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Adenoma Characteristics at First Colonoscopy as Predictors of Adenoma Recurrence and Characteristics at Follow-up

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Background & Aims: All patients with colorectal adenomas may not require identical follow-up. We aimed to determine if adenoma characteristics at initial colonoscopy could predict adenoma recurrence or characteristics at follow-up. *Methods:* The number of adenomas and the size, type, and degree of atypia in 479 patients in a polyp prevention trial were evaluated as predictors of the same characteristics at follow-up using odds ratios (ORs) with 95% confidence intervals (CIs). Multiple logistic regression analysis was performed to determine if several baseline characteristics were simultaneously associated with outcome. *Results:* Although several characteristics were significant predictors of recurrence univariately, by multivariate analysis, multiple adenomas at follow-up were more likely when patients had ≥3 baseline adenomas (OR, 2.25; 95% CI, 1.20–4.21) or at least 1 tubulovillous adenoma (OR, 2.12; 95% CI, 1.12–4.02). No specific characteristic was associated with recurrence of high-risk polyps (≥1 cm, villous, severe atypia). Seventy percent of patients with 1 or 2 baseline adenomas had no recurrence, and only 3.3% had any adenomas of clinical concern. *Conclusions:* Number and type of baseline adenomas predict recurrent adenomas, but the recurrence is rarely of clinical concern. Patients with 1 or 2 tubular adenomas constitute a low-risk group for whom follow-up might be extended beyond 3 years.

Colorectal adenomas are common benign neoplastic lesions found in up to 40% of Americans older than 50 in colonoscopy studies.[1–3] Age, site, and population characteristics are similar in patients with large bowel adenomas and those with colorectal cancer.[4–6] These older epidemiological data underlie the universal acceptance of the adenoma-carcinoma hypothesis. Until recently, all patients found to have adenomas were assumed to be at substantial risk of developing colorectal cancer and thus were believed to benefit from lifelong aggressive polyp surveillance.[5,7–9] However, most adenomas never become cancerous,[10] and recent reports have suggested that there are both low- and high-risk populations among patients with large bowel adenomas.[11–13]

Larger size, increased atypia, and villous histology increase the likelihood that a specific polyp may have cancer already within it[14–16] or will develop cancer over time.[17,18] Patients with multiple adenomas or adenomas with advanced pathological features have been found to have an increased risk of developing colon cancer.[11,15,19] However, these studies were conducted before systematic excision of all polyps was common during colonoscopy and thus may overestimate the risk of cancer developing after removal of colorectal adenomas.

We used data from a chemoprevention trial of adenoma recurrence to clarify whether baseline adenoma characteristics could be helpful in assessing either the risk of adenoma recurrence or the features of recurrent adenomas. Specifically, we wished to address whether baseline adenoma characteristics were predictive of the number of adenomas or the features of adenomas that were subsequently detected.

Materials and Methods

The Polyp Prevention Study was a randomized, double-blind, placebo-controlled clinical trial of antioxidant vitamins (β-carotene and vitamins C and E) to prevent recurrent colorectal adenomas.[20] The study involved six clinical centers in the United States. Patients were eligible if they had a large bowel adenoma removed during the previous 3 months, underwent a complete colonoscopy and were judged free of polyps, were younger than 80 years, and were in good health. The study design included a baseline colonoscopy to identify patients with adenomas, a 1-year clearing examination, and a final study examination 3 years later (year 4). The primary study end point was the occurrence of new adenomas between the colonoscopic examinations at year 1 and year 4. Of 864 patients randomized,

Abbreviations used in this paper: CI, confidence interval; OR, odds ratio.

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751 patients had both follow-up examinations and provided data for the primary efficacy analysis.

Because the antioxidant vitamins studied had no effect on polyp recurrence or characteristics,[20] we evaluated the adenoma data from all subjects rather than only those who received placebo. Of the 751 patients completing the parent trial, 541 were patients for whom the initial colonoscopy was their first colonoscopy ever, defined as the baseline examination. Complete histological data were available in 479 of these patients (77% male; mean age, 60 years; age range, 25–78). This comprised the final group used for analysis. It should be noted that the 62 patients excluded for incomplete histology did not differ from the final study group with respect to age, gender, race, and number or type of adenomas.

