Origin of Colorectal Cancers in Hyperplastic Polyps and Serrated Adenomas: