6	65.8±8.5	62.0±9.5
Sex (%)									
Male	79.2	71.5	72.3	64.8	66.8	98.0	63.5	67.5	71.2
Female	20.8	28.5	27.7	35.2	33.2	2.0	36.5	32.5	28.8
Race (%)									
White	85.0	90.5	85.1	89.5	96.1	83.2	85.6	93.0	89.1
Black	6.8	7.0	8.0	8.2	0.8	9.6	5.8	0.7	5.7
Other	8.2	2.4	6.9	2.3	3.1	7.1	8.6	6.4	5.2
Family history of colorectal cancer ^b (%)									
No	78.5	77.6	67.6	69.8	75.8	84.5	51.4	71.3	71.4
Yes	19.4	22.4	21.2	24.8	17.0	15.5	30.7	27.8	22.8
Unknown	2.2	0.0	11.2	5.5	7.2	0.0	18.0	0.9	5.8
Cigarette smoking status (%)									
Never	30.9	N/A ^c	33.4	38.3	34.2	23.0	42.4	30.0	34.1
Former	45.4	N/A	47.4	48.2	52.1	55.1	42.5	56.3	49.6
Current	21.5	N/A	19.2	13.4	13.6	21.8	15.0	11.9	15.8
Unknown	2.2	N/A	0.0	0.0	0.2	0.1	0.1	1.8	0.5
Body mass index (kg/m ²) ^d (%)									
<25	31.6	N/A [§]	31.3	26.4	34.2	13.4	30.7	29.7	28.4
25–<30	48.9	N/A	44.2	46.6	45.0	45.2	46.8	44.6	45.9
30+	19.6	N/A	24.5	26.9	20.8	41.4	22.5	25.7	25.7
Previous polyp ^e (%)									
No	75.4	100.0	78.0	81.8	53.8	100.0	69.7	56.6	75.7

	APPS ^a (N=837)	NPS (N=939)	CPPS (N=913)	PPT (N=2024)	WBF (N=1304)	VA (N=871)	AFT (N=1086)	UDCA (N=1193)	Total (N=9167)
Unknown	23.5	0.0	21.5	18.2	34.7	0.0	29.9	43.4	22.4
	1.1	0.0	0.5	0.0	11.6	0.0	0.4	0.0	1.8
Mean no. of adenomas ^f	1.9±1.4	1.9±1.5	1.9±1.4	1.7±1.2	1.5±0.9	2.1±1.9	1.6±1.0	1.7±1.1	1.7±1.3
Location (%)									
Distal colorectum	58.7	60.4	52.8	52.3	46.8	39.8	40.0	37.2	48.4
Proximal only	19.1	14.7	24.1	28.3	31.8	34.7	34.5	36.7	28.6
Proximal and distal	22.2	21.4	22.9	17.4	15.3	25.5	13.7	19.7	19.1
Unknown	0.0	3.5	0.2	2.0	6.1	0.0	11.8	6.4	3.9
Size of largest adenoma, mean (SD) ^g , mm	8.7±6.0	11.2±7.3	7.4±5.6	8.3±7.1	8.3±5.9	7.7±6.5	7.3±5.3	8.9±5.9	8.5±6.4
Adenoma histology (%)									
Tubular ^h	57.2	81.8	81.1	79.6	78.7	87.8	85.8	79.3	79.3
Tubulovillous/villous	42.8	18.2	18.9	20.4	21.3	12.2	14.2	20.7	20.7
High-grade dysplasia (%)									
No	96.2	91.1	N/A ⁱ	92.1	79.0	94.7	N/A ^j	92.6	90.5
Yes	3.8	8.9	N/A	7.9	21.0	5.3	N/A	7.4	9.5

^aAPPS, Antioxidant Polyp Prevention Study²¹; NPS, National Polyp Study⁸; CPPS, Calcium Polyp Prevention Study²⁰; WBF, Wheat Bran Fiber study;¹² VA, Veterans Affairs Cooperative Study²³; AFT, Aspirin Folate Trial⁷; UDCA, Ursodeoxycholic Acid study²².

^bHistory of colorectal cancer in one or more parent, sibling or child.

^cExcludes 15 patients with missing data.

^dNo data available for NPS study patients.

^eHistory of previous polyps or adenomas prior to qualifying colonoscopy; NPS and VA study included only participants with a first-time adenomatous polyp.

^fExcludes 55 participants with missing data.

^gExcludes 353 participants with missing data.

^hIncludes 957 participants with adenomas where histology was not specified, unknown, or other histologies.

No data available for CPPS and AFT participants.

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Table 3

Patient Summary Endpoints During Surveillance Follow-up^a

	APPS ^b (N=837)	NPS (N=939)	CPPS (N=913)	PPT (N=2024)	WBF (N=1304)	VA (N=871)	AFT (N=1086)	UDCA (N=1193)	Total (N=9167)
Median follow-up, months (range)	49.1 (11.4–75.8)	36.9 (6.1–57.0)	48.6 (10.9–91.4)	52.1 (6.5–84.5)	39.1 (6.7–88.6)	59.0 (7.8–66.0)	36.9 (11.5–66.4)	38.0 (6.4–88.1)	47.2 (6.1–91.4)
Median number of colonoscopies (range)	2.0 (1.0–8.0)	1.0 (1.0–6.0)	2.0 (1.0–7.0)	2.0 (1.0–7.0)	2.0 (1.0–6.0)	1.0 (1.0–7.0)	1.0 (1.0–5.0)	1.0 (1.0–5.0)	2.0 (1.0–8.0)
Any adenoma during follow-up ^c , n (%)	432 (51.6)	324 (34.5)	428 (46.9)	1077 (53.2)	641 (49.2)	395 (45.4)	476 (43.8)	507 (42.5)	4280 (46.7)
Large adenoma ^d , n (%)	53 (6.3)	60 (6.4)	55 (6.0)	159 (7.9)	137 (10.5)	66 (7.6)	66 (6.1)	115 (9.6)	711 (7.8)
Tubulovillous/villous histology ^e , n (%)	110 (13.1)	15 (1.6)	103 (11.3)	82 (4.1)	82 (6.3)	23 (2.6)	76 (7.0)	89 (7.5)	580 (6.3)
High-grade dysplasia, n (%)	4 (0.5)	6 (0.6)	2 (0.2)	23 (1.1)	12 (0.9)	6 (0.7)	0 (0.0)	1 (0.1)	54 (0.6)
Advanced adenoma ^f , n (%)	128 (15.3)	64 (6.8)	120 (13.1)	195 (9.6)	177 (13.6)	69 (7.9)	108 (9.9)	163 (13.7)	1024 (11.2)
Colorectal cancer, n (%)	5 (0.6)	3 (0.3)	8 (0.9)	13 (0.6)	8 (0.6)	8 (0.9)	6 (0.6)	7 (0.6)	58 (0.6)

^aRefers to period beginning with six months after baseline colonoscopy to last colonoscopy included in the analysis.

^bAPPS, Antioxidant Polyp Prevention Study²¹; NPS, National Polyp Study⁸; CPPS, Calcium Polyp Prevention Study²⁰; WBF, Wheat Bran Fiber study¹²; VA, Veterans Affairs Cooperative Study²³; AFT, Aspirin Folate Trial⁷; UDCA, Ursodeoxycholic Acid study²².

^cPatients with one or more adenoma(s) or cancer detected at follow-up.

^dPresence of one or more adenoma(s) 10 mm or larger in diameter.

^ePresence of one or more adenoma(s) with greater than 25% villous features.

^fPresence of one or more advanced adenoma(s), defined as lesions having one or more of the following features: 10 mm or larger in diameter, greater than 25% villous features, or high-grade dysplasia.

Table 4

Risk of New Neoplasia at Follow-up, according to Baseline Patient and Adenoma Characteristics