At baseline colonoscopy, we identified the number of adenomas and the size, histological type, and degree of atypia of the most advanced adenoma in each patient. The designation most advanced was determined ranking atypia from most severe to least, then type, and finally size. For the majority of our patients (96%), the most advanced adenoma was also the largest. The characteristics of adenomas at baseline and follow-up are given in Table 1. The adenoma characteristics from the baseline colonoscopy were then compared with those found at the final (year 4) colonoscopy. This is the analysis reported in our paper.

The original study design included a 1-year clearance examination that was standard practice at the time of patient recruitment and was based on the concern of polyps missed at the initial examination. The National Polyp Study addressed the 1-year examination specifically and determined that intervention at a 1-year time point did not alter the findings of important adenomas at a 3-year follow-up examination. Our study reports on adenoma characteristics at a first colonoscopy as predictors of recurrence and characteristics at a follow-up examination 3 years after clearance (at year 4). Adenomas found at the year 4 examination were assumed to be recurrent. To test our assumption that the findings at year 1 would not alter our results, we repeated our analysis (results not shown) adding the polyp data from year 1 to the baseline data. We also repeated the analysis adding the polyp data from year 1 to the year 4 findings. Our results were not altered and are not reported here. The mean (SD) interval between the baseline and year 4 colonoscopy was 4.2 (0.3) years.

Table 1. Characteristics of Polyps at Baseline and Follow-up

Characteristics	Baseline	Follow-up
No. of adenomas	n = 479	n = 479
None	—	65%
1	64%	21%
2	19%	8%
≥3	17%	6%
Maximum size (*cm*)	n = 479	n = 166[a]
<0.5	25%	58%
0.5–1	29%	32%
1–2	35%	9%
>2	11%	1%
Histological type of worst adenoma	n = 479	n = 166[a]
Tubular	54%	82%
Tubulovillous	46%	17%
Villous	1 Patient	1 Patient
Atypia	n = 479	n = 166[a]
Mild/moderate	95%	100%
Severe	4%	—
Invasive cancer	1%	—

[a]Three hundred thirteen patients had no adenomas at follow-up.

Statistical Analysis

The association of baseline adenoma characteristics to adenoma characteristics at the year 4 follow-up examination was assessed using odds ratios (ORs) and their confidence intervals (CIs). Multiple logistic regression analysis was used to determine whether several baseline polyp characteristics were simultaneously associated (significance level of ≤ 0.05) with outcome at the follow-up examination. The importance of each predictor was summarized by its OR and 95% CI. A CI that does not include 1.0 indicates that there is a significant relationship of the predictor with the outcome at the 5% significance level. Age, gender, clinical center, and the time interval between the baseline and year 4 colonoscopies were also included in the logistic model to adjust for the effect of these factors.

Comparison Groups

Number of adenomas. The number of baseline adenomas was analyzed as predictors in several ways. We first evaluated recurrence risk in patients with 1 adenoma vs. 2 or more adenomas at baseline. We then repeated the analysis using 1 or 2 adenomas vs. 3 or more adenomas at baseline. We chose 1 or 2 adenomas vs. 3 or more to perform most of the analyses because evidence from several studies suggests that patients with 1 or 2 adenomas have a similar and lower risk of adenoma recurrence and subsequent cancer than patients with more than 2 adenomas.[11,12,19,21]

Adenoma number as an outcome was also grouped in various categories (e.g., zero vs. any adenomas, or zero and 1 vs. 2 or more adenomas) to determine if specific baseline polyp characteristics predicted recurrence of multiple adenomas or only any adenoma recurrence. We report both, but our main analysis addresses the finding of multiple adenomas because patients with recurrence of multiple adenomas represent those at higher risk of continuing adenoma formation and cancer.[11,12,22]

Size of the most advanced adenoma. The size of the most advanced adenoma at baseline was combined into two groups: those with adenomas <1 cm and those with adenomas ≥1 cm. Adenomas found at follow-up were smaller than at baseline, and so the size of the recurrent adenomas was considered in two groups: <0.5 cm vs. polyps ≥0.5 cm. To accurately predict the occurrence of adenomas ≥0.5 cm at follow-up out of all 479 baseline patients, patients with no follow-up adenomas were counted in the smaller polyp size group. We considered using a cut-point of 1 cm as an outcome; however, the numbers were too small (17) to allow meaningful analysis.

Type of the most advanced adenoma. For both baseline and outcome, only the relationship of tubular adenomas vs. tubulovillous adenomas was examined because there was only 1 patient each with a villous adenoma at baseline and at year 4, respectively.

Atypia of the most advanced adenoma. Atypia as a baseline feature was combined into two groups: mild or moderate atypia vs. severe atypia combined with any malignant polyps (adenomas containing invasive cancer). Prediction of atypia as an outcome was not feasible because there were no polyps with severe atypia at year 4.

Results

Predictors of Multiple Adenomas

When each baseline characteristic was considered individually, the number of adenomas was the strongest predictor of any adenoma recurrence at a year 4 colonoscopy or of the recurrence of multiple adenomas. This was true when the analysis was performed using 1 vs. 2 or more adenomas and when the analysis was performed using 1 or 2 vs. 3 or more adenomas as the risk factor (Figure 1). Persons with 3 or more adenomas at baseline had more than three times the risk of having 2 or more adenomas after year 1 compared with those with only 1 or 2 baseline adenomas (Table 2). Indeed, patients with only 1 or 2 adenomas at baseline had an almost 90% chance (352 of 395) of having 1 or fewer adenomas at follow-up and a 70% chance (275 of 395) of having none.

The presence of tubulovillous type and severe or greater atypia also were significantly associated univariately with patients who later had 2 or more adenomas (Table 2). Polyp size at baseline was not associated with a higher rate of adenoma recurrence at year 4.

In multivariate analysis with all baseline predictors considered simultaneously and adjusted for age, gender, clinical center, and the time interval between the two colonoscopies, having 3 or more adenomas or a tubulovillous adenoma at baseline both independently increased the risk of having 2 or more adenomas at follow-up (Table 2).

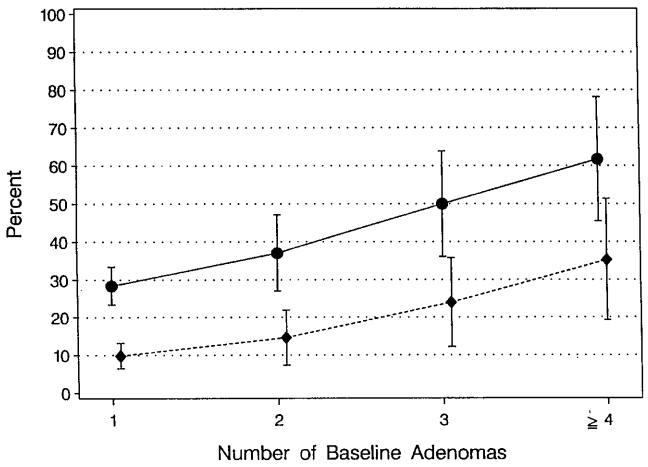

Figure 1. Percent of patients with any adenoma (——) or two or more adenomas (----) at year 4 colonoscopy depending on the number of baseline adenomas. 95% CIs are shown by the vertical bars.

Table 2. Relationship of Baseline Characteristics to Having Two or More Adenomas at Follow-up

Baseline adenoma characteristic	% With ≥2 adenomas	Univariate OR (95% CI)	Multivariate[a] OR (95% CI)
Number (n = 479)			
1 or 2 (395)	10.9	1.0	1.0
≥3 (84)	28.6	3.27 (1.85–5.79)	2.25 (1.20–4.21)[b]
Size (n = 479)			
<1 cm (259)	12.0	1.0	1.0
≥1 cm (220)	16.4	1.44 (0.86–2.42)	0.86 (0.46–1.59)
Type (n = 477)			
Tubular (257)	9.3	1.0	1.0
Tubulovillous (220)	19.5	2.36 (1.38–4.03)	2.12 (1.12–4.02)[b]
Atypia (n = 479)			
Mild/moderate (453)	13.0	1.0	1.0
Severe/carcinoma in situ or any invasion (26)	30.8	2.97 (1.24–7.13)	2.41 (0.90–6.47)

[a]Includes baseline characteristics shown as well as age, gender, clinical center, and time interval between the baseline and year 4 colonoscopies.
[b]A CI that does not include 1.0 implies there is a significant relationship of the factor with the outcome at the 5% significance level.

Predictors of Adenoma Size

A greater number of baseline adenomas also was associated with having subsequent adenomas >0.5 cm when each predictor was considered individually (Table 3). In addition, tubulovillous type was significantly associated with the size of recurrent adenomas. Baseline size seemed to be a marginally important predictor of later polyp size but did not reach statistical significance. When all baseline predictors were considered together, only having 3 or more adenomas at baseline was significantly related to having a polyp of ≥0.5 cm.

Predictors of Histological Type

When predicting the likelihood of having a tubulovillous adenoma at follow-up, baseline size and the presence of severe or worse atypia individually were important (Table 4). The number of adenomas and the type were not significantly associated with recurrent adenomas of tubulovillous type. By multivariate analysis, no factor was significantly related to having a tubulovillous adenoma after baseline. However, size and atypia were marginally important (Table 4).

Table 3. Relationship of Baseline Characteristics to Having at Least One Adenoma of > 0.5 cm at Follow-up

Baseline adenoma characteristic	% With adenoma of >0.5 cm	Univariate OR (95% CI)	Multivariate OR (95% CI)
Number (n = 479)			
1 or 2 (395)	11.1	1.0	1.0
≥3 (84)	31.0	3.58 (2.05–6.25)	2.71 (1.48–4.99)
Size (n = 479)			
<1 cm (259)	12.0	1.0	1.0
≥1 cm (220)	17.7	1.58 (0.95–2.64)	1.30 (0.71–2.38)
Type (n = 477)			
Tubular (257)	10.9	1.0	1.0
Tubulovillous (220)	19.1	1.93 (1.15–3.24)	1.39 (0.75–2.58)
Atypia (n = 479)			
Mild/moderate (453)	14.1	1.0	1.0
Severe/carcinoma in situ or any invasion (26)	23.1	1.82 (0.71–4.71)	1.31 (0.46–3.72)

To answer the question of whether having both a large size (≥1 cm) and ≥3 adenomas at baseline would result in an increased risk of having multiple subsequent adenomas above that predicted by each factor contributing separately, we examined whether there was an interaction between the size and number of adenomas. No significant interaction was found between these two factors or between any of the four baseline characteristics in their association with the number, size, or type of follow-up adenomas.

We then asked whether any characteristics predicted adenomas considered clinically important at follow-up, one that was ≥1 cm, of villous type, or had severe or worse atypia. No characteristic, either singly or in combination, was significantly associated with finding important adenomas subsequently (Table 5).

Table 4. Relationship of Baseline Characteristics to Having a Tubulovillous Adenoma at Follow-up

Baseline adenoma characteristic	% With a tubulovillous adenoma	Univariate OR (95% CI)	Multivariate OR (95% CI)
Number (n = 165)			
1 or 2 (119)	18.5	1.0	1.0
≥3 (46)	15.2	0.79 (0.31–2.00)	0.57 (0.20–1.63)
Size (n = 165)			
<1 cm (83)	10.8	1.0	1.0
≥1 cm (82)	24.4	2.65 (1.13–6.24)	2.74 (0.93–8.03)
Type (n = 164)			
Tubular (73)	15.1	1.0	1.0
Tubulovillous (91)	19.8	1.39 (0.61–3.16)	0.71 (0.24–2.14)
Atypia (n = 165)			
Mild/moderate (156)	16.0	1.0	1.0
Severe/carcinoma in situ or any invasion (9)	44.4	4.19 (1.05–16.71)	4.29 (0.83–22.17)

Discussion

The analysis suggests that the number of adenomas at first colonoscopy is a significant predictor of having recurrent adenomas found at a follow-up examination performed 3 years after clearance of the colon. This is a finding that is similar to results from the National Polyp Study.[12] Number was an important predictive factor of any adenoma recurrence as well as recurrence of 2 or more adenomas. Having 3 or more baseline adenomas also increased the likelihood that adenomas found at the follow-up examination were larger in size (≥0.5 cm). Having a tubulovillous adenoma at baseline also seems to be a predictor of multiple recurrent adenomas, a risk factor not reported by the National Polyp Study. Our data show that patients with 1 or 2 tubular adenomas, regardless of size or degree of atypia, are an identified group with a low risk (11%) of recurrence of multiple adenomas. In addition, 70% of such patients had no adenomas at follow-up.

Larger size of adenomas at baseline was not found to be a risk factor either for adenoma recurrence or for adenomas of larger size at follow-up, a finding that is contrary to several other published reports.[9,23–25] This is, in part, explained by the difference in study design. In our

Table 5. Relationship of Baseline Characteristics to Having a Clinically Important Adenoma at Follow-up

Baseline adenoma characteristic	% With important adenoma	Univariate OR (95% CI)	Multivariate OR (95% CI)
Number (n = 477)			
1 or 2 (393)	3.3	1.0	1.0
≥3 (84)	6.0	1.85 (0.64–5.34)	1.13 (0.40–3.18)
Size (n = 477)			
<1 cm (258)	4.3	1.0	1.0
≥1 cm (219)	3.2	0.74 (0.28–1.95)	0.49 (0.16–1.51)
Type (n = 475)			
Tubular (256)	3.5	1.0	1.0
Tubulovillous (219)	4.1	1.18 (0.46–3.02)	1.34 (0.44–4.04)
Atypia (n = 477)			
Mild/moderate (451)	3.5	1.0	1.0
Severe/carcinoma in situ or any invasion (26)	7.7	2.27 (0.49–10.43)	2.50 (0.45–13.73)

NOTE. At follow-up, 65% had no adenomas and only 3.5% had an adenoma ≥1 cm. A clinically important adenoma was defined as ≥1 cm, villous type, or with severe atypia or invasive cancer.

analysis, the follow-up for all patients was 4 years ±2 months. Other studies reported overall recurrence at follow-up intervals of wide range. It is to be expected that recurrent adenomas and larger lesions will be found in a patient population followed up for a longer time.

One possible explanation of the relationship between higher numbers of baseline adenomas and the finding of moderate-sized adenomas at outcome is that patients with numerous adenomas are more likely to have some polyps missed during their first examination. Studies addressing the miss rate of polyps at colonoscopy have indicated that the majority of missed polyps are small,[26] and one recent study reported similarly a higher miss rate in patients with multiple polyps.[22] Our analysis confirms the clinical suspicion that a mucosa that permits the growth of numerous tubular adenomas at baseline is the sort that is likely to have more adenomas found at follow-up, whereas a mucosa with few or no adenomas does not represent a similar fertile field for adenoma growth.

Since the publication of results from the National Polyp Study, the standard recommendation for the follow-up of most patients with colonic adenomas has been extended from 1 to 3 years.[12] Patients with 3 or more adenomas were identified as a subgroup with a higher risk for adenomas with advanced pathological features at the first follow-up examination, regardless of whether that examination was at 1 or 3 years. Histological type as a risk factor was not reported. A comprehensive Polyp Guideline published in 1993 included a statement that patients with multiple adenomas might require colonoscopy at 1 and 4 years but did not specify the definition of "multiple" and did not include a discussion of type as a risk factor.[27] Our analysis, in contrast, has evaluated patient risk by analyzing the characteristics of baseline adenomas that are known by the clinician after colonoscopic polypectomy. Knowing the number and the histological type of baseline adenomas at first colonoscopy allows the clinician to stratify patients into low- and high-risk groups for adenoma recurrence. Most adenomas detected at follow-up were of minor clinical concern. However, there is low power in our study to detect an increased relative risk for clinically important adenomas because of the low rate of such lesions.

From a clinical standpoint, the most useful part of polyp characteristic analysis at baseline is probably the identification of a low-risk group. Assuming that the colon lining has been well seen and all polyps have been completely removed, virtually all patients (excluding those with a genetic syndrome), regardless of polyp number, size, type, or degree of atypia, can probably safely wait 3 years for a follow-up examination. Furthermore, patients with only 1 or 2 tubular adenomas are at particularly low risk and might be equally well served by a longer interval before their first follow-up examination.

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