

**TABLE 9. Comparison of the vascular pattern of traditional and serrated adenomas: exploration conducted in magnification with NBI**

Vascular pattern*	Adenoma		Total
	tubular or villous	Serrated adenoma	
Faint†	1	14	15
Network	446	8	454
Dense	119	12	131
Irregular	1	0	1
Sparse	0	0	0
Total	567	34	601

\*The vascular pattern is analyzed at the surface of tubular or villous adenomas and of serrated adenomas in the series the Yokohama Northern Hospital during the period January 2006 through August 2007.

†Faint pattern that suggests an HP lesion is observed in 41% of serrated adenomas.

irregular diameter, or the absence of symmetry in the direction of capillaries. The abnormal aspects are classified in 5 groups: "faint," "network," "dense," "irregular," and "sparse." In the same endoscopy unit, the vascular pattern at the surface of superficial lesions of the colorectal mucosa was correlated to histology during the period January 2006 through September 2007 (S. Kudo, H. Kashida, unpublished data, 2008). A "faint" vascular pattern occurred in 37 of 41 HP lesions and in only 15 of 843 neoplastic lesions. The sensitivity and specificity of the "faint" pattern for HP polyps were 98.2% and 90.2%, respectively. A "nonfaint" vascular pattern, which regrouped all 4 other abnormal patterns, occurred in 823 of 843 neoplastic lesions and in only 4 of 41 HP lesions. The "nonfaint" patterns characterize neoplastic lesions. The classification of the vascular pattern helps in the distinction among non-neoplastic lesions, premalignant neoplastic lesions, and cancer (Table 8), and in the distinction between traditional adenomas and serrated adenomas (Table 9).

## GENETIC FACTORS THAT CONTROL THE GROWTH OF TUMORS IN THE COLORECTAL MUCOSA

Considerable progress<sup>78-96</sup> has occurred during the most recent years in the description of genetic events for the adenoma-carcinoma sequence, the HP serrated carcinoma sequence, hereditary cancer,<sup>97-99</sup> and cancer in inflammatory bowel disease.<sup>100-104</sup> A link has been established between the genetic events that control the development of the neoplastic lesions and their morphology (Tables 10 and 11). Colorectal carcinoma develops in 3 distinct genetic pathways: (1) CpG-island methylation phenotype (CIMP), which is classified as

high, low, or negative, will inactivate encoding regions of DNA by methylation, (2) CIN, with losses of suppressor genes (APC and TP53) will result in LOH, and mutations with activation of oncogenes (KRAS) 3-MIS, which concerns nonencoding repetitive DNA sequences, is classified as high (MIS-H), low (MIS-L), or stable (MSS). The combination of the 3 pathways results in 5 categories of neoplastic lesions (Table 10), which were classified by Jass.<sup>67</sup> It is estimated that CIN with MSS accounts for around 77% of cases (including the germline mutation of the APC gene), then carcinogenesis is based on the sequence APC-KRAS-TP53. Chromosome stability with MIS results in inactivation of multiple genes; it occurs in close association with BRAF mutation in around 20% of cases or in the germline mutation of a MMR gene (hMLH1).

## Genetic factors involved in the development of polypoid carcinoma

**Mutations in epithelial cells.** In the normal colorectal mucosa, stem cells are thought to reside at the base of crypts; the Fearon and Vogelstein<sup>15</sup> described the progression from the initial subset of neoplastic cells in the "top-down" direction, which, in spite of some diverging opinions,<sup>78</sup> is the most accepted theory.<sup>15,79</sup> In line with the top-down theory, the same group<sup>79</sup> compared, in the early stage of an adenoma, the molecular characters of cells with a neoplastic morphology at the luminal surface of the crypts and that of cells with a normal morphology at the base of these same crypts. The cells at the top of the crypts often exhibited genetic alterations that were not observed in cells located at the base of the same crypts. The genetically altered cells arise in the upper pole of the crypt, progress down in the crypt, and spread laterally in adjacent crypts. The growth of neoplastic cells with crypt fission ends in a macroscopic lesion.

The traditional sequence described in 1990 by Fearon and Vogelstein,<sup>15</sup> is responsible for the majority of sporadic colorectal cancer. The mutation of the APC tumor suppressor gene on the long arm of chromosome 5 (5q21) is followed by CIN and LOH, ie, loss of segments of chromosomes, and successive mutations of suppressor genes or activation of oncogenes: *Kras* gene on chromosome 12q, *DCC* gene on chromosome 18p, and *TP53* gene on chromosome 17p (Fig. 6). The repetitive nucleotide sequences of DNA in the microsatellites are not modified by mutations, and the tumor is MSS.

Hirata et al<sup>80</sup> analyzed APC, KRAS, and TP53 gene mutations in 96 cases of primary colorectal cancer and stressed the variable prevalence of associations in altered chromosomes: the combination APC and KRAS occurred in 21.9%; the prevalence of *Kras* and TP53 and of APC and TP53 combinations was 12.5% and 10.4%, respectively; and the combination of APC, *Kras*, and TP53 mutations was the less frequent (6.3%). This variability suggests an interaction between exogenous environmental factors

TABLE 10. Relationship between molecular groups and morphology of neoplastic lesions\*

CIMP status	CIN status	MIS status	Inaugural mutation	Related neoplastic lesions	Proportion (%)
High	Stable	MIS-H	BRAF	Serrated lesion; sporadic cancer	12
	Stable	MSS	BRAF	Serrated lesion	8
Low	Unstable	MSS	KRAS	Sporadic adenoma; serrated lesion	20
Negative	Unstable	MSS	KRAS	Sporadic adenoma; FAP; germline mutation	57
	Stable	MIS-H	MLH1	HNPCC; germline mutation	3

MIS-H, High microsatellite instability; MIS-L, low microsatellite instability.

\*Colorectal carcinoma develops in 3 distinct pathways: (1) CIMP, which is high, low, or negative; (2) chromosomal instability (CIN) with losses of suppressor genes by LOH; (3) microsatellite instability, which is high (MIS-H), low (MIS-L), or stable (MSS); a combination of the 3 pathways results in 5 categories of neoplastic lesions (see reference 67).

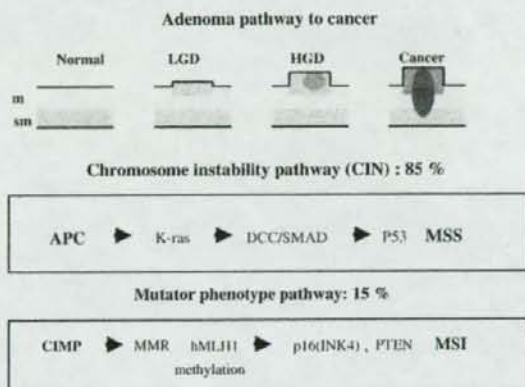
TABLE 11. Mutations that occur in neoplastic and nonneoplastic colorectal lesions\*

Mutation	% Serrated pathway			
	% Traditional adenoma	HP polyp (microvesicular)	TSA	Sessile serrated lesion
APC	33	0	0	0
KRAS oncogene	15	15	30	7
BRAF protein-kinase	0.3	75	60	80
CIMP	10	50	80	75

\*The APC mutation characterizes the adenomatous pathway to cancer. The BRAF mutation characterizes the serrated pathway and is common to HP nonneoplastic polyps and to serrated adenomas (see references 11, 12, 50, 51, 54, 67).

and the somatic genetic alterations. Hermsen et al<sup>81</sup> assessed the role of specific associations of mutations in the progression of polypoid adenomas to cancer. They compared chromosome alterations in 66 benign and 46 malignant colorectal adenomas. Three distinct combinations are linked to the progression toward cancer: 17p loss and *Kras* mutation, 8q and 13q gain, and 18q loss and 20q gain.

**Genetic instability in epithelial cells.** An alternative sequence occurs in up to 20% of cases of sporadic colorectal cancer in relation to the CIMP. Epigenetic methylation and inactivation of hMLH1, one of the MMR genes, results in MIS-H and inactivation of many suppressor genes (p16 and PTEN). The tumors with epigenetic methylation of the DNA are highly correlated with a mutation of the BRAF-kinase encoding gene located on the long arm of chromosome 7 (7q34). This group of MIS tumors offers similarities with neoplastic lesions developed in the serrated pathway, which suggests that the precursor



**Figure 6.** Adenoma pathway to sporadic colorectal cancer. Two distinct sequences monitor the morphologic steps from low-grade neoplasia to invasive cancer. The first is based on initial APC mutation, CIN, and LOH; DNA microsatellites are stable (MSS). The other sequence is based on CIMP, with methylation and inactivation of many suppressor genes (eg, p16, PTEN). Note: familial cancer, caused by germline mutations, is linked to the APC sequence in the FAP syndrome and to the CIMP sequence in the HNPCC, in which the germline mutation of one of the MMR gene results in high MIS.

lesion is similar. Kambara et al<sup>94</sup> screened BRAF mutations in different categories of neoplastic colorectal lesions—serrated adenomas, conventional adenomas, and hereditary and sporadic colorectal cancer—and found that BRAF mutation is more frequent in sessile serrated lesions and in sporadic MIS-H cancers, both of which are associated with DNA methylation. Sporadic MIS-H cancers may originate in sessile serrated lesions rather than in conventional adenomas.

**Genetic instability in the stroma.** Recent studies suggest that, just as for breast cancer, genetic instability in the stroma may influence the progression of neoplastic colorectal lesions. Ishiguro et al<sup>95</sup> analyzed, with microsatellites and chromosome 17 markers, the epithelial and stromal compartments of colorectal adenomas for LOH



and instability in the sequences of microsatellites. In epithelial cells, the prevalence of LOH and MIS, which is extremely low in HP polyps, increases with the progression of the alterations in premalignant adenomas and, furthermore, in invasive carcinoma. In the stroma, the prevalence of LOH or MIS does not vary with the progression of neoplasia. Therefore, genetic instability in the stroma is a very early event in the development of colorectal neoplasia. Matsumoto et al<sup>96</sup> tested MIS with 4 markers in 40 cases of sporadic colorectal cancer: the frequencies of positive MIS in the epithelial and in the stromal compartments were 34% and 41%, respectively. In the epithelial compartment, positive MIS is more frequent in poorly differentiated than in well-differentiated cancer. In the stromal compartment, an opposite variation occurs: positive MIS is more frequent (54%) in well-differentiated cancer (54%) than in poorly differentiated cancers (10%). It is concluded that, rather than being a reaction to epithelial stromal cells, stromal genetic instability in chromosome markers may control the development and differentiation of the tumor.

### Genetic factors involved in the development of nonpolypoid or flat carcinoma

The distinct sequence of genetic events that controls the development of nonpolypoid lesions in the colorectal mucosa is progressively being confirmed with techniques that vary from immunochemistry in tissue sections to microdissection and DNA sequencing.<sup>47,81-89,92</sup> Molecular events that occur in nonpolypoid lesions were analyzed in 3 distinct circumstances: (1) flat adenomas, classified as premalignant lesions, either when including all depressed and nondepressed subtypes or when including only the flat depressed adenomas, (2) LST lesions, which were classified with ambiguity in granular, nongranular, and homogenous subtypes, rather than in subtypes of the Paris classification, (3) flat carcinomas or, more precisely, flat carcinomas that show no remnants of adenoma, which are often called *de novo* cancer. The heterogeneity of early neoplastic lesions in patients with inflammatory bowel disease is beyond the scope of this discussion, in spite of the unusual high proportion of neoplastic areas with a flat morphology.<sup>100-104</sup>

**Mutations in epithelial cells.** In flat adenomas, *Kras* mutations have a lower frequency in flat nonpolypoid lesions than in polypoid lesions, as shown by Yamagata et al<sup>87</sup>; the figures in their study were 23% and 67%, respectively. More precisely, the frequency of *Kras* mutations in depressed adenomas and in polypoid adenomas were estimated in 2 other studies: the figures were at 0% and 31%, respectively, in the study by Umetani et al<sup>89</sup> and at 8.6% and 25%, respectively, in the study by Morita et al,<sup>82</sup> restricted to diminutive lesions less than 5 mm in diameter. The frequency of APC mutations has also been estimated in depressed lesions and is lower (7%) in non-

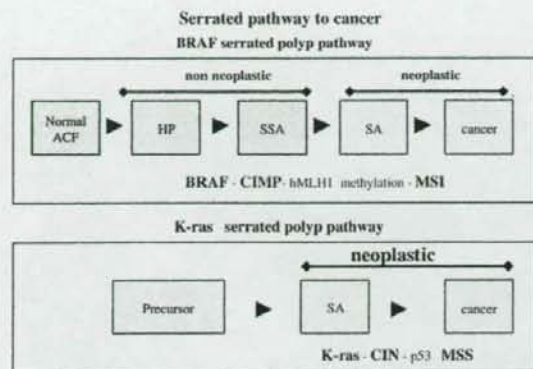
polypoid depressed adenomas than in polypoid lesions (43%), as shown by Umetani et al<sup>89</sup> in 2000.

In LST lesions, Mukawa et al<sup>85</sup> compared the frequency of *Kras* mutations in subtypes of LST lesions and found a lower prevalence of the mutation (26.3%) in 19 cases with a nongranular type (which is usually flat) than in 17 cases with a granular type (76.5%). This was confirmed by Hiraoka et al,<sup>84</sup> who compared *Kras* mutations in LST lesions at least 1 cm in diameter: the prevalence of the mutation was lower (16%) in the flat type with a homogenous surface, than in the more protruding granular type (78%). Takahashi et al<sup>85</sup> obtained different results when comparing *Kras* mutations in 101 LST lesions, called flat advanced adenomas, and in 68 polypoid advanced adenomas: the prevalence of *Kras* mutations was higher (35%) in LST lesions than in polypoid adenomas (13%). The divergence in the results of these studies may relate to the imprecision in the morphologic classification of LST lesions.

In flat carcinomas (1) in various studies that compared flat carcinomas with polypoid carcinomas, the low frequency of *Kras* mutations is confirmed: the published figures were 11% and 56%,<sup>89</sup> 0% and 44%,<sup>88</sup> and 0% and 36%,<sup>47</sup> respectively, (2) frame-shift mutations of the APC gene do not occur in nonpolypoid carcinomas and occur in 66% of polypoid carcinomas, as shown by Kaneko et al,<sup>47</sup> (3) mutations of the TP53 gene were analyzed by Fujii et al<sup>91</sup> in 13 cases of early flat cancer: LOH on chromosome 17p locus, near the TP53 gene occurs early and is frequent (77%), genetic heterogeneity is similar to that observed in more advanced polypoid cancer in the preinvasive stages. The prevalence of TP53 mutations in early and flat cancer was also analyzed in European series.<sup>90-93</sup> Mueller et al<sup>90</sup> compared the frequencies of LOH at the 17p locus near the TP53 gene in 35 cases of early colorectal cancer without residual adenoma (*de novo* cancer) and in 36 cases of superficial (pT1) cancer developed in the adenoma sequence: the prevalences were 73% and 37%, respectively. In conclusion, the more aggressive character of the *de novo* carcinoma is confirmed by the higher rate of LOH at 17p locus with more frequent TP53 mutations.

**Genetic instability in epithelial cells and stroma.** In advanced carcinomas,<sup>47</sup> nonpolypoid and polypoid tumors show a similar proportion of MIS. In 99 superficial (early) colorectal carcinomas with invasion of the submucosa, Ogawa et al<sup>84</sup> analyzed genetic instability with microsatellite markers from the National Cancer Institute and for chromosome 17 instability. The frequency of epithelial MIS is significantly higher in nonpolypoid (33.3%) than in polypoid superficial cancer (10.4%). In the stroma of the tumor, instability of chromosome 17 markers is higher in nonpolypoid than in polypoid superficial cancers. It is concluded that epithelial and stromal MIS of chromosome 17 markers contributes more to carcinogenesis in nonpolypoid lesions.





**Figure 7.** Serrated pathway to sporadic colorectal cancer. Two distinct molecular sequences monitor the morphologic steps from nonneoplastic lesions to neoplasia and invasive cancer. Serration is included in both sequences. The first is based on initial BRAF mutation and CIMP, with inactivation of hMLH1, which results in MIS. The HP lesion, eventually arises from ACF and is not neoplastic; a sessile serrated lesion is often called sessile serrated adenoma as well; serrated adenoma (SA) is a neoplastic lesion and may progress to cancer. The other sequence, based on early K-ras mutation and CIN, results in a serrated adenoma (SA) which may progress to cancer; the DNA microsatellites are stable (MSS).

**Combined chromosomal alterations in flat carcinomas.** *K-ras* and APC mutations are less frequent in nonpolypoid than in polypoid lesions. The difference was confirmed in various categories of lesions: flat adenomas, depressed flat adenomas, nongranular type of LST lesions, flat carcinomas, and de novo carcinomas. In the majority of studies, flat lesions are considered as a single group, and a specific behavior of depressed lesions is not underlined. Also, chromosomal alterations may be combined to convey a more aggressive behavior of the tumor. The simultaneous and early occurrence of multiple LOH, including 17p, 18p, 18q, and 22q in colorectal flat tumors suggests their classification as a de novo cancer with more aggressive clinical behavior.<sup>55</sup> In the Netherlands, Postma et al<sup>86</sup> analyzed 6 flat adenomas and 12 flat adenocarcinomas, and found higher frequencies of 20q gain and 18q loss than in previously analyzed polypoid neoplastic lesions. Combined alterations in these 2 chromosomal regions were already linked to tumor aggressiveness by the same group.<sup>81</sup> Epithelial MIS is more frequent in nonpolypoid lesions.

#### Genetic factors involved in hereditary cancer

Hereditary cancer syndromes are caused by germline mutations. In familial adenomatous polyposis (FAP), the colorectal tumor shows MSS and is caused by a dominant germline mutation in the APC gene on chromosome 5q; a clinical syndrome of attenuated FAP is caused by a mutation of a BER (base excision gene, located on chromosome 1p). In the hereditary nonpolyposis colon cancer (HNPCC) syndrome, the tumor with MIS is caused by a dominant

germline mutation of one of the MMR genes, which results in high instability of the repeated sequences of nucleotides in MIS-H and multiple mutations of suppressor genes in the CIMP phenotype.<sup>97-99</sup>

#### Genetic factors involved in the development of serrated lesions

**Mutations with MIS.** Serrated lesions cover a spectrum of nonneoplastic and neoplastic lesions and share a persisting serrated pattern of the crypts. The majority of serrated neoplastic lesions show MIS with a MIS-H status. Mutation of the BRAF-kinase gene on chromosome 7q (Fig. 7) and DNA epigenetic methylation are early events in this pathway to neoplasia, and the frequency of this mutation in colorectal polypoid lesions has often been analyzed.<sup>69,72,94</sup> The methylator phenotype is absent in simple HP lesions and frequent in HP polyposis; the prevalence of this phenotype progressively increases in the continuum that leads to a serrated carcinoma. After the initial BRAF mutation, the molecular events include inactivation through methylation of the MMR gene hMLH1, with MIS-H and successive mutations of suppressor genes. Spring et al<sup>72</sup> explored the frequency of BRAF mutations in different categories of lesions detected in patients who had colonoscopy: the mutation, rare in adenomas (0.4%), was frequent in the microvesicular type of HP lesion (70%), in sessile serrated lesions (78%), and in TSAs (66%). Kambara et al<sup>94</sup> analyzed BRAF mutations in patients undergoing colectomy for either colorectal cancer or HP polyposis; a high prevalence was confirmed in sessile serrated lesions and in sporadic colorectal cancer with a MIS-H status. The microvesicular type of the HP lesion is considered the precursor of sessile serrated lesions, which can progress to neoplasia but should not be misclassified as a TSA, which is a neoplastic lesion. Torlakovic et al<sup>73</sup> showed that the distribution of cells labeled with Ki-67 is the most helpful feature for the distinction between the 2 categories of lesions: the expression of Ki-67 is irregular and highly variable in sessile serrated lesions and is localized in the ectopic crypts, which characterize the architecture of TSAs. Most likely, sporadic MIS-H cancers originate from sessile serrated lesions as a consequence of the CIMP, which leads to successive mutations of suppressor genes.

**Mutations with MSS.** An alternative sequence that leads to a serrated carcinoma is based on an initial *K-ras* mutation with CIN. Successive mutations of suppressor genes result in a TSA that may progress to a serrated cancer; the DNA microsatellites are MSS in this category of tumor.

#### ROLE OF ABERRANT CRYPT FOCI ON THE ORIGIN OF COLORECTAL CARCINOMA

Aberrant crypt foci (ACF) are defined as small clusters (2 or more) of enlarged crypts with dilated openings,



which rise above the adjacent mucosa.<sup>105-114</sup> ACF can be identified and numbered at the surface of the mucosa with magnification chromoendoscopy, by using indigo carmine solution at 0.2%, or methylene blue solution at 0.01%. The numeration is usually performed with a high-power field, which may vary according to the material used and the investigators, in a 20-cm or 10-cm length of the rectum. The count increases with the age of the patient, just as the risk of colorectal cancer increases.<sup>112</sup> The ACF count is not temporally stable, as shown in a study by Schoen et al,<sup>114</sup> who identified and counted ACF again, after a 1-year interval, in the rectum: less than half the specific ACF could be reidentified, and more than 50% of the subjects had new ACF. ACF are postulated to represent the monocryptal initial event in the development of neoplastic lesions or serrated lesions in the colorectal mucosa.

### Diversity of ACF phenotypes

ACF are classified into 3 categories: (1) HP ACF have a nonserrated morphology, the crypt lumen is round but enlarged, and the mucin content is not increased, (2) HP serrated ACF show a serrated crypt lumen with increased mucin, and (3) neoplastic ACF are less frequent and show enlarged and stratified nuclei. ACF with a neoplastic type can be considered a microadenoma and can have proliferation in the upper part of the crypt, and are more common in FAP than in patients with sporadic colorectal neoplasia. In contrast, the nonneoplastic categories of ACF (called heteroplastic) have proliferation mainly in the lower part of the crypts.

### Diversity of ACF genotypes

The distinct sequences that lead to neoplasia across the nonserrated and serrated pathways have been studied after direct polymerase chain reaction (PCR) sequencing of the DNA from isolated ACF with an HP, serrated, or neoplastic architecture. BRAF mutations are linked to HPACF with a serrated phenotype, and *Kras* mutations are linked to ACF with a nonserrated phenotype. In the study conducted by Rosenberg et al,<sup>110</sup> BRAF mutation was present in 10 of 16 serrated ACF and in only 1 of 33 nonserrated ACF; conversely, *Kras* mutation was present in 3 of 16 serrated ACF and in 14 of 33 nonserrated ACF. Beach et al<sup>69</sup> confirmed that BRAF mutation was rare in nonserrated neoplasia, did not occur in ACF from patients with hereditary cancer (FAP), and only occurred in 3% of ACF from patients with sporadic colorectal cancers. *Kras* mutation was present in only 4% of ACF from patients with hereditary cancer (FAP) and occurred in 40% of ACF from patients with sporadic colorectal cancers.

### ACF and the risk of cancer

The count of ACF in the rectum follows a stepwise progression in patients with a negative colonoscopy, adenomatous polyps, or colorectal cancer, and in the study

conducted by Adler et al,<sup>105</sup> the values of the count of ACF in these 3 categories were  $n = 5$ ,  $n = 6.9$ , and  $n = 9.9$ , respectively, and in the study conducted by Takayama et al,<sup>109</sup> the figures were  $n = 1$ ,  $n = 5$ , and  $n = 26.5$ , respectively. Kukitsu et al<sup>111</sup> showed that the number of ACF is higher in patients with ulcerative colitis when a neoplastic lesion is associated. The relationship between the prevalence of ACF in the rectum and the presence of nonpolypoid neoplastic lesions in the proximal portion of the colon was also analyzed. In the study conducted by Hurlstone et al,<sup>106</sup> the mean number of ACF in the rectum was  $n = 1$  in patients with a negative colonoscopy,  $n = 9$  in those with nonpolypoid adenomas, and  $n = 38$  in those with a nonpolypoid cancer in the proximal portion of the colon.

In hereditary cancer, Nucci et al<sup>113</sup> showed that most ACF in patients with a FAP syndrome have a neoplastic morphology, whereas those observed in patients with sporadic colorectal cancer have an HP morphology. In the study conducted by Beach et al,<sup>69</sup> 91% of ACF from patients with a FAP syndrome had a neoplastic morphology, whereas 87% of ACF from patients with sporadic colorectal cancer were HP. Stevens et al<sup>108</sup> established a relationship between the count of ACF and the familial risk of cancer. The count was lower ( $n = 4.4$ ) in patients without a family history of cancer than in patients with a family history of cancer ( $n = 9$ ) or with a personal history of cancer ( $n = 7.5$ ).

In conclusion, ACF are considered as the earliest and monocryptal precursors of neoplastic lesions in the colon and are postulated as valuable biomarkers for the risk of colorectal cancer. They could prove helpful in surveillance protocols of patients at increased risk of cancer, including those with inflammatory bowel disease. In addition, genetic alterations in ACF differ in the serrated and nonserrated neoplasia.

## ENDOSCOPIC FEATURES OF NONPOLYPOID LESIONS

### Endoscopic prevalence of superficial neoplastic lesions

The prevalence of superficial lesions detected during complete colonoscopy in the colorectal mucosa of asymptomatic patients is high in Japan.<sup>115,116</sup> In a study conducted at the National Cancer Center in Tokyo in 2004 by the Research Cancer Center for Prevention and Screening,<sup>116</sup> the prevalence of neoplastic lesions was 60% in 2968 patients. In Western countries, the figures depend on the recourse to high-resolution endoscopy and image processing during colonoscopy. In the United States, Imperiale et al<sup>117</sup> proceeded to colonoscopic screening in 906 patients: the percentage of patients with adenoma was 10%. A higher proportion (37.5%) was found in 3121 patients by Lieberman et al,<sup>118</sup> and



**TABLE 12. Superficial neoplastic colorectal lesions and numbers and proportion of depressed nonpolypoid types: comparison between Japanese and Western series\***

Study	No. all lesions	No. flat and depressed lesions (0-Ic, 0-IIc + IIa, 0-IIa + IIc) (%)	
Okuno et al, <sup>124</sup> multicenter study (8 groups), Japan	66,670	1291	(1.9)
Togashi et al, <sup>125</sup> Japan	5408	152	(2.8)
National Cancer Center, 2004, Tokyo, Japan	4303	31	(0.7)
Fujii et al, <sup>130</sup> U.K.	68	2	(2)
Rembacken et al, <sup>132</sup> U.K.	446	4	(0.9)
Hurlstone et al, <sup>131</sup> U.K.	745	51	(6.8)
Kiesslich et al, <sup>5</sup> Germany	105	2	(2)
Tsuda et al, <sup>133</sup> Sweden	973	14	(1.4)
Soetikno et al, <sup>137</sup> U.S.	1535	18	(1.2)

\*The proportion of depressed (0-Ic) lesions that occur in the Western series is similar to that observed in the Japanese series. Misclassification between some subtypes (0-Ic vs 0-IIa and 0-IIb vs 0-IIa) may occur in the Western series. In all series, lesions with intramucosal or submucosal cancer are included; cancer with invasion beyond submucosa is not included.

even higher figures (67%) were displayed by Rex and Helbig<sup>119</sup> in a recent cohort of 434 patients aged 50 years or older.

Follow-up studies give an indication about the natural evolution of polypoid adenomas that were not removed after detection. In Denmark, a prospective follow-up study was conducted over 3 years in 58 patients undergoing annual colonoscopy, whereas all polyps smaller than 10 mm were maintained.<sup>120-122</sup> In this study, adenomas and HP polyps smaller than 5 mm showed a tendency to net growth, whereas lesions in the size range 5 to 9 mm showed a tendency to net regression.<sup>120-122</sup> In the United States, the "observed" incidence of adenomas and colorectal cancers that occurred in the National Polyp Study during surveillance procedures was compared with the simulated outcomes of a MISCAN-COLON model.<sup>123</sup> The discordance between the high incidence of adenomas detected and the low incidence of colorectal cancer suggest that the rise of new adenomas is accompanied by the regression of many others.

### Proportions of polypoid and nonpolypoid lesions

In Japan, the proportions of polypoid and nonpolypoid superficial lesions of the colorectal mucosa were estimated in very large series<sup>124,125</sup> collected during a prolonged period (15-20 years). In the endoscopy

units from the Akita and Yokohama hospitals (1985-2007), the proportion of nonpolypoid lesions was high, with 10,948 nonpolypoid lesions (42%) of 25,862 superficial neoplastic lesions detected. In a similar analysis from the endoscopy unit of the Hiroshima University Hospital (1991-2007), the proportion of nonpolypoid lesions was still high, with 2711 nonpolypoid lesions (27%) of 12,811 superficial neoplastic lesions detected.

In Western countries, the finding of flat or depressed nonpolypoid neoplastic lesions in the population was acknowledged in recent years,<sup>126-130</sup> and the proportions of polypoid and nonpolypoid lesions were also analyzed or reviewed in some studies.<sup>131-137</sup> In the United States, O'Brien et al<sup>26</sup> revised the classification of data in the National Polyp Study and estimated the proportion of nonpolypoid lesions at 31.4%. In the recent study of Soetikno et al,<sup>137</sup> the overall prevalence of nonpolypoid neoplastic lesions was 9.35%; in this series, nonpolypoid neoplastic lesions, irrespective of their size, were more likely to contain carcinoma than polypoid lesions. Saitoh et al<sup>135</sup> detected, with dye-assisted colonoscopy, flat and depressed lesions in 22.7% of 211 patients; depressed lesions were also more likely to show invasive cancer (4.5%) than were polypoid lesions (0%). Lieberman et al<sup>134</sup> analyzed the yield of recurrent neoplastic lesions that occurred after an interval of 5.5 years but did not describe the morphology of the lesions. In Europe, the proportions of nonpolypoid lesions were estimated at 27.3% by Rembacken et al,<sup>132</sup> 40.9% by Hurlstone et al,<sup>131</sup> and only at 8.4% by Tsuda et al.<sup>133</sup>

### Endoscopic prevalence of depressed nonpolypoid lesions

The attention is drawn, in spite of their relative rarity, on depressed lesions (0-Ic, 0-IIc + IIa, or 0-IIa + IIc), because, even when small, they are more advanced in their progression to cancer. In published data from Japan and from Western countries, these lesions represent 1% to 6% of the total count of superficial colorectal lesions, as shown in various series (Table 12). In Japan and, specifically, in the large series from the Akita and Yokohama Hospitals, all subtypes of premalignant and malignant depressed lesions (0-Ic, 0-IIc + IIa, and 0-IIa + IIc) represent 2.3% of all superficial lesions (polypoid and nonpolypoid) and 5.5% of all nonpolypoid types (585 of 10,948) (Table 13). The proportions for the series of the Hiroshima University Hospital are 2.2% of all lesions and 10.5% of nonpolypoid lesions (285 of 2711) (Table 14).

The relative rarity of depressed lesions is still confirmed when the count is restricted to early cancer. In the statistics of the national cancer screening in Japan (2004-2005), 0-Ic lesions represent 8.7% (367/4180) of all cases of early cancer (Table 15); the lesions were detected in patients positive for the immunologic fecal blood test. The

**TABLE 13. Morphology of superficial neoplastic lesions and the proportion of Ca in the submucosa: results in 25,762 lesions from the series of the endoscopy unit at Akita and Yokohama Northern Hospitals, Japan, for the period April 1985 through July 2007\***

	No. lesions				
	Total	Up to 5 mm	6-10 mm	11-19 mm	≥20 mm
<b>Polypoid, 0-I, Ips, Is</b>					
No. all lesions	14,814	7046	5582	1863	323
No. submucosal Ca only (%)	358 (2.4)	0 (0)	72 (1.3)	192 (10.3)	94 (29.1)
<b>Nonpolypoid, 0-IIa, IIb</b>					
No. all lesions	10,363	7583	1436	929	415
No. submucosal Ca only (%)	138 (1.3)	2 (0.03)	5 (0.35)	50 (5.3)	81 (19.5)
<b>Nonpolypoid, depressed, all 0-IIc</b>					
No. all lesions	585	263	172	127	23
No. submucosal Ca only (%)	210 (35.9)	22 (8.4)	75 (43.6)	93 (73.2)	20 (87.0)
<b>Total superficial neoplastic lesions</b>	<b>25,862</b>	<b>14,892</b>	<b>7190</b>	<b>2919</b>	<b>761</b>

Ca, Cancer.

\*Proportions of polypoid, nonpolypoid not depressed and polypoid depressed lesions were 57%, 40%, 2.3%, respectively. Submucosal invasion occurs in 706 lesions, of which 348 are nonpolypoid. The number of nonpolypoid depressed lesions is small, but the proportion of Ca with submucosal invasion is high.

**TABLE 14. Morphology of superficial neoplastic lesions and proportion of cancer in the submucosa: results in 12,811 lesions from the series of the endoscopy unit at the Hiroshima University Hospital during the period January 1991 through November 2007\***

	No. lesions				
	Total	Up to 5 mm	6-10 mm	11-19 mm	≥20 mm
<b>Polypoid (0-I, Ips, Is)</b>					
No. all lesions	10,100	5846	2606	1211	437
No. submucosal Ca only (%)	177 (0.7)	4 (0.07)	41 (1.6)	71 (5.8)	61 (14)
<b>Nonpolypoid (0-IIa, IIb)</b>					
No. all lesions	2426	1050	746	455	175
No. submucosal Ca only (%)	51 (2.1)	0 (0)	13 (1.7)	25 (5.4)	13 (7.4)
<b>Nonpolypoid, depressed (all 0-IIc)†</b>					
No. all lesions	285	100	96	64	25
No. submucosal Ca only (%)	77 (27)	6 (6)	17 (17.7)	34 (53.4)	20 (80.0)
<b>Total superficial neoplastic lesions</b>	<b>12,811</b>	<b>6996</b>	<b>3448</b>	<b>1730</b>	<b>637</b>

\*Proportions of polypoid, nonpolypoid not depressed, and polypoid depressed lesions are 78.8%, 18.9%, 2.2%, respectively. Submucosal invasion occurs in 510 lesions, of which 256 are nonpolypoid. The number of nonpolypoid and depressed lesions is small, but the proportion of cancer with submucosal invasion is high.

†LST lesions type LST-granular (n = 510) are not included; pseudodepressed lesions type LST-nongranular are included in nonpolypoid depressed lesions.

proportion is slightly higher in the study conducted at Jichi University, where 0-IIc lesions represent 10.4% of all cases of early cancer (39/373) (Table 16).

#### Distribution of subtypes in LST lesions

In Japan, the distribution of the morphologic subtypes of 1751 lesions classified as LST, is shown in a cumulative

analysis of the experience of the endoscopy units of Akita and Yokohama Hospitals and of the National Cancer Center in Tokyo (S. Kudo, T. Fujii, unpublished data, 2008): 889 LST lesions were classified as granular, and 862 LST lesions were classified as nongranular. The sizes of the lesions were less than 20 mm in 1144 and 20 mm or greater in 607 (Table 17). In the recent experience at the



**TABLE 15. Morphology of superficial colorectal cancer and proportion of submucosal invasion: results of the National Colorectal Cancer Screening in Japan in 187 of 207 selected sites for the period 2004 to 2005\***

	Subtype 0	No.	No.
		Ca m and sm	Ca sm (%)
Polypoid	lp/lsp	2522	465 (18.4)
	ls	637	198 (31.0)
Nonpolypoid	lla	645	196 (30.0)
	lla+ llc	271	181 (66.7)
	llb and llc	96	54 (56.2)
Excavated	lll	9	2 (22.2)

Ca, Cancer.

\*Total number of superficial Ca m or sm detected and classified in subtypes 0 is 4180. Total number of Ca sm is 1096. The proportion of submucosal invasion is much higher in the 2 groups of type 0-llc lesions.

Yokohama Hospital (S. Kudo, H. Kashida, unpublished data, 2008) of 699 LST lesions (Table 18), the proportion of LST lesions with a nongranular and pseudodepressed morphology is 9.8% (69/699). This subtype of LST lesion corresponds to a more advanced stage in the progression to cancer. When compared with polypoid neoplastic lesions, LST lesions were characterized by different molecular markers.<sup>83,138,139</sup>

### Proportions of adenomatous and serrated lesions

In Japan, the size and location in the colon and rectum of HP lesions were analyzed in the National Cancer Center Hospital East, Chiba,<sup>55</sup> in 226 patients who harbored such lesions at colonoscopy: the majority of HP lesions (3020/3060) were less than 6 mm in diameter and were located in the distal portion of the colon (95%); only 5% of these lesions were in the proximal portion of the colon. In this series, which excluded patients with HP polyposis, mid-sized HP lesions (6-10 mm) were rare (28/3060) and were located either in the distal portion (58%) or in the proximal portion (42%) of the colon, whereas lesions 10 mm and larger were extremely rare (2/3060) and were located in the proximal portion of the colon.

In the United States, a multicenter study assessed the proportions of adenomatous and serrated lesions during colonoscopies performed in the Minnesota Community Practice study during the period February 1 through December 31, 2007 (J. Allen, unpublished data, 2008). Among 15,015 lesions detected, 8897 were classified as adenomatous (58%) and 5229 were serrated (37%) (the others were not analyzable with precision). Among adenomatous lesions, 1413 corresponded to advanced neoplasia (19.1%) (tubular adenoma at least 10 mm, villous adenoma, HGIN, or cancer). Among serrated lesions, 3742

were classified as HP, and 1688 were classified as sessile serrated lesions.

A similar study was conducted by Spring et al<sup>72</sup> in 414 superficial lesions detected during colonoscopies at the Royal Brisbane Hospital, Australia. The proportions of adenomatous and serrated lesions were 60% and 40%, respectively. Of the 248 adenomatous lesions, 237 were found to be tubular and 11 tubulovillous. Among 166 serrated lesions, there were 120 HP, 36 sessile serrated lesions, 3 mixed polyps, and 7 TSAs.

### ENDOSCOPIC FEATURES OF MALIGNANT NONPOLYPOID LESIONS

#### Cancer in polypoid and nonpolypoid lesions

The proportion of cancer with invasion of submucosa was analyzed in relation to morphology in endoscopic series from Japan. At the Akita and Yokohama Northern Hospitals (Table 13), the proportion of cancers with invasion of the submucosa was very high in depressed nonpolypoid lesions: 35.9% (210 of 585 lesions). In the series of the Hiroshima University Hospital (Table 14), the figure was also very high for the same category of lesions: 27% (77 of 285 lesions). In contrast, in both series, the proportions of cancer with invasion of the submucosa were very low in polypoid lesions: 2.4% and 0.7%, respectively. In the statistics of the national cancer screening in Japan for the period 2004 to 2005, the proportion of cancer with invasion of the submucosa in depressed nonpolypoid lesions with early cancer was also high and was estimated at 64% (Table 15). A study of the depth of invasion in the submucosa was conducted at the pathology department of the National Cancer Center, Tokyo, Japan, (T. Shimoda, unpublished data, 2008) in 146 superficial colorectal cancers with submucosal invasion. The analysis included polypoid and nonpolypoid early cancers. The depth of invasion was estimated from the muscularis mucosae and was classified as sm1, if invasion was less than 1000  $\mu$ m, and sm2, if invasion was more than 1000  $\mu$ m.

In 87 polypoid carcinomas, sm1 invasion occurred in 52.9%, and the average size of sm1 tumors was 21.5 mm; sm2 invasion occurred in 47.1%, and the average size of sm2 tumors was 27.7 mm. In 59 nonpolypoid carcinomas, sm1 invasion of the submucosa occurred in 27.1%, and the average size of sm1 tumors was 12.2 mm; sm2 invasion occurred in 72.9%, and the average size of the tumor was 14.8 mm. It was concluded that nonpolypoid lesions with invasion of the submucosa show a higher proportion of massive invasion and are smaller than polypoid lesions. In Western countries, the proportion of cancer (without distinction between intramucosal or submucosal invasion) was analyzed in relation to morphology and was also high for depressed lesions, and varied from 11.7% to 50% in several endoscopic series. In contrast, the



**TABLE 16. Morphology of superficial neoplastic lesions and proportion of Ca (mucosal or submucosal) in each category: comparison between Japanese and Western series\***

	No. neoplastic lesions and proportion of Ca					
	All polypoid lesions		All nonpolypoid lesions (0-Ila, IIb, IIc)		Depressed lesions (all IIc)	
	No. lesions	No. lesions with Ca (%)	No. lesions	No. lesions with Ca (%)	No. lesions	No. lesions with Ca (%)
Togashi et al, <sup>125</sup> Japan	4279	298 (6.9)	1129	75 (6.6)	152	39 (25.6)
Rembacken et al, <sup>132</sup> U.K.	327	2 (0.6)	119	6 (5.1)	4	2 (50)
Hurlstone et al, <sup>131</sup> U.K.	470	4 (0.8)	275	8 (2.9)	51	6 (11.7)
Tsuda et al, <sup>133</sup> Sweden	907	11 (1.2)	66	5 (7.5)	14	4 (22)
Soetikno et al, <sup>137</sup> U.S.	1308	13 (1)	227	15 (6.6)	18	6 (33)

Ca, Cancer.

\*Cancer is either intramucosal or with submucosal invasion; Ca with invasion beyond the submucosa is not included.

**TABLE 17. Predictive value of the morphology of LST of neoplastic lesions for Ca in the submucosa: subtype and size of LST in the series from the Akita and Yokohama Hospitals (n = 1209) in the period April 1985 through July 2007, and of the National Cancer Center, Tokyo (n = 542) during the period January 1999 through December 2003\***

LST	< 20 mm		≥ 20 mm	
	No.	No. Ca in submucosa (%)	No.	No. Ca in submucosa (%)
Granular				
Akita-Yokohama	284	4 (1.4)	314	41 (13.0)
Tokyo	202	9 (4.4)	89	15 (16.8)
Nongranular				
Akita-Yokohama	426	27 (6.4)	185	40 (21.6)
Tokyo	232	25 (11)	19	8 (42)

Ca, Cancer.

\*The risk of cancer with submucosal invasion increases with the size of the lesion.

proportion of cancer in polypoid lesions was very low and varied from 0.6% to 1.2% (Table 16).

### Cancer in LST lesions

The risk of cancer in LST lesions increases with size and varies with morphologic subtypes. At the Akita and Yokohama Hospitals during the period from April 1985 to July 2007 (S. Kudo, H. Kashida, unpublished data, 2008), 1209 LST lesions were distributed according to their size in 3 groups: 10 to 19 mm, 20 to 29 mm, and 30 mm and larger;

the proportions of cancer with invasion of the submucosa were 4.4%, 13.1%, and 20.6%, respectively. The risk of cancer varied with the subtype of the LST lesion and was higher in the granular with mixed nodules and in the nongranular and pseudodepressed subtypes. In 181 lesions of the subtype granular with mixed nodules, the proportions of cancer with submucosal invasion in the 3 groups of increasing size, 10 to 19 mm, 20 to 29 mm, and 30 mm and larger, were 7.1%, 20.4%, and 38.0%, respectively, and, in 123 lesions of the subtype nongranular and pseudodepressed, the figures were 12.5%, 32.4%, and 83.3%, respectively.

### Cancer in serrated lesions

The malignant potential of serrated adenomas is lower than that of traditional adenomas. A study conducted by Song et al<sup>60</sup> in Korea compared 124 serrated adenomas with serration of 20% of crypts and cytologic alterations of nuclei with 419 traditional adenomas. The incidence of HGIN or carcinoma was lower (3.2%) in serrated adenomas than in traditional adenomas (9.3%). Although most sessile serrated lesions never progress to cancer, some of them with a large diameter in the proximal portion of the colon may progress rapidly to a serrated carcinoma.<sup>71</sup> Large lesions in the proximal portion of the colon with a preponderant nonpolypoid pattern at endoscopy deserve special attention with respect to the early detection of serrated cancer and its precursors. The broad categories of large lesions located at this level include sessile serrated lesions, as well as precursors of nonserrated cancer, such as flat or slightly elevated adenomas and LST lesions.

The proportions of serrated and nonserrated cancer can be evaluated because colorectal cancer, developed in a serrated lesion, shows some distinct characteristics in addition to specific genetic markers and some MIS.



**TABLE 18. Predictive value of the morphology of LST of neoplastic lesions for Ca in the submucosa: results of 699 lesions from the Yokohama Hospital during the period April 2001 through July 2007\***

	Subtype of LST	Total no.	No. lesion (% submucosal)		
			10-19 mm	20-29 mm	≥ 30 mm
Granular type	Homogenous	251	0/120 (0)	1/65 (1.5)	0/66 (0)
	Nodular mixed	81	2/16 (12.5)	4/24 (16.7)	13/41 (31.7)
Nongranular type	Elevated	298	13/203 (6.4)	7/67 (10.4)	8/28 (28.6)
	Pseudodepressed	69	10/36 (27.8)	12/29 (41.4)	4/4 (100)

Ca, Cancer.

\*Ca with submucosal invasion occurs rarely in the granular homogenous type and is frequent in the nongranular pseudodepressed type.

**TABLE 19. Predictive value of the pit pattern for Ca in the submucosa—exploration conducted in magnification with chromoscopy or NBI: no. Ca with submucosal invasion in relation to pit pattern of 7749 colorectal lesions in the series at the Yokohama Northern Hospital during the period between April 2001 and July 2007\***

Pit pattern	No. total	No. adenoma		No. Ca sm
		Low-grade IEN	High-grade IEN	
III L	5519	5228	291	0
III s	73	56	15	2
IV	1577	1190	343	44
VI (irregular)	463	109	198	156
VN (amorphous)	117	0	10	107

Ca, Cancer; IEN, intraepithelial neoplasia.

\*Adenoma is classified in low-grade IEN and high-grade IEN (of the Vienna classification); mucosal Ca is included in high-grade IEN; high-grade adenoma includes intramucosal Ca. Most adenomas show a pit pattern type III or IV, most Ca show a pit pattern type V.

These criteria<sup>57</sup> include a persisting serrated growth pattern, pools of mucin, cytoplasmic eosinophilia, and an absence of necrosis.<sup>57</sup> Serrated adenocarcinoma accounts for about 7.5% of all colorectal cancers and up to 17.5% of the most proximal cancers.<sup>57</sup> The proportion of serrated cancer is higher in the proximal portion of the colon and lower in the rectum.

### MAGNIFYING ENDOSCOPY IN MALIGNANT NONPOLYPOID LESIONS WITH SUBMUCOSAL INVASION

#### Evaluation of submucosal invasion from the superficial pit pattern

The pit pattern of the colonic mucosa can be assessed by using magnifying endoscopy in conjunction with chro-

moscopy or NBI. The studies conducted by various endoscopy groups in Japan, with histologic controls, confirmed that some categories of the pit pattern are predictive of cancer extension into the submucosa. In 7740 neoplastic colorectal lesions analyzed at the Northern Yokohama Hospital (Table 19), submucosal cancer was confirmed by histology in 33.7% of lesions that showed a category V "irregular" pit pattern and in 91% of the lesions that showed an "amorphous" category V pit pattern, whereas the proportion in lesions that showed pit patterns III or IV was extremely low (0.64%). Furthermore, the "irregular" or "amorphous" subtypes of the pit pattern in category V showed a predictive value for the slight or massive invasion in the submucosa, as shown in Table 20. The slight or massive submucosal invasion is classified in reference to 3 successive levels (sm1, sm2, and sm3) in vertical extension and to 3 successive degrees of transversal extension of the cancer, estimated just below the level of the muscularis mucosae (sm1a, sm1b, and sm1c). Slight invasion of submucosa corresponds to sm1a or sm1b. Massive invasion corresponds to sm1c, sm2, and sm3. The pit pattern V "amorphous" always corresponds to a massive invasion of the submucosa in the experience at the Northern Yokohama Hospital.

#### Evaluation of submucosal invasion from the superficial vascular pattern

The vascular pattern of the colonic mucosa can be assessed by using magnifying endoscopy with NBI and has a predictive value for the detection of cancer. The vascular pattern at the surface of 843 superficial neoplastic lesions of the colon was analyzed in the endoscopy unit at the Yokohama Northern Hospital. The "irregular" or "sparse" patterns were found in only 1 of 639 adenomas or serrated adenomas, in 22 of 133 intramucosal cancers, and in 59 of 71 cancers with submucosal invasion (Table 21). The reliability of the vascular pattern in predicting the depth of invasion of the submucosa was explored by the same group during the period from January 2006 to September 2007 (S. Kudo, H. Kashida, unpublished observations, 2008)



**TABLE 20. Predictive value of the pit pattern for the depth of submucosal invasion in superficial Ca: depth of invasion in 178 colorectal lesions that showed a surface pit pattern VI or VN in the series from the Akita and Yokohama Northern Hospitals during the period April 1992 through July 2007**

Pit pattern V	Total no.	Ca with submucosal invasion	
		Slight	Massive*
Pattern type VI irregular histology (low-grade IEN)†	35	29	6 (17%)
Pattern type VI irregular histology (high-grade IEN)†	80	12	68 (85%)
Pattern type VN (amorphous)	63	0	63 (100%)

Ca, Cancer; IEN, intraepithelial neoplasia.

\*Massive invasion shows either a pit pattern VN or VI.

†Pit pattern type VI is highly suggestive of a superficial invasion of the submucosa.

**TABLE 21. Predictive value of the vascular pattern for Ca in the submucosa, with exploration conducted in magnification with NBI: distribution of the categories of vascular pattern in relation to histology of 843 lesions in the series of the Yokohama Northern Hospital, in the period January 2006 through September 2007**

Vascular pattern	No. adenoma + adenoma serrated	No. carcinoma	
		Intramucosal	Submucosal invasion
Faint	15	0	0
Network*	484	60	7
Dense	139	51	5
Irregular‡	1	17	27
Sparse‡	0	5	32
Total	639	133	71

\*Suggests adenoma.

‡Suggests carcinoma with submucosal invasion.

in 204 superficial neoplastic lesions with histologic controls. The invasion was classified as slight or massive, with the criteria already used for the evaluation of the pit pattern. The patterns "network" or "dense" were observed in 123 lesions, of which 120 had a slight invasion of the submucosa and 3 had massive invasion. The patterns "irregular" or "sparse" were observed in 81 lesions, of which 28 had slight invasion and 53 had massive invasion. The sensitivity and specificity of "irregular + sparse" pat-

terns for massive submucosal invasion were 94.6% and 81.1%, respectively. It was concluded that the pit pattern has a high predictive value for a massive invasion of the submucosa.

## PROTECTION AFFORDED BY COLONOSCOPY AGAINST COLORECTAL CANCER

The role of colonoscopy in the prevention of colorectal cancer depends on its double function: first, in the diagnosis of cancer at an early curable stage and for the diagnosis of the precursors of cancer—this occurs in opportunistic screening of asymptomatic patients and in organized screening after a positive fecal occult blood test; second, as a therapeutic procedure that allows the endoscopic resection of precursors of cancer and of superficial cancers without massive invasion of the submucosa. The degree of protection afforded by colonoscopy can be explored in patients in whom the initial colonoscopy was negative or in patients in whom the index procedure detected and removed neoplastic lesions. This raises the question of the interval to be proposed for surveillance colonoscopy.