Characteristic	Number (%)	Non-advanced adenoma % (95% CI)	Advanced adenoma % (95% CI)	Cancer % (95% CI)
Age, y				
< 40	154 (1.7)	18.8 (12.7–25.0)	3.9 (0.8–7.0)	0.0
40–49	804 (8.8)	27.7 (24.6–30.8)	6.3 (4.7–8.0)	0.1 (0.0–0.4)
50–59	2397 (26.1)	34.9 (33.0–36.8)	8.6 (7.5–9.8)	0.3 (0.1–0.6)
60–69	3676 (40.1)	36.0 (34.4–37.5)	12.2 (11.1–13.2)	0.6 (0.3–0.8)
70–79	2074 (22.6)	36.9 (34.9–39.0)	14.5 (13.0–16.0)	1.3 (0.8–1.7)
80+	62 (0.7)	33.9 (22.1–45.7)	17.7 (8.2–27.3)	1.6 (0.0–4.7)
Sex				
Female	2642 (28.8)	29.0 (27.3–30.7)	9.8 (8.7–10.9)	0.3 (0.1–0.5)
Male	6525 (71.2)	37.3 (36.1–38.4)	11.7 (10.9–12.5)	0.8 (0.6–1.0)
Race				
White	8166 (89.1)	35.0 (34.0–36.1)	11.4 (10.7–12.0)	0.6 (0.4–0.8)
Black	527 (5.7)	37.6 (33.4–41.7)	10.4 (7.8–13.0)	0.8 (0.0–1.5)
Other	474 (5.2)	29.1 (25.0–33.2)	8.9 (6.3–11.4)	1.3 (0.3–2.3)
Family history of colorectal cancer ^a				
No	6547 (71.4)	34.5 (33.4–35.7)	11.0 (10.3–11.8)	0.6 (0.4–0.8)
Yes	2089 (22.8)	36.7 (34.6–38.7)	11.6 (10.3–13.0)	0.6 (0.3–0.9)
Unknown	531 (5.8)	32.2 (28.2–36.2)	11.1 (8.4–13.8)	1.3 (0.3–2.3)
Cigarette smoking status ^b				
Never	2805 (34.1)	33.6 (31.9–35.4)	11.1 (9.9–12.2)	0.5 (0.2–0.8)
Former	4081 (49.6)	36.9 (35.4–38.4)	12.1 (11.1–13.1)	0.9 (0.6–1.2)
Current	1299 (15.8)	36.8 (34.2–39.4)	11.8 (10.0–13.5)	0.2 (0.0–0.5)
Unknown	43 (0.5)	34.9 (20.6–49.1)	9.3 (0.6–18.0)	2.3 (0.0–6.8)
Body mass index (kg/m ²) ^{c, d}				
<25	2332 (28.4)	32.2 (30.3–34.1)	11.7 (10.4–13.1)	0.5 (0.2–0.8)
25–<30	3771 (45.9)	36.6 (35.0–38.1)	11.6 (10.6–12.7)	0.7 (0.4–1.0)
30+	2110 (25.7)	38.1 (36.0–40.2)	11.6 (10.2–12.9)	0.8 (0.4–1.2)
Previous Polyp ^e				
No Yes	6941 (75.7)	33.4 (32.3–34.5)	9.8 (9.1–10.5)	0.6 (0.4–0.8)
Unknown	2057 (22.4)	39.5 (37.4–41.6)	15.2 (13.7–16.8)	0.8 (0.4–1.2)
	169 (1.8)	38.5 (31.1–45.8)	16.6 (11.0–22.2)	0.6 (0.0–1.7)
Adenoma Number ^f				
1	5465 (60.0)	30.2 (29.0–31.4)	8.6 (7.8–9.3)	0.5 (0.4–0.7)
2	2054 (22.5)	38.3 (36.2–40.4)	12.7 (11.3–14.1)	0.5 (0.2–0.9)

