The Risk of Metachronous Neoplasia in Patients With Serrated Adenoma

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Key Words: Hyperplastic polyp; Serrated adenoma; Growth rate; Cancer risk; Colorectal cancer

DOI: 10.1309/VBAGV3BR96N2EQTR

Abstract

Serrated adenomas are the precursors of at least 5.8% of colorectal cancers; otherwise little is known of their clinical significance in comparison with conventional adenomas and hyperplastic polyps. We compared the risk of metachronous lesions in colorectal serrated adenomas, conventional adenomas, and hyperplastic polyps. A consecutive series of patients with colorectal polyps first diagnosed from January 1978 to December 1982 and follow-up specimens to the end of 2000 was reviewed, and 239 polyps fulfilling the selection criteria were chosen as index polyps. The type of polyp seen in follow-up correlated significantly with the type of the initial lesion. Serrated adenomas were estimated to grow faster than conventional adenomas, but the incidence of colorectal cancer did not differ significantly between serrated (2/38 [5%]) and conventional adenomas (2.2%). The results indicate that serrated adenomas are lesions with a significant risk of metachronous serrated adenomas and the development of cancer. We emphasize the need for the proper recognition and management of serrated adenomas.

Serrated adenomas are colorectal polyps that have the architectural but not the cytologic features of hyperplastic polyps.[1,2] Distinguishing between hyperplastic polyps and serrated adenomas might be difficult owing to the morphologic similarity of these lesions,[3] but their histogenetic relationship is uncertain. Serrated adenomas harbor malignant potential, and high-grade dysplasia has been observed in 11% of serrated adenomas.[1] Recently, Mäkinen et al[4] observed that serrated adenocarcinoma arising from serrated adenoma is a distinct clinicopathologic entity accounting for at least 5.8% of colorectal carcinomas. The hyperplastic polyp, generally considered a nonneoplastic lesion, has also been implicated in the development of this type of colorectal cancer through the putative hyperplastic polyp–serrated adenoma–colorectal cancer continuum,[4-10] owing to similarities in morphologic features, mucin production profile,[1,8,11] and DNA microsatellite instability.[4,12] A subset of serrated polyps show low expression of DNA mismatch repair enzymes hMLH1 and hMSH2,[13] which is possibly related to the CpG island hypermethylation of the *hMLH1* gene observed in serrated adenomas.[14] This supports the role of abnormal methylation in the putative serrated adenoma pathway of colorectal cancer pathogenesis and is in contrast with the conventional adenoma-carcinoma pathway.[14]

Serrated adenomas were characterized as a distinct entity by Longacre and Fenoglio-Preiser,[1] but the division of serrated polyps into hyperplastic polyps and serrated adenomas still is controversial in some cases. There has been a renewed interest in the classification of hyperplastic polyps and serrated adenomas.[2,13,15] Little is known about the actual behavior of serrated adenomas and their role in the putative hyperplastic polyp–serrated adenoma continuum.[6,10] Cohort follow-up studies evaluating the significance of colorectal polyps have

not, to date, considered serrated adenomas as a separate entity; therefore, these study results potentially are biased. The importance of distinguishing serrated adenomas from conventional adenomas and hyperplastic polyps in recurrence pattern, types of additional polyps, and cancer risk is not known. The aim of our study was to evaluate these features in a representative retrospective series of consecutive patients with serrated adenomas, conventional adenomas, and hyperplastic polyps during a 20-year follow-up period.

Materials and Methods

All studies were approved prospectively by the Oulu University Hospital Ethical Committee (Oulu, Finland). The initial cohort consisted of a consecutive series of 380 patients who had undergone biopsies of colorectal polypoid lesions at Oulu University Hospital from January 1978 through December 1982. The following groups were excluded: patients with nonneoplastic polyps other than hyperplastic polyps, such as inflammatory polyps and other reactive lesions (n = 113); patients with any known previous malignant neoplasm (n = 6); and patients with colorectal carcinomas occurring simultaneously or within 12 months (n = 22). This left 239 cases for follow-up analysis. Patients with a known family history of polyposis syndromes were not encountered in this material. The initial examinations included colonoscopy (49.4%), sigmoidoscopy (2.9%) and proctoscopy (45.2%); in 6 cases (2.5%), the type of procedure was not recorded.

If more than 1 endoscopy with biopsies was performed within the 6-year period (1978-1982), the earliest biopsy specimen was used as an index specimen, and the later ones were included in the follow-up material. All colorectal follow-up biopsy, surgical, and autopsy specimens until the end of 2000 were obtained from the files. All available demographic and follow-up data, including age, sex, and endoscopy findings about the size and location of the polyps, were obtained from pathology reports and patient records.

All slides were reevaluated separately by a pathologist (M.J.M.) and a trainee (O.E.J.), who were unaware of the patient's clinical details and any previous pathologic results. When there was disagreement, the diagnosis was decided after discussion between them. Polyps were classified as serrated adenomas, conventional adenomas, hyperplastic polyps, or admixed polyps **Image 1** and **Image 2**.

Conventional adenomas consisted of tubular, tubulovillous, and villous adenomas. Serrated epithelium was not a dominant feature in these adenomas.[10,16] Some hyperplastic polyps demonstrated mild architectural atypia, such as variation in crypt dimensions, cell proliferation extending throughout the basal half of the crypts, or occasional round nuclei in the surface with or without a prominent nucleolus (Image 2B). However, they had no dysplastic features (see the following discussion of serrated adenoma). These polyps initially had been classified as atypical hyperplastic polyps.[3]

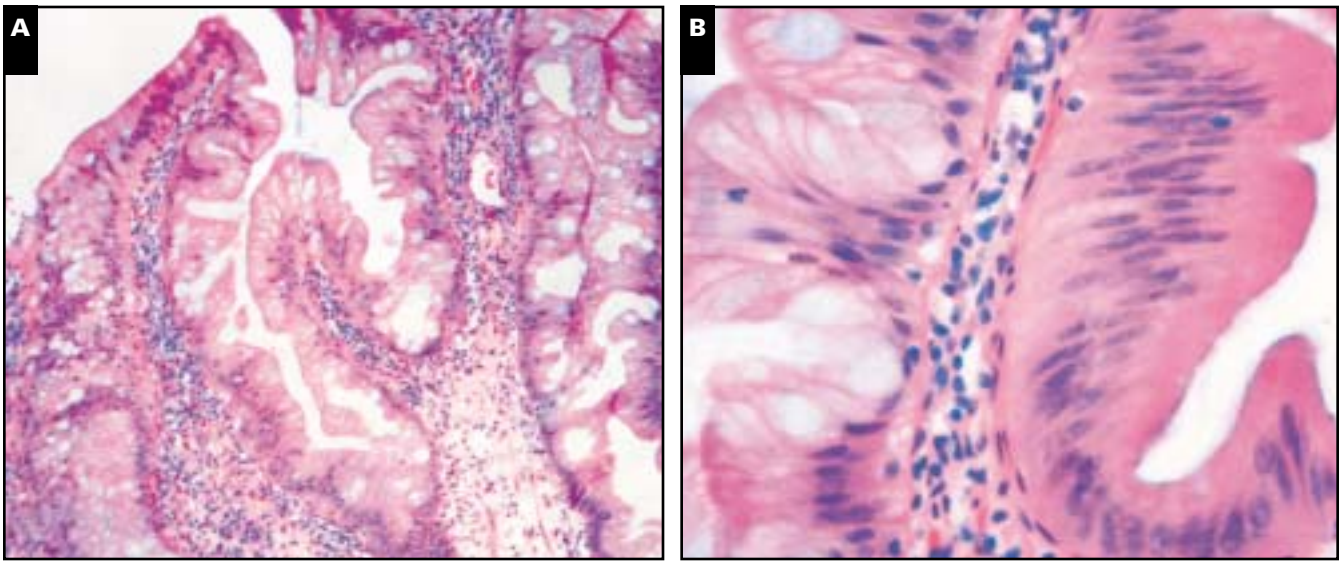

Image 1 Morphologic features of serrated adenoma (**A** and **B**), tubular adenoma (**C** and **D**), and villous adenoma (**E** and **F**). **A**, Serrated adenoma with the lowest grade of dysplasia is composed of serrated epithelial proliferation extending from the basal part of the crypts toward the surface (bottom-up manner). Crypts vary in size and shape and there are branching crypts (upper left). **B**, Higher magnification of the same polyp reveals serrated epithelium composed of cells with clear cytoplasm and very mild atypia (left), whereas in the neighboring crypt (right), cells have eosinophilic cytoplasm, penicillate nuclei, and more evident features of mild dysplasia.

DOI: 10.1309/VBAGV3BR96N2EQTR

Admixed polyps (mixed adenomatous/hyperplastic polyps) were composed of a conventional adenomatous component and benign hyperplastic component without cytological atypia.

Serrated epithelial proliferation and the presence of dysplasia were essential criteria for a diagnosis of serrated adenoma. The pattern of dysplasia in serrated adenomas differed from conventional adenomas. Serrated adenomas were characterized by the bottom-up growth of dysplastic cells, ie, atypical epithelium proliferating from the bottom of the crypts showing variable degrees of surface maturation (Image 1A).[10]

Minimum cellular changes required for the diagnosis of dysplasia in serrated adenoma consisted of nuclear atypia (enlargement, size and shape variation) and epithelial disorganization (nuclear stratification, nuclear polarity irregularities) at the superficial part of the crypts and the presence of cellular atypia with or without cellular disorganization at the surface epithelium (Images 1B and 2C). Structural irregularity, such as irregular branching or crowding of the crypts (Image 1A), was used as an additional criterion for dysplasia, but in the absence of cellular abnormalities, it was not considered diagnostic.

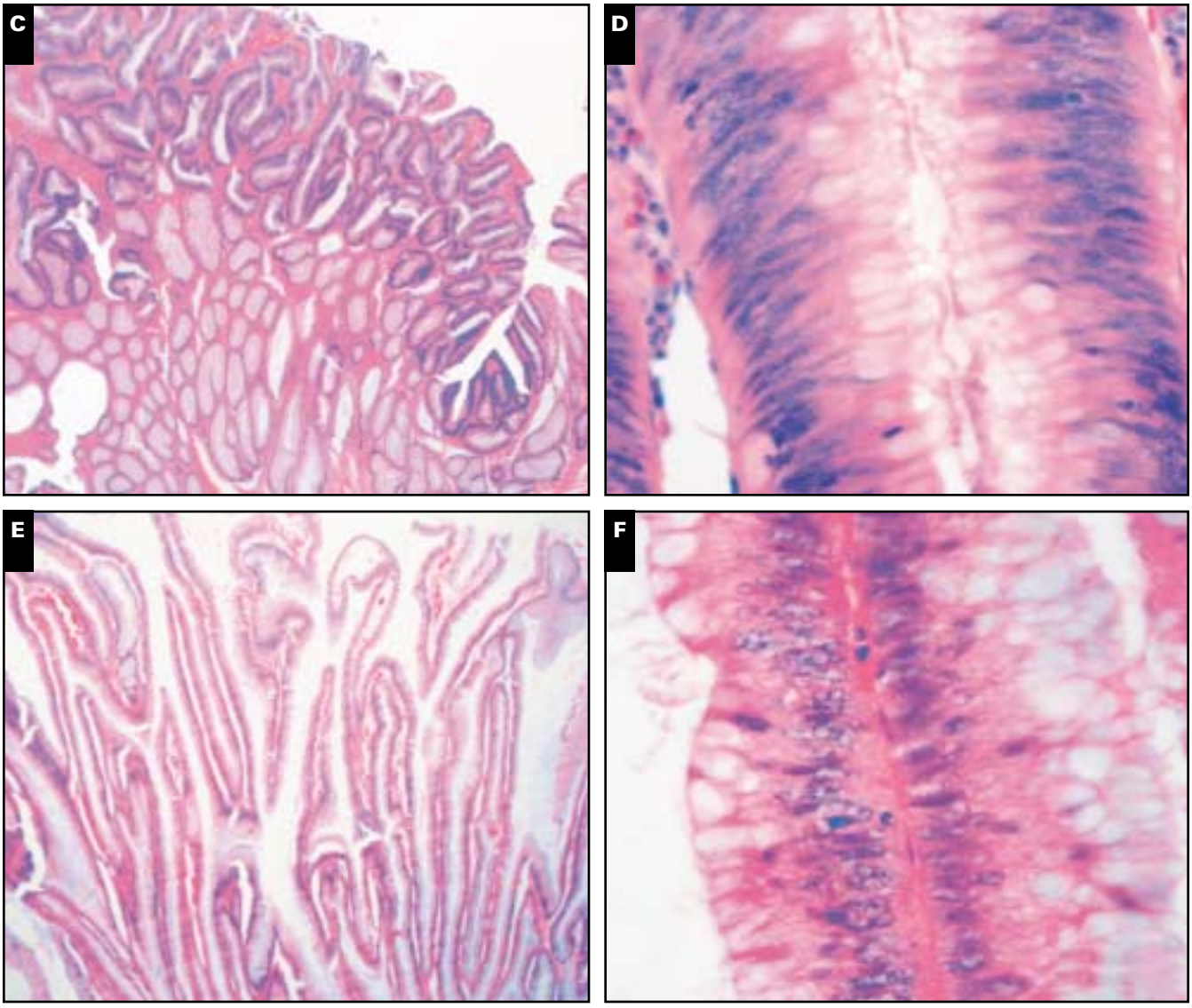

Image 1 **C**, A conventional tubular adenoma with moderate dysplasia is composed of cells growing in a top-down manner. **D**, Higher magnification reveals nuclear stratification and penicillate nuclei, but the epithelium of conventional adenoma lacks evidence of serration. **E**, Conventional villous adenoma with moderate dysplasia is composed of villous structures without serrations. **F**, Higher magnification reveals nuclear stratification, and cells show variable differentiation toward goblet cells. (H&E; **A**, ×42.5; **B**, ×360; **C**, ×25; **D**, ×320; **E**, ×20; **F**, ×360)

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In mild serrated dysplasia, the maturation of the cells toward the surface epithelium was even and reminiscent of hyperplastic polyps (Images 1B and 2C). Nuclear stratification, usually present in the basal or upper parts of the crypts, was not necessarily observed in the surface epithelium. In moderate serrated dysplasia (Image 2D), cells usually were eosinophilic, showing nuclear hyperchromasia and coarse chromatin and stratification of the nuclei. In severe serrated dysplasia, the epithelium often was basophilic and lacked epithelial maturation. A higher degree of nuclear stratification was present, and there were varied amounts of conspicuous serration (Image 2E).

Conventional, ie, nonserrated adenomatous epithelium was not present in serrated adenomas, and serrated dysplasia was not a predominant feature in conventional adenomas (Images 1C through 1F). Dysplasia in conventional adenomas was characterized by the top-down growth of dysplastic cells (Image 1C), and, in contrast with serrated adenomas, penicillate nuclei and cytoplasmic basophilia were frequent features of all conventional adenomas (Images 1D through 1F).[16] In mild adenomatous dysplasia, tubular or villous structures were nonserrated and the cells had slightly decreased mucin production, elongated nuclei, and preserved polarity and maturation. In moderate dysplasia, the nuclei were penicillate or ovoid, enlarged, and

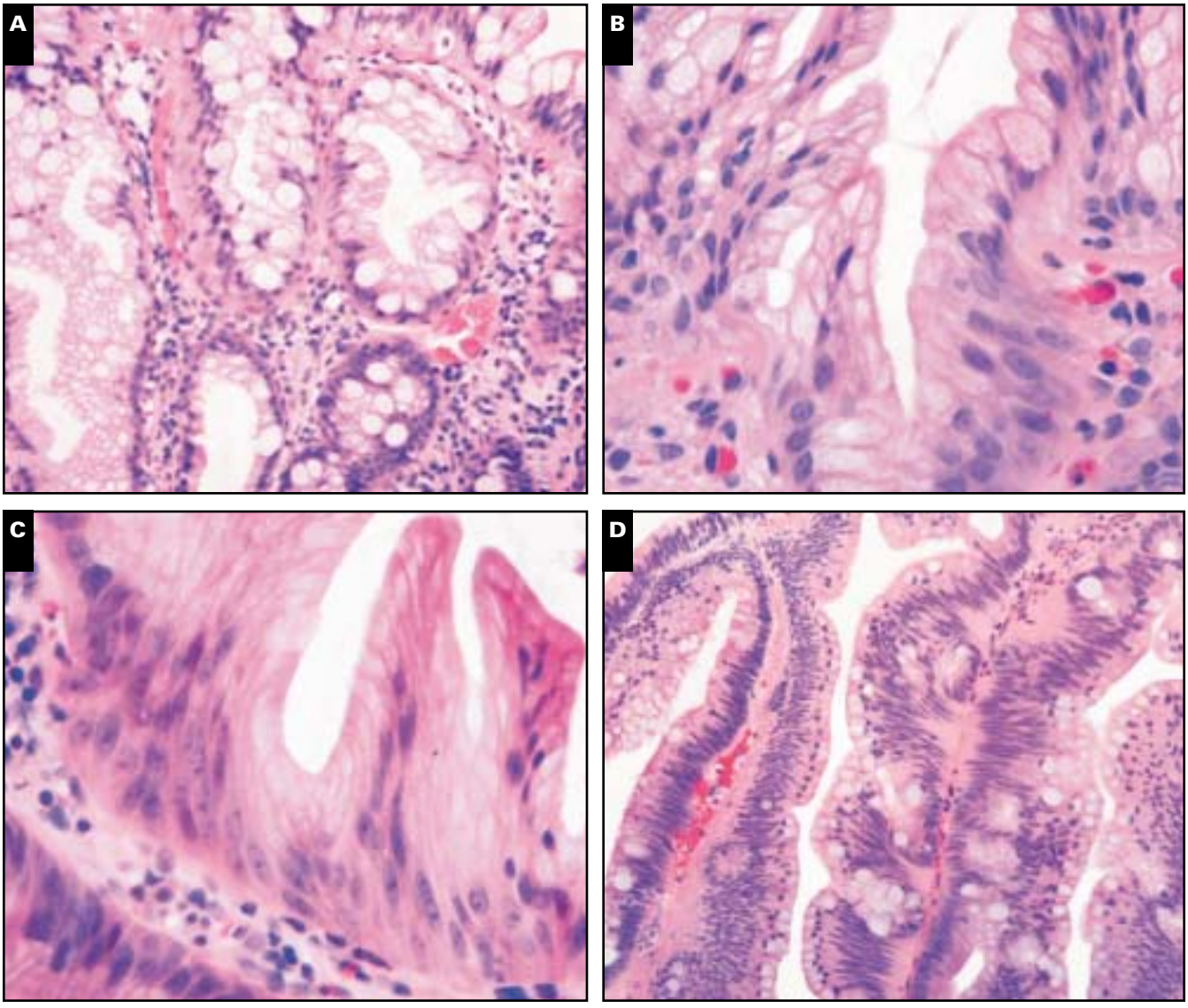

Image 2 Morphologic features of hyperplastic polyps (**A** and **B**), serrated adenomas (**C**, **D**, and **E**), and serrated adenocarcinoma (**F**). **A**, Hyperplastic polyps are composed of mature serrated epithelium and crypts of uniform size. **B**, Another sample of a hyperplastic polyp shows nuclear stratification in the surface epithelium but without features of dysplasia. **C**, **D**, and **E**, Serrated adenomas with various degrees of dysplasia. **C**, In mild dysplasia, cells resemble hyperplastic polyps, but nuclei are enlarged and nucleoli are present. **D**, In moderate dysplasia, a serrated adenoma shows nuclear stratification with some resemblance to tubulovillous adenoma, but cells are eosinophilic and a serrated pattern is recognizable.

DOI: 10.1309/VBAGV3BR96N2EQTR

hyperchromatic and the loss of goblet cell maturation was evident. In severe dysplasia, cribriform, budding, or back-to-back glandular, nonserrated structures were present and accompanied by a high nuclear/cytoplasmic ratio and high-grade nuclei.

If more than 1 polyp type was encountered in the initial endoscopy specimen, the one with the highest grade of dysplasia was chosen as the index polyp. When synchronous serrated adenomas and conventional adenomas were present, the polyp with the higher grade of dysplasia was chosen, and in the case of 2 or more similar polyps, the largest was chosen as the index polyp.

Statistical Analysis

Computer-assisted statistical analyses were used (SPSS version 9.0, SPSS, Chicago, IL, and CIA 2.0.0, London, England). Analyses used were the *t* test, Kruskal-Wallis test, χ^2 test, and Fisher exact test for small numbers and confidence interval analysis.

Role of the Funding Source

The sponsors of this study had no role or influence in the design, planning, or data collection, analysis, and interpretation or in manuscript preparation.

Results

Index Polyps

The distribution of index polyp types in relation to sex and age in 239 cases included in the follow-up are given in **Table 1**, and examples of different polyp types are shown in Images 1 and 2. In each case, a polyp with the presumed highest clinical significance was selected as the index polyp, as described in the "Materials and Methods" section.

Of 56 hyperplastic polyps, 23 (41%) showed features of "atypical hyperplastic polyp."[3] Because follow-up analysis showed that these polyps did not differ from other hyperplastic polyps in type and cancer evolution, we combined them with other hyperplastic polyps for analysis. Of 38 serrated adenomas, 17 (45%) originally were diagnosed as hyperplastic polyps and 17 (45%) as adenomatous polyps, including 7 (18%) tubular adenomas, 9 (24%) tubulovillous adenomas, and 1 (3%) villous adenoma. Two cases were diagnosed as inflammatory polyps and another 2 were not otherwise specified. Reevaluation of serrated adenomas revealed that 21 (55%) showed low, 11 (29%) moderate, and 6 (16%) severe dysplasia; corresponding values among 137 conventional adenomas were 55 (40.1%), 77 (56.2%), and 5 (3.6%), respectively.

No statistically significant differences were observed in the sex distribution among polyp types. Patients with serrated polyps (hyperplastic polyps and serrated adenomas, n = 94; mean age, 53.4 years) were younger than patients with conventional adenomas (n = 138; mean age, 58.0 years; $P = .009$; *t* test). There was a weak trend toward younger age for patients with hyperplastic polyps than for patients with serrated adenomas (Table 1; $P = .114$; *t* test) and for patients with conventional adenomas ($P = .104$). Patients with hyperplastic polyps were younger than patients with conventional tubular (Table 1;

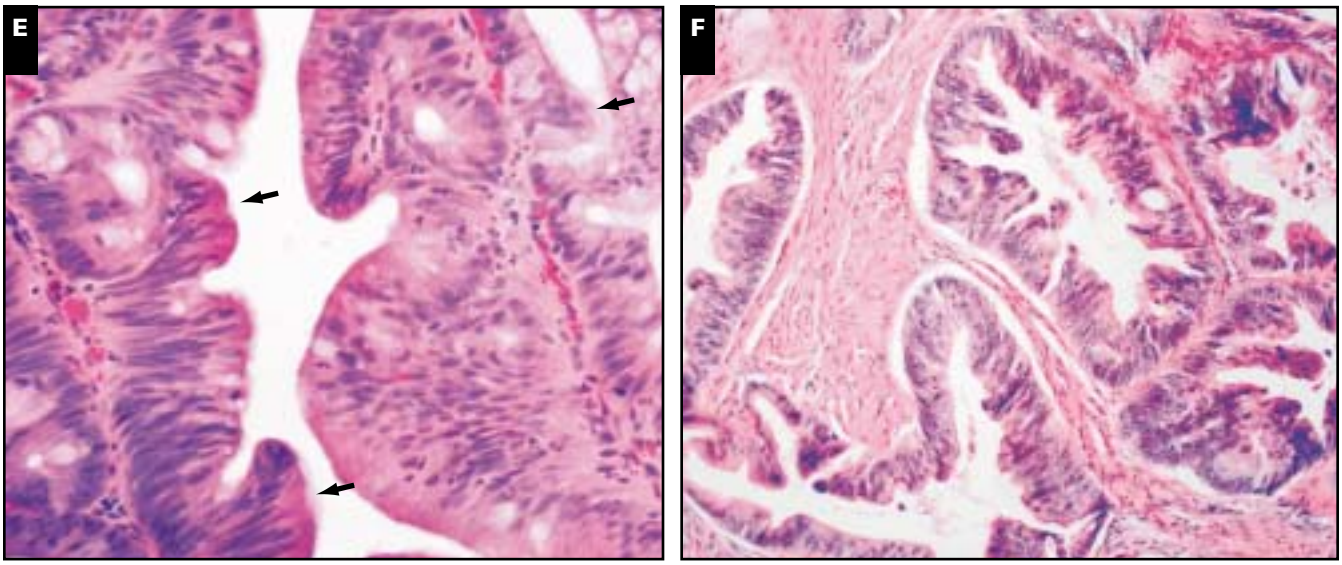

Image 2 **E**, In severe dysplasia, the architecture is disorganized and the polarization of the cells is disturbed, but a serrated contour is still present (arrows). **F**, Serrated adenocarcinoma from a patient with preexisting serrated adenoma. (H&E; **A**, ×150; **B**, ×400; **C**, ×400; **D**, ×160; **E**, ×200; **F**, ×100)

DOI: 10.1309/VBAGV3BR96N2EQTR

Table 1
Sex and Age Distribution of 239 Patients by Type of Index Polyp

Index Cases	No. of Cases	M/F	Sex Ratio (M/F)	Mean Age (Range), y
Hyperplastic polyp	56	31/25	1.2:1	51.3 (3-72)
Serrated adenoma	38	23/15	1.5:1	56.4 (22-85)
Mixed hyperplastic polyp	7	4/3	1.3:1	60.2 (43-70)
Conventional tubular adenoma	119	75/44	1.7:1	57.4 (30-84)
Conventional tubulovillous (n = 17) and villous adenoma (n = 2)	19	10/9	1.1:1	61.6 (33-82)

P = .002) and patients with tubulovillous adenomas (Table 1; P = .005), but no significant age difference was observed between patients with serrated adenomas and those with conventional adenomas.

In our analysis of the relationship of polyp type to age of the patient at the time of diagnosis of each serrated polyp, we found that in whole case material, in which follow-up polyps also were included, hyperplastic polyps (n = 59; 55.1%) were more common than serrated adenomas (n = 48; 44.9%) in patients younger than 48 years at initial examination. However, hyperplastic polyps (n = 86; 42.2%) were less common than serrated adenomas (n = 118; 57.8%; P = .029; χ^2) in patients older than 48 years.

The follow-up period ranged from 1 to 254 months (mean, 94 months) and totaled 1,271 person-years. During this time, 489 colorectal procedures were done in 153 (64.0%) of 239 cases. During follow-up, pan-colonoscopy was performed at least once in 109 subjects (71.2%), whereas a minority received less extensive procedures. Seven patients (4.6%) received sigmoidoscopy and 28 (18.3%) proctoscopy.

Colectomy was performed in 7 cases (4.6%). In 2 cases (1.3%), no description of the type of follow-up-procedure was available.

Polyps occurring before 6 months of follow-up were omitted from the study, based on the assumption that they represented a residual polyp rather than a metachronous lesion. No difference was observed in the length of the follow-up between different types of index polyps (P = .604; Kruskal-Wallis test), but the number of follow-up procedures was lower after an initial diagnosis of hyperplastic polyp than in other groups (P = .024, Kruskal-Wallis test). In 155 follow-up endoscopies, no polyps were found and mucosal biopsy results were normal. In 68 endoscopies, all polyps removed were inflammatory polyps. The distribution of follow-up polyps in relation to the index diagnosis is given in **Table 2**. The subsequent polyp type was strongly dependent on the index polyp type (Table 2). When the index polyp was hyperplastic, the follow-up polyps were most likely to be hyperplastic polyps. Conversely, all other index polyp types were less likely to manifest with hyperplastic polyps on follow-up at a 95% confidence interval level (Table 2). The same was true for serrated adenomas and conventional adenomas (Table 2).

Table 2
Relationship Between Index and Follow-up Polyp Types

Index Polyp Type (No. of Cases)	Type of Follow-up Polyp (No. of Polyps)	Mean No. (Range)	Percentage	95% CI	99% CI
Hyperplastic polyp (56)	Hyperplastic polyp (174)	3.10 (0-33)	93.0	1.419 to 4.795	0.860 to 5.355
	Serrated adenoma (3)	0.05 (0-1)	1.6	–0.007 to 0.114	–0.027 to 0.135
	Conventional adenoma (10)	0.17 (0-3)	5.3	0.033 to 0.324	–0.015 to 0.372
Serrated adenoma (38)	Hyperplastic polyp (17)	0.45 (0-8)	18.3	0.004 to 0.891	–0.147 to 1.042
	Serrated adenoma (70)	1.84 (0-7)	75.3	1.368 to 2.316	1.206 to 2.478
	Conventional adenoma (6)	0.16 (0-2)	6.5	0.017 to 0.307	–0.032 to 0.357
Admixed polyp (7)	Hyperplastic polyp (1)	0.14 (0-1)	3.4	–0.207 to 0.492	–0.387 to 0.672
	Serrated adenoma (3)	0.42 (0-2)	10.3	–0.299 to 1.156	–0.674 to 1.531
	Conventional adenoma (25)	4.16 (0-9)	86.2	0.589 to 7.795	–1.254 to 9.588
Conventional tubular adenoma (119)	Hyperplastic polyp (100)	0.84 (0-14)	19.2	0.486 to 1.195	0.372 to 1.309
	Serrated adenoma (54)	0.46 (0-15)	10.4	0.148 to 0.768	0.048 to 0.868
	Conventional adenoma (366)	3.07 (0-48)	70.4	2.129 to 4.022	1.824 to 4.327
Conventional tubulovillous adenoma (17)	Hyperplastic polyp (3)	0.18 (0-2)	5.5	–0.095 to 0.448	–0.198 to 0.551
	Serrated adenoma (3)	0.18 (0-2)	5.5	–0.095 to 0.448	–0.198 to 0.551
	Conventional adenoma (49)	2.88 (0-49)	89.1	0.968 to 4.797	0.245 to 5.520
Conventional villous adenoma (2)	Hyperplastic polyp (0)	—	0.0	—	—
	Serrated adenoma (0)	—	0.0	—	—
	Adenoma (7)	3.50 (3-4)	100.0	–2.853 to 9.853	–28.328 to 35.328

CI, confidence interval.

DOI: 10.1309/VBAGV3BR96N2EQTR

Development of Cancer

During follow-up, 5 colorectal cancers were diagnosed after a mean of 12 years. Clinical and pathologic data are described in **Table 3**. Our data suggest that patients with serrated adenomas may have a higher risk of cancer (2/38 [5%]) than patients with conventional tubular adenoma (1/119 [0.8%]; $P = .146$; Fisher exact test). No significant differences were found in cancer rates between serrated adenoma and conventional tubulovillous adenoma cases (2/17 [12%]; $P = .363$; Fisher exact test) or serrated adenoma and any conventional adenoma cases (3/138 [2.2%]; $P = .295$; Fisher exact test). The difference between conventional tubular and tubulovillous adenoma was statistically significant ($P = .041$; Fisher exact test). With Kaplan-Meier analysis, no difference in the risk for cancer was observed between serrated adenomas and conventional adenomas (log rank = 0.35; $P = .552$). The carcinomas arising from patients with serrated adenoma were serrated adenocarcinomas (ie, they were composed of a serrated malignant epithelium [Image 2F]), while no such feature was seen in other carcinomas (Table 3).

Site, Size, and Growth Rate of Polyps

The location of polyps observed in pan-colonoscopy specimens in index and follow-up lesions is described in **Table 4**. Nearly 90% of serrated polyps were located in the rectum or sigmoid colon (Table 4). The anatomic distributions of hyperplastic polyps and serrated adenomas did not differ ($P = .081$; Fisher exact test). More than 63% of conventional adenomas were found in the rectum and sigmoid colon, but elsewhere in the colon, their distribution was more even, differing from hyperplastic polyps ($P < .00001$; Fisher exact test) and serrated adenomas ($P = .029$; Fisher exact test), which were distributed mostly in the rectum or sigmoid colon.

To study size distribution, the largest polyp at each follow-up endoscopy was used. The 528 polyps used for analysis included 110 serrated adenomas, 276 conventional adenomas, and 142 hyperplastic polyps **Table 5**. Serrated adenomas and conventional adenomas were significantly larger than hyperplastic polyps (Table 5), whereas no significant difference in size was found between serrated and conventional adenomas ($P = .746$; Kruskal-Wallis test; Table 5).

In most cases, synchronous polyps identified during the index endoscopy were of the same histologic type as the index polyp **Table 6**. In patients with a hyperplastic index polyp, 41 (73%) of 56 had at least 1 accompanying hyperplastic polyp. In cases with a serrated adenoma index polyp, 33 (87%) of 38 had 1 or more accompanying serrated adenomas and 2 (5%) of 38 had hyperplastic polyps but no conventional adenomas. In cases of conventional adenoma, 94.2% had 1 or more accompanying conventional adenomas (Table 6).

The number of polyps per year in cases with recurring polyps is shown in **Table 7**. The mean number of recurring serrated adenomas was higher than other polyps, although the difference between the groups was not significant because the 95% confidence intervals overlapped (Table 7).

To assess the growth rates of hyperplastic polyps, serrated adenomas, and conventional adenomas, we analyzed a subset of recurring polyps. The selection criteria were as follows:

Table 3
Clinical and Pathologic Data From Five Cases of Cancer That Developed During Follow-up*

Case No.	Index Polyp Type	Size (mm)	Dysplasia	Sex	Time (y)	Age (y)	Follow-up Polyp Type /Site	Site of Index Polyp/Cancer	Serrated Morphologic Features	Grade/ Stage
57	SA	7	Moderate	F	17.1	50	1 SA/AC	AC/AC	Yes	G3/T3 N0 M0
239	SA	10	Severe	M	11.4	66	1 SA/R; 1 TA/SC	R/R	Yes	G2/T4 N2 M1
95	CTA	2	Mild	F	10.9	67	0	R/DC	No	G2/T3 N0 M0
220	CTVA	15	Mild	M	7.3	76	1 HP/R	SC/SC	No	G2/T2 N0 M0
221	CTVA	10	Moderate	M	13.3	56	2 R	R/R	No	G2/T2 N0 M0

AC, ascending colon; CTA, conventional tubular adenoma; CTVA, conventional tubulovillous adenoma; DC, descending colon; HP, hyperplastic polyp; R, rectum; SA, serrated adenoma; SC, sigmoid colon.
* Time is from index polyp diagnosis to cancer diagnosis; age is given at the time of diagnosis of index polyp; grades are the World Health Organization histologic grade.

Table 4
Location of Polyps Observed at Pan-Colonoscopy (n = 279)*

Location	Hyperplastic Polyp	Serrated Adenoma	Conventional Adenoma	Total
Rectum and rectosigmoid junction	46 (65)	24 (53)	47 (28.8)	117 (41.9)
Sigmoid colon	20 (28)	11 (24)	57 (35.0)	88 (31.5)
Descending colon and splenic flexure	0 (0)	2 (4)	17 (10.4)	19 (6.8)
Proximal colon	5 (7)	8 (18)	42 (25.8)	55 (19.7)
Total	71 (100)	45 (100)	163 (100.0)	279 (100.0)

* Data are given as number (percentage).

DOI: 10.1309/VBAGV3BR96N2EQTR

Table 5
Size Distribution of Hyperplastic Polyps, Serrated Adenomas, and Conventional Adenomas*

Size (mm)	Hyperplastic Polyp	Serrated Adenoma	Conventional Adenoma	Total
1-4	108 (76.1)	42 (38.2)	115 (41.7)	265 (50.2)
5-9	11 (7.7)	15 (13.6)	57 (20.7)	83 (15.7)
10-14	1 (0.7)	10 (9.1)	19 (6.9)	30 (5.7)
≥15	22 (15.5)	43 (39.1)	85 (30.8)	150 (28.4)
Total	142 (100.0)	110 (100.0)	276 (100.0)	528 (100.0)

*Data are given as number (percentage). For size, $P < .00001$ (hyperplastic polyp vs conventional adenoma); $P < .00001$ (hyperplastic polyp vs serrated adenoma); $P = .746$ (serrated adenoma vs conventional adenoma); Kruskal-Wallis test.

Table 6
Number of Other Polyps Identified at Index Endoscopy*

	Index Polyps		
Other Polyps	Hyperplastic Polyps (n = 56)	Serrated Adenomas (n = 38)	Conventional Adenomas (n = 138)
Hyperplastic polyps			
None	15 (27)	36 (95)	123 (89.1)
1	31 (55)	2 (5)	9 (6.5)
2	6 (11)	0 (0)	3 (2.2)
≥3	4 (7)	0 (0)	3 (2.2)
Serrated adenomas			
None	56 (100)	5 (13)	132 (95.7)
1	0 (0)	31 (82)	4 (2.9)
2	0 (0)	1 (3)	2 (1.4)
≥3	0 (0)	1 (3)	0 (0.0)
Conventional adenomas			
None	56 (100)	38 (100)	8 (5.8)
1	0 (0)	0 (0)	99 (71.7)
2	0 (0)	0 (0)	14 (10.1)
≥3	0 (0)	0 (0)	17 (12.3)

* Data are given as number (percentage).

Table 7
Mean Number and Range of Polyps Found in Cases With Recurring Polyps With Follow-up Longer Than 12 Months

Index Diagnosis	No. of Polyps	Mean No. of Polyps Per Year (Range)	95% CI
Hyperplastic polyp	28	0.40 (0.05-1.47)	0.272-0.520
Serrated adenoma	22	0.81 (0.11-3.53)	0.399-1.217
Conventional adenoma	65	0.41 (0.05-2.29)	0.313-0.517

CI, confidence interval.

(1) the interval between 2 endoscopies was at least 6 months and (2) the subsequent polyp was within reach of the previous investigation, ie, all polyps were evaluated when the previous endoscopy was a colonoscopy; polyps from descending colon to rectum were evaluated when the previous endoscopy was a sigmoidoscopy, and only rectal polyps were included in the evaluation when the previous endoscopy was a proctoscopy. The growth rates of the polyps (growth in diameter in millimeters per year) were estimated by dividing the size of the polyp (in millimeters) by the time between 2 endoscopies. The results were based on the assumption that observed polyps would have been removed. There were 26 serrated adenomas, 50 conventional adenomas, and 42 hyperplastic polyps that met the selection criteria **Table 8**. Hyperplastic polyps were estimated to be slower growing lesions than serrated adenomas ($P = .0001$; Kruskal-Wallis test), but their growth rates did not differ from the estimated growth rates of conventional adenomas ($P = .207$; Kruskal-Wallis test). The estimated growth rate of serrated adenomas was higher than that of conventional adenomas ($P = .017$; Kruskal-Wallis test).

Discussion

To our knowledge, estimates of the growth potential, subsequent polyp rates, and carcinoma risk of serrated adenomas have not been published previously. The retrospective nature of this study makes it difficult to draw results as reliable as those that could have been achieved from a large prospective study. However, we believe that the main results of this study are plausible and at least show that additional prospective studies are needed urgently.

In this retrospective analysis, the incidence of subsequent cancers in patients with serrated adenoma (2/38 [5%]) did not differ from that of patients with conventional adenoma (2.2%; $P = .295$; Fisher exact test). This shows that serrated adenoma has a significant risk of subsequent colorectal cancer development, comparable to that of conventional adenomas (log rank = 0.35; $P = .552$). Serrated adenomas differed from conventional adenomas by their estimated higher growth rate and their pattern of recurrence in terms of polyp type. These findings support the idea that the serrated pathway to colorectal cancer is distinct from the conventional adenoma–cancer pathway and might have implications for the follow-up of colorectal lesions.

In this study, the proportion of serrated adenomas among all index lesions including nonepithelial polyps was 10.0% (38/380), and serrated adenomas represented 15.9% of epithelial polyps (38/239). These figures are considerably higher than the frequency of 1% to 2.4% previously reported.[1,17] It is interesting that in a recent study, 22.6% of rectosigmoid polyps originally diagnosed as hyperplastic polyps demonstrated features of serrated adenoma on reanalysis.[15] For several reasons, we believe that previously reported low figures for the prevalence of serrated adenoma are underestimates. Earlier studies indicating a 1% to 2.4% prevalence of serrated adenoma[1,17] and the observed 5.8% prevalence of colorectal cancer arising in serrated adenomas[4] would suggest a higher malignant potential for serrated adenoma than conventional adenoma, unless the 1% to 2.4% prevalence of serrated

DOI: 10.1309/VBAGV3BR96N2EQTR

Table 8
Mean and Median Growth Rates of Polyps Found in Cases With Recurring Polyps With Follow-up Intervals Longer Than 6 Months

	Growth Rate (mm/y)				
	Mean	Median	95% CI of the Mean	Range (mm/y)	*P*[*]
Hyperplastic polyp (n = 42)	1.36	1.03	1.03-1.69	0.18-4.22	.0001[†]
Serrated adenoma (n = 26)	3.76	3.04	2.68-5.10	0.17-11.12	.207[‡]
Conventional adenoma (n = 50)	2.79	1.08	1.67-3.91	0.19-84.16	.017[§]

CI, confidence interval.
[*] Kruskal-Wallis test.
[†] Hyperplastic polyp vs serrated adenoma.
[‡] Hyperplastic polyp vs conventional adenoma.
[§] Serrated adenoma vs conventional adenoma.

adenoma is an underestimate. Also the 5.8% prevalence of serrated adenocarcinoma arising from serrated adenoma is likely to be an underestimate because the overgrowth of carcinoma frequently destroys the adenomatous part in large tumors.[18]

Differences in the diagnostic criteria of serrated adenomas are a likely explanation for the variation in reported prevalence. In their original article, Longacre and Fenoglio-Preiser[1] indicated that nuclear stratification and abnormal nuclear/cytoplasmic ratios were less common in serrated adenomas than in traditional adenomas, and "significant" dysplasia was present in only 37% of serrated adenomas. This statement probably has given the impression that lesions with high-grade dysplasia should be classified as conventional adenomas. Therefore, if serrated adenoma is regarded as an adenoma with no more than low-grade dysplasia, the definition is likely to be biased with the high-grade end of the lesion spectrum classified differently. In our material, all cases of serrated adenomas showed dysplasia, 45% (17/38) originally were classified as adenomas, and 45% of them (17/38) showed moderate to severe dysplasia. In our experience, serrated adenoma with higher degrees of dysplasia is not difficult to distinguish from conventional adenoma, although in some cases with the highest grade of dysplasia, serrations are less prominent and the cytoplasm becomes more basophilic (Images 2D and 2E).

Another possible difference in the classification is in the low end of the spectrum of dysplasia. Longacre and Fenoglio-Preiser[1] found some mitotic activity and occasional nucleolar abnormalities on the surface of some of their hyperplastic polyps. These features, according to 2 recent articles (Torlakovic et al[19] and Goldstein et al[15]), are more indicative of sessile serrated adenoma, a lesion differing from classic serrated adenoma, typically a pedunculated polyp with clear-cut dysplasia of serrated epithelium and cytoplasmic eosinophilia. These reports[15,19] were not available when our analysis was performed and, therefore, could not be used in our polyp classification. We presume that a proportion of our serrated adenomas with mild dysplasia might represent sessile serrated adenoma as defined by Torlakovic et al[19] and Goldstein et al,[15] whereas some of our atypical hyperplastic polyps also might be classified in the same group. However, we found that our atypical hyperplastic polyps did not have any prognostic difference from other hyperplastic polyps (data not shown), and, therefore, they were not analyzed separately. It should be noted, however, that sessile serrated adenoma might manifest with abnormal mismatch repair[19] and develop into microsatellite-unstable adenocarcinomas.[15]

In colorectal lesions, dysplasia has been considered a marker of neoplastic nature. The pattern of dysplasia in serrated and conventional adenomas differs. Both share the presence of nuclear atypia, but the maturation of serrated adenomatous epithelium is more conspicuous, sometimes including hypermaturation as seen in hyperplastic polyps.[10] Nuclear stratification and irregular polarity of the cells are hallmarks of dysplasia in adenomatous epithelium but are not necessarily a feature of serrated adenomatous epithelium with mild dysplasia.[10] In serrated adenomas, the serrated configuration is retained in dysplastic epithelia, whereas serration is absent in conventional adenomas,[1] although a minor degree of epithelial tufting resembling serration might be seen in some conventional adenomas.[17]

The presence of serrated dysplasia in surface and upper crypt epithelium has been considered the main diagnostic criterion for serrated adenomas.[1,17,20] Torlakovic et al[19] and Goldstein et al[15] described an appearance they call "immature crypt"[19] or "dysmature crypt,"[15] an abnormal characteristic of sessile serrated adenomas, composed of proliferation extending abnormally high into the crypt epithelium with or without nuclear atypia. Such a change might correspond to dysplasia in our terminology, although we might categorize lesser degrees of "dysmaturity" as atypia. These terminological issues emphasize a need for further refinement of criteria and a need for a consensus of diagnostic terms so that serrated lesions can be classified reproducibly.