### Protection after a negative colonoscopy

**Evaluation of the miss rate in back-to-back colonoscopy.** Neoplastic lesions detected a few years after a negative colonoscopy may result from a missed diagnosis, ie, false negative for neoplasia. The magnitude of such a miss rate has been determined in Western countries when a second procedure is performed on the same day (back-to-back colonoscopy) by another observer. In a demonstrative study conducted by Rex et al<sup>140</sup> in the United States, the tandem procedure detected adenomas in 24% of 183 patients who had a negative colonoscopy at the initial procedure. The rate varied with the size of the missed adenomas and the figures were 27% for adenomas up to 5 mm, 13% for adenomas between 6 and 9 mm, and 6% for adenomas 10 mm or larger. One may think that this proportion should decrease with the use of recent high-resolution endoscopes. However, in a recent study of back-to-back colonoscopies in 286 patients conducted in France by Heresbach et al,<sup>141</sup> the global miss rate was still high (20%), with proportions of 26% for adenomas up to 5 mm and 9% for adenomas larger than 5 mm. Regardless, when the colorectal mucosa was systematically scrutinized with a high-resolution colonoscope, the prevalence of diminutive adenomas was so high (in the range of 30% to 50%) that some degree of miss rate was unavoidable.

**Neoplastic lesions found after a negative colonoscopy.** Despite the absence of neoplastic lesions at the initial colonoscopy, benign or malignant metachronous neoplastic lesions can develop in the interval before a second procedure. Interval neoplasia results either from an



**TABLE 22. Risk of finding neoplastic lesions in the years after a negative colonoscopy: a retrospective case-control study conducted in patients affiliated with the Medicaid Program for California and having continuous eligibility since at least 60 months preceding the index examination\***

	No. cases (Ca)	No. controls (no Ca)	RR†
All Ca; both sexes			
Had no screening	3746	37,155	1.00
Had negative colonoscopy‡	151	2426	0.55
Had negative sigmoidoscopy‡	68	750	0.82
All Ca, men			
Had no screening	1448	14,209	1.00
Had negative colonoscopy	33	837	0.35
All Ca, women			
Had no screening	2298	22,946	1.00
Had negative colonoscopy	118	1589	0.66
Right-sided Ca, men			
Had no screening	442	3802	1.00
Had negative colonoscopy	11	228	0.38
Right-sided Ca, women			
Had no screening	861	7796	1.00
Had negative colonoscopy	50	523	0.81

Ca, Cancer; RR, relative risk; Right-sided Ca, cancer in the proximal colon.

\*Colorectal Ca detected up to 5 years after a negative colonoscopy or sigmoidoscopy in a retrospective case-control study conducted in patients affiliated to the Medicaid Program for California and having continuous eligibility since at least 60 months preceding index (G. Triadafilopoulos, unpublished data, 2008).

†Estimation of the RR after a negative procedure.

‡Colonoscopy offers better protection against Ca than sigmoidoscopy but is less effective in prevention in women than in men; the difference is because of poor effectiveness in prevention of right-sided cancer.

initial miss rate or from the development of metachronous evolute lesions. Interval cancer found shortly after a complete colonoscopy is often a metachronous tumor with rapid growth rather than a lesion missed at the first examination. This particularly applies to flat and depressed nonpolypoid lesions, which are often classified as *de novo* cancers. The proportion of MIS-positive tumors was analyzed by Sawhney et al<sup>142</sup> in 51 patients, with interval cancers that occurred within 5 years after a colonoscopy and in 112 noninterval colorectal cancers, and a 3.7-fold higher frequency of MIS-positive tumors occurred in the group of interval cancers. Many studies on interval cancers have been conducted in the United States.

Squillace et al<sup>143</sup> examined 29 patients after an average interval of 5.7 years of a negative colonoscopy; adenomas were detected in 12 (41.4%). Neugut et al<sup>144</sup> repeated colonoscopy in 99 patients after an average interval of 3 years after the negative first procedure and detected adenomas in 24 patients (24%). Rex et al<sup>145</sup> examined 154 patients after an average interval of 5.5 years after the negative colonoscopy and found adenomas in 41 patients (27%). The Lilly multicenter study (D. Ransohoff, unpublished data, 2008), with 1256 subjects evaluated after an average interval of 5.3 years after a negative colonoscopy, detected adenomas in 201 (16%) and advanced neoplasia in 16 subjects (1.2%).

**Evaluation of neoplasia protection after a negative colonoscopy.** Despite its limitations, a negative colonoscopy offers an appreciable protection against the risk of developing colorectal cancer.<sup>146</sup> The degree of protection was assessed in a large retrospective case-control study conducted in the United States by using the California MediCal database (Table 22). The occurrence of a negative colonoscopy or sigmoidoscopy in the recent years was explored in patients with (cases) or without cancer (controls). It was concluded that colonoscopy offers better protection than sigmoidoscopy and that such protection was more effective in men than in women, the latter difference being a consequence of a less efficient assessment of the proximal portion of the colon in women. In Japan, the protection afforded against incident neoplastic lesions by a negative colonoscopy was assessed in a retrospective cohort study conducted by 6 distinct centers: the relative risk of finding a incident lesion was very low at 1 year (0.1) and higher at 3 years (0.8) (Table 23).

**Neoplasia protection after a colonoscopy with polypectomy.** Neoplastic lesions of the colorectal mucosa detected a few years after a colonoscopy with complete resection of all superficial neoplastic lesions may result from 3 possible scenarios: (1) the lesions were missed at the first procedure, (2) new lesions developed during the interval, and (3) lesions were incompletely treated during the first procedure. The proportion of neoplastic lesions detected during the second procedure was explored in Western countries<sup>147-153</sup> and, as shown in Table 24, this figure varies between 32% and 60%. In the United States, the National Polyp Study showed that the percentage of patients with incident adenomas 3 years after the inclusion colonoscopy was 32.0%.<sup>152</sup> In Denmark, in the Funen adenoma follow-up study, the figure was 35% after 4 years, and 60.1% after 8 years.<sup>153</sup> A lower proportion occurs when counting is restricted to metachronous lesions with advanced neoplasia.

The detection of lesions upon surveillance colonoscopy confirms a persistent increased risk in patients with positive findings at the first procedure; however, the risk of recurrence is modulated in relation to the initial findings. In the United States, in the Veterans Affairs cooperative study (Table 25), which was conducted in 13 distinct centers, the relative risk for interval lesions



**TABLE 23. Relative risk of recurrent neoplasia in relation to findings at first colonoscopy: retrospective cohort study from the Japan Polyp Study Working Group**

Colonoscopy at inclusion	No. cases	No. index lesions detected after follow-up of mean 5.1 y <sup>†</sup>	Relative risk for finding a index lesion <sup>‡</sup>	
			At 1 y	At 3 y
Negative	2006	52	0.1	0.8
Adenoma, up to 5 mm	1655	111	1.0	2.9
Adenoma, more than 5 mm	1123	150	2.5	5.4
Intramucosal cancer	525	66	2.9	5.7

\*From the Retrospective Cohort Study from the Japan Polyp Study Working group (T. Matsuda, unpublished data, 2008).

†Index (recurrent) lesions detected during follow-up (mean 5.1 y) after colonoscopy were defined as adenoma > 10 mm, intramucosal cancer, invasive cancer (submucosa or deeper); after 5 years, the number of index lesions was higher after polypectomy than after a negative colonoscopy and increased with the severity of initial findings.

‡In relation to the relative risk of finding an index lesion, colonoscopy should be performed after 3 years for patients without polyps or with polyps <5 mm and after 1 year for patients with large polyps or intramucosal cancer.

detected after a negative colonoscopy varied in relation to the increased severity of the index lesions, from 1.92 to 13.56. A similar study has been conducted in 6 centers by the Japan Polyp Working Group (Table 23). The relative risk of recurrent lesions, compared with patients who had a negative colonoscopy at inclusion, varied at 3 years, from 0.8 to 5.7, according to the severity of the index lesions.

## STRATEGY OF ENDOSCOPIC DIAGNOSIS

Superficial neoplastic lesions of the colorectal mucosa were first described by using rigid rectosigmoidoscopes, then with fiber-colonoscopes. Since then, there has been a considerable technical evolution, and the most recent electronic video colonoscopes offer high resolution, magnification, and image processing, including the NBI technique. Because of this, the proportion of patients with abnormal findings at colonoscopy is higher than in previous reports; yet seeing more does not mean more clinically relevant abnormalities. High-resolution endoscopy is not a substitute to the careful exploration of the mucosa during endoscopy and expert discriminative analysis.