Characteristic	Number (%)	Non-advanced adenoma % (95% CI)	Advanced adenoma % (95% CI)	Cancer % (95% CI)
3	890 (9.8)	45.4 (42.1–48.7)	15.3 (12.9–17.6)	1.1 (0.4–1.8)
4	326 (3.6)	45.4 (40.0–50.8)	19.6 (15.3–23.9)	1.2 (0.0–2.4)
5+	377 (4.1)	51.2 (46.1–56.2)	24.1 (19.8–28.5)	0.8 (0.0–1.7)
Adenoma location				
Distal colorectum	4434 (48.4)	30.4 (29.1–31.8)	8.5 (7.7–9.3)	0.4 (0.2–0.6)
Proximal only	2620 (28.6)	37.3 (35.4–39.1)	11.8 (10.6–13.1)	0.8 (0.5–1.2)
Proximal and distal	1754 (19.1)	44.2 (41.9–46.6)	17.5 (15.7–19.3)	1.0 (0.6–1.5)
Unknown	359 (3.9)	26.7 (22.2–31.3)	8.1 (5.3–10.9)	0.0
Adenoma size ^g				
<5mm	2540 (28.8)	36.4 (34.5–38.3)	7.7 (6.6–8.7)	0.5 (0.2–0.8)
5–<10 mm	3115 (35.3)	36.8 (35.1–38.5)	8.7 (7.7–9.7)	0.5 (0.2–0.7)
10–<20mm	2487 (28.2)	31.4 (29.6–33.3)	15.9 (14.5–17.4)	0.8 (0.5–1.2)
20+ mm	672 (7.6)	31.8 (28.3–35.4)	19.3 (16.4–22.3)	1.2 (0.4–2.0)
Adenoma histology				
Tubular ^h	7268 (79.3)	35.1 (34.0–36.2)	9.7 (9.0–10.4)	0.6 (0.4–0.7)
Tubulovillous/villous ⁱ	1899 (20.7)	33.9 (31.8–36.0)	16.8 (15.1–18.5)	0.9 (0.5–1.4)
High-grade dysplasia ^j				
No	6485 (90.5)	35.3 (34.2–36.5)	10.6 (9.8–11.3)	0.5 (0.4–0.7)
Yes	683 (9.5)	35.9 (32.3–39.5)	16.0 (13.2–18.7)	1.3 (0.5–2.2)
Low-risk group ^k	4644 (50.7)	34.5 (33.1–35.8)	6.9 (6.2–7.6)	0.5 (0.3–0.7)
High-risk group	4523 (49.3)	35.3 (33.9–36.7)	15.5 (14.5–16.6)	0.8 (0.5–1.0)

^aPercent of patients with a particular outcome reported during surveillance + standard error.

^bHistory of colorectal cancer in one or more parent, sibling, or child.

^cNo data available for National Polyp Study participants (n=939)

^dExcludes 15 participants with missing data.

^eHistory of previous polyps or adenomas prior to qualifying colonoscopy; National Polyp Study and VA Cooperative Study included only participants with a first-time adenoma (n=1810).

^fNumber of adenomas detected at qualifying examination; excludes 55 participants with missing data.

^gSize of largest adenoma; excludes 353 participants with missing data.

^hIncludes participants with adenomas where histology was not specified, unknown, or other histologies (n=957).

ⁱOne or more adenoma(s) with greater than 25% villous features.

^jOne or more adenoma(s) with high-grade dysplasia. No data available for 1999 Calcium Polyp Prevention Study and Aspirin Folate Trial participants.

^kDefined according to the most recent surveillance guidelines³. The low-risk group includes patients with 1 to 2 small (less than 1 cm), tubular adenoma(s) with low-grade dysplasia; the high-risk group includes patients with 3 or more adenomas, or any adenomas 1 cm or larger in size, or with greater than 25% villous features, or with high-grade dysplasia.

Table 5

Pooled Odds Ratios of Colorectal Neoplasia for Baseline Patient and Adenoma Characteristics

	Crude OR (95% CI)		Adjusted O	R ^a (95% CI)
Characteristic	Non-advanced	Advanced	Non-advanced	Advanced
Age				
< 40	0.39 (0.26 – 0.59)	0.32 (0.14–0.73)	0.47 (0.31–0.72)	0.41 (0.18–0.94)
40–49	0.68 (0.57 – 0.81)	0.61(0.45–0.85)	0.72 (0.60–0.87)	0.67 (0.48–0.93)
50–59	1.00	1.00	1.00	1.00
60–69	1.13 (1.01–1.26)	1.56 (1.31–1.86)	1.10 (0.98–1.24)	1.39 (1.16–1.68)
70–79	1.25 (1.10–1.43)	2.09 (1.72–2.52)	1.21 (1.05–1.38)	1.72 (1.40–2.11)
80+	1.16 (0.66–2.05)	2.59 (1.30–5.15)	1.24 (0.69–2.25)	2.70 (1.31–5.57)
			<i>P</i> -trend<0.0001	<i>P</i> -trend<0.0001
Sex				
Female	1.00	1.00	1.00	1.00
Male	1.56 (1.41–1.72)	1.50 (1.29–1.74)	1.45 (1.30–1.62)	1.40 (1.19–1.65)
Race				
White	1.00	1.00	1.00	1.00
Black	1.11 (0.92–1.34)	0.97 (0.73–1.30)	1.12 (0.92–1.37)	1.08 (0.79–1.47)
Other	0.72 (0.59–0.89)	0.74 (0.54–1.01)	0.83 (0.67–1.03)	0.83 (0.60–1.16)
Family history of colorectal cancer ^b				
No	1.00	1.00	1.00	1.00
Yes	1.12 (1.00–1.24)	1.11 (0.94–1.29)	1.15 (1.03–1.29)	1.17 (0.99–1.38)
Cigarette smoking status ^c				
Never	1.00	1.00	1.00	1.00
Former	1.20 (1.08–1.33)	1.23 (1.05–1.43)		
Current	1.17 (1.02–1.35)	1.11 (0.90–1.38)	1.07 (0.96–1.20)	1.08 (0.92–1.27)
			1.16 (1.00–1.35)	1.13 (0.90–1.42)
Body mass index ^d (kg/m ²)				
<25	1.00	1.00	1.00	1.00
25–<30	1.23 (1.10–1.38)	1.09 (0.93–1.29)	1.10 (0.98–1.24)	1.00 (0.84–1.19)
30+	1.32 (1.16–1.51)	1.13 (0.94–1.36)	1.23 (1.08–1.41)	1.13 (0.93–1.38)
			<i>P</i> -trend=0.003	<i>P</i> -trend=0.226
Previous Polyp ^e				
No	1.00	1.00	1.00	1.00
Yes	1.50 (1.34–1.66)	1.95 (1.68–2.26)	1.37 (1.21–1.55)	1.76 (1.48–2.09)
Adenoma number				
1	1.00	1.00	1.00	1.00