Reproducibility of classification was not assessed formally in our material. The classification was, however, performed

DOI: 10.1309/VBAGV3BR96N2EQTR

by 2 independent observers (O.E.J. and M.J.M.); the final classification was determined after discussion in case of disagreement. Furthermore, both observers were unaware of any outcome information. Significant correlation of the classification of index polyps and outcome in terms of types of follow-up polyp types supports the validity and reproducibility of the classification.

There was a variation in the intensity of follow-up between hyperplastic and other types of polyps. Follow-up endoscopies initially were performed according to routine histopathologic diagnosis and the recognized relationships between conventional adenomas and colorectal cancer. The number of follow-up endoscopies or the length of the follow-up period was not significantly different between groups of index polyps with the exception of the hyperplastic polyp group. In addition, the effect of variable lengths of time between individual endoscopies was diminished in our analysis by expressing the numeric changes of the polyps and their growth as time-related indexes. The incidence of synchronous polyps or polyps beyond the reach of the rigid proctoscope and flexible sigmoidoscope has been shown to be 50%.[21] Because not all examinations were full colonoscopies, polyps probably have been missed in these cases.

The cancer risk of untreated adenomas during 20 years has been observed to be around 14.6%.[22] In another study, the risk of colorectal cancer during a 20-year period in patients who underwent excision of conventional adenomas was 3%.[23] The significant decrease in cancer risk by polypectomy is accepted widely and forms the basis for the current clinical management of conventional adenomas. The 5% cancer incidence (2/38) in our study relates to individuals who underwent excision of serrated adenomas. In 75% of cases, there was a follow-up endoscopy with biopsies at some point during the 20-year follow-up. It is probable that the rate of malignant conversion of untreated serrated adenoma would be greater than the observed 5% after polypectomy.

The topography and morphologic features of the serrated polyps and the subsequent cancers suggest that the malignant tumors might have had their origins in serrated polyps. In both cases of serrated adenoma followed by cancer, the adenocarcinoma appeared in the same region as the previous serrated adenoma and shared the serrated morphologic features (Image 1F).

Jass[6] suggested that the development of carcinomas via the serrated pathway might be rapid, analogous to that of hereditary nonpolyposis colorectal cancers with microsatellite instability. Mäkinen et al[24] also recently observed exceptionally rapid development of serrated adenocarcinoma from a serrated adenoma. However, reliable information about the growth rate of serrated adenoma is not available. In the present study, we attempted to estimate the time-related recurrence and growth rates of new polyps. The estimated recurrence rate was higher in cases of serrated adenoma than in cases of hyperplastic polyp or conventional adenoma (Table 7). Serrated adenomas were significantly larger than hyperplastic polyps and tended to be larger than conventional adenomas (Table 5). We also found that serrated adenomas had higher estimated growth rates than conventional tubular adenomas (Table 8). Because serrated polyps also occurred in younger patients than conventional adenomas, the long-time risk for colorectal cancer in patients with serrated adenoma might be even higher than observed in the present study.

Clearer differences than in cancer risk rate were observed in the type distribution of concurrent and subsequent polyps. The presence of a serrated index polyp predicted the presence of concurrent serrated polyps and the development of subsequent serrated polyps but not conventional adenomas. In patients with hyperplastic polyps, 94.7% (177/187) of the subsequent polyps were serrated polyps; in patients with serrated adenomas, 93.5% (87/93) of the subsequent polyps were serrated polyps. Similarly, conventional adenomas were more common in patients with an index conventional adenoma, a finding that has been described previously.[25] These observations suggest that the effect of genetic and environmental factors in determining the predominant type of polyp is constant. Further studies are necessary to identify the specific environmental and genetic factors.

Several findings in the present study support the hypothesis that hyperplastic polyps are precursor lesions of serrated adenomas: (1) Hyperplastic polyps were more common in people younger than 48 years, whereas serrated adenomas were more common in persons 48 years or older. (2) Hyperplastic polyps were smaller than serrated adenomas. (3) Hyperplastic polyps and serrated adenomas commonly were found in the same anatomic locations, as opposed to conventional adenomas. (4) Some patients who initially had hyperplastic polyps later developed serrated adenomas. (5) Patients with serrated adenomas more frequently had hyperplastic polyps than conventional adenomas during follow-up.

The histologic features of serrated adenomas and hyperplastic polyps further suggest that these lesions are related. The morphologic features of hyperplastic polyps and serrated adenomas were similar except for dysplasia in the latter, making differential diagnosis of these lesions difficult at times.[1,3,15,17,19] Finally, the common genetic alterations reported in hyperplastic polyps and serrated adenomas and carcinomas associated with serrated adenoma, eg, microsatellite instability, support the existence of a hyperplastic polyp–serrated adenoma–serrated adenocarcinoma pathway.[7,8,9,12] There were no cancers in patients with hyperplastic polyp as the index polyp, suggesting that not all hyperplastic polyps are involved equally in the hyperplastic polyp–serrated adenoma–serrated adenocarcinoma continuum. If not all hyperplastic polyps are indicators of risk of development of serrated adenoma, it will be necessary to search for markers of such a risk.

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Serrated adenomas have a substantial risk for subsequent malignancy, comparable to that of conventional adenomas. They are likely to grow more rapidly than tubular adenomas and tend to recur more often than conventional adenomas. Thus, proper recognition, management, and follow-up of serrated adenoma is necessary for the efficient prevention of colorectal cancer. We found evidence suggesting that in some cases, hyperplastic polyps might be a marker for development of serrated adenoma. However, further follow-up studies and more work on the histopathologic criteria for serrated colorectal lesions are needed to determine the appropriate management of these lesions.

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Supported by the Northern Finland Cancer Foundation, Oulu.

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Acknowledgments: We express our most sincere thanks to Risto Bloigu, MSc, for assistance in statistical methods and Martin Pike, MBBCh, for editing the manuscript.

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DOI: 10.1309/VBAGV3BR96N2EQTR

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