### The 4-steps strategy

Good practice in endoscopic diagnosis requires a step-by-step methodology as the only protection against over-detection and overtreatment.<sup>154</sup>

1. A complete intestinal preparation is an essential first step, because any solid and liquid matter that persists at the surface of the mucosa can mask small nonpolypoid lesions.
2. Detection of an abnormal area is the second step that is performed in a standard visualization, without image processing or chromoscopy. Here, nonpolypoid lesions may easily be missed if the operator lacks the cognitive training to detect a slight change in the color of the mucosa and the deviation of the subepithelial capillaries at the demarcation.
3. Characterization of the lesion is the third step. The routine practice of chromoscopy with indigo carmine (0.1%-0.5% solution) is required to assess the lesion margins and identify elevations or depressions of the lesion's surface. The morphology of the lesion is then identified according to the categories of the Paris classification. Chromoscopy with cresyl violet (0.2% solution) or crystal violet (0.05% solution), achieves a more durable staining, but the use of these stains is reserved for very small areas observed in magnification. The microarchitecture of the epithelial surface is then explored in magnification combined either with chromoscopy or with NBI, and the categories of the pit pattern bring forth a predictive value for histology. The microvascular network is also explored in "transparency," without chromoscopy and with some magnification. NBI is now the criterion standard technique for the classification of the capillary pattern in nonneoplastic and neoplastic lesions.
4. The fourth step is classification and treatment decision and takes into account the lesion's morphology and



**TABLE 24. Interval cancer in the years after polypectomy: proportion of recurrent neoplastic lesions found in the endoscopic surveillance after a colonoscopy with complete resection of the index lesions\***

Investigator/country	Study	No. patients	Interval (years of follow-up)	% Patients with neoplasia	% Patients with advanced neoplasia†
Winawer et al, <sup>152</sup> U.S.	Surveillance National Polyp Study	766	3	32	3.3
Jørgensen et al, <sup>153</sup> Denmark	Surveillance Funen trial	1056 at inclusion	4	35.5	8.6
Alberts et al, <sup>147</sup> U.S.	Controls of fiber trial	584	3	51.2	31.4
Schatzkin et al, <sup>151</sup> U.S.	Controls of celecoxib trial	947	4	39.5	7
Arber et al, <sup>148</sup> Israel	Controls of fiber trial	557	3	49.3	10.4
Baron et al, <sup>150</sup> U.S.	Controls of rofecoxib trial	1218	3	55	17.4
Bertagnolli et al, <sup>149</sup> U.S.	Controls of celecoxib trial	613	3	60.7	17.2

\*Recurrent lesions result either from incomplete polypectomy, from missed detection during the first procedure, or from fast-developing incident lesions. †Advanced neoplasia, defined as tubular adenoma, at least 10-mm villous adenoma, high-grade atypia, or Ca.

**TABLE 25. Relative risk of recurrent neoplasia in relation to findings at first colonoscopy: estimation of the relative risk of finding an advanced neoplasia during a 5-year surveillance after screening colonoscopy in relation to the baseline findings\***

Baseline finding at colonoscopy	Advanced neoplasia, no. (%)†	Relative risk
No neoplasia (n = 298)	7 (2.4)	1.00
Neoplasia (n = 895)		
Tubular adenoma: 1 or 2, less 10 mm	23 (4.6)	1.92
Tubular adenoma: 3 and more, less 10 mm	15 (11.9)	5.01
Tubular adenoma: over 10 mm	19 (15.5)	6.40
Villous adenoma	13 (16.1)	6.05
Adenoma with high-grade atypia	8 (17.4)	6.87
Cancer	8 (34.8)	13.56

\*Results of the Veterans Affairs Cooperative Study no. 380 (D. Lieberman, unpublished data, 2008) in 2007. There is a strong association between the occurrence of advanced neoplasia and the results of the baseline screening colonoscopy.

†Advanced neoplasia is defined as tubular adenoma at least 10-mm, villous adenoma, adenoma with high-grade atypia or cancer.

location. The treatment decision offers the choice between abstention, endoscopic resection, or surgery. The en bloc endoscopic resection of nonpolypoid lesions may require the complex technique of endoscopic submucosal dissection.

### A pragmatic choice for treatment

1. Superficial lesions in the proximal portion of the colon are often more advanced or evolutive than those in the distal portion of the colon; most small HP lesions are nonneoplastic; large HP lesions in the proximal portion of the colon often host high-grade neoplasia.
2. Large polypoid or nonpolypoid lesions are more at risk of malignancy; most small lesions that show a 0-IIa or 0-IIb morphology host low-grade neoplasia; lesions that show a 0-IIc depressed morphology often host

high-grade neoplasia with frequent submucosal invasion.

### Quality control in colonoscopy

Major requirements in quality control include the use of a new-generation high-resolution video colonoscope, the routine application of chromoscopy with indigo carmine as a first step in the characterization of each lesion that, in turn, should be attributed to a subtype according to the Paris classification. This subtyping must be mentioned in the endoscopy report (as well as in the pathology report if the lesion is resected). When there is a suspicion of high-grade neoplasia, magnifying endoscopy, combined with image processing, has the capacity to evaluate, with more precision, the severity of neoplasia and its possible invasion of the submucosa.



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## DISCLOSURE

The authors report that there are no disclosures relevant to this publication.

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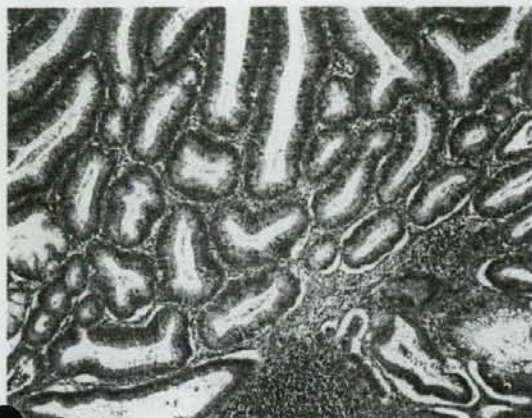
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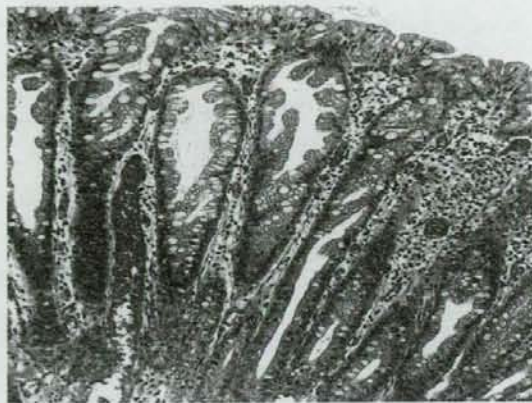
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**IMAGE ATLAS**



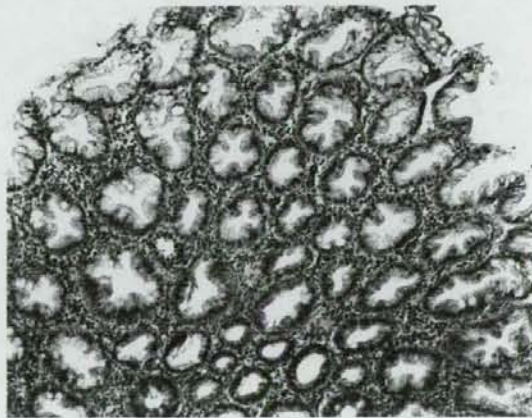
**A1.** Histopathology of tubular adenoma. Hyperchromatic palisading elongated nuclei in highly prismatic columnar epithelium (H&E, orig. mag.  $\times 100$ ).



**A3.** Histopathology of HP lesion. Serration in upper half of crypts (H&E, orig. mag.  $\times 150$ ).



**A2.** Histopathology of HP lesion. Serration in upper half of crypts. Normal proliferation in basal half: small, regular, basal orientated nuclei (H&E, orig. mag.  $\times 100$ ).



**A4.** Histopathology of HP lesion. Transverse section of the serrated crypts (H&E, orig. mag.  $\times 100$ ).





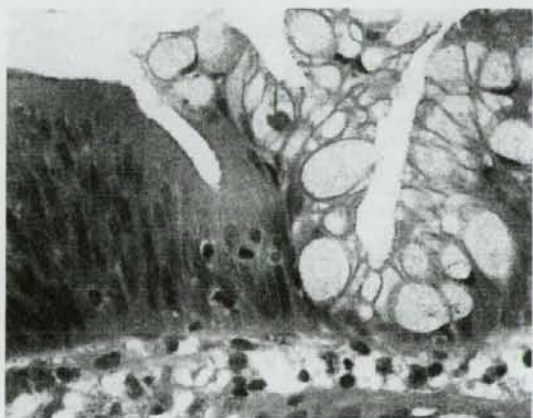
**A5.** Histopathology of sessile serrated lesion. Dilated crypts in basal area. No cell atypia (H&E, orig. mag.  $\times 100$ ).



**A7.** Histopathology of serrated adenoma. Intraepithelial microacini in upper half. Low-grade intraepithelial neoplasia, eosinophilic cytoplasm, elongated nuclei (H&E, orig. mag.  $\times 150$ ).



**A6.** Histopathology of sessile serrated lesion. Proliferation, architectural distortion: serration in basal half of crypts, enlarged with horizontal growth; abundant mucus (H&E, orig. mag.  $\times 120$ ).



**A8.** Histopathology of mixed polyp: adenoma (*left*), with elongated hyperchromatic nuclei; sessile hyperplastic polyp with goblet cells (*right*) (H&E, orig. mag.  $\times 300$ ).