	Crude OR (95% CI)		Adjusted O	R ^a (95% CI)
Characteristic	Non-advanced	Advanced	Non-advanced	Advanced
2	1.58 (1.42–1.77)	1.81 (1.54–2.14)	1.46 (1.30–1.64)	1.39 (1.17–1.66)
3	2.38 (2.04–2.79)	2.85 (2.30–3.54)	2.05 (1.73–2.42)	1.85 (1.46–2.34)
4	2.70 (2.09–3.48)	4.11 (2.99–5.63)	2.23 (1.71–2.92)	2.41 (1.71–3.40)
5+	4.30 (3.33–5.56)	6.94 (5.12–9.40)	3.63 (2.76–4.78)	3.87 (2.76–5.42)
			<i>P</i> -trend < 0.0001	<i>P</i> -trend < 0.0001
Adenoma location ^f				
Distal colorectum	1.00	1.00	1.00	1.00
Any proximal	1.78(1.62–1.95)	2.27 (1.98–2.60)	1.29 (1.16–1.44)	1.68 (1.43–1.98)
Size of largest adenoma				
<5 mm	1.00	1.00	1.00	1.00
5–<10 mm	1.03 (0.92–1.16)	1.15 (0.95–1.39)	1.01 (0.90–1.14)	1.17 (0.95–1.42)
10–<20 mm	0.92 (0.82–1.04)	2.18 (1.82–2.62)	0.94 (0.82–1.08)	2.27 (1.84–2.78)
20+ mm	1.02 (0.84–1.23)	2.92 (2.28–3.73)	1.00 (0.80–1.25)	2.99 (2.24–4.00)
			<i>P</i> -trend= 0.4944	<i>P</i> -trend < 0.0001
Adenoma histology				
Tubular ^g	1.00	1.00	1.00	1.00
Tubulovillous/villous ^h	1.09 (0.97–1.22)	1.96 (1.69–2.27)	1.05 (0.92–1.20)	1.28 (1.07–1.52)
High-grade dysplasia				
No	1.00	1.00	1.00	1.00
Yes	1.16 (0.97–1.38)	1.77 (1.41–2.22)	1.04 (0.86–1.26)	1.05 (0.81–1.35)

^a Adjusted for age, sex, race, family history of colorectal cancer, previous polyp, cigarette smoking, body mass index, baseline number of adenoma, adenoma size, location, histology, high-grade dysplasia, and study.

^b History of colorectal cancer in one or more parent, sibling, or child. Excludes 531 patients with unknown or missing data.

^c No data available for NPS study participants (n=939); excludes 43 participants with unknown or missing data from other studies.

^d No data available for NPS study participants (n=939); excludes 15 participants with missing data from other studies.

^e History of previous polyps or adenomas prior to qualifying colonoscopy. Excludes 169 participants with unknown or missing data.

^f Excludes 359 participants with unknown or missing data on location.

^g Includes 957 participants with adenomas where histology was not specified, unknown, or other histologies.

^h Adenomas with greater than 25% villous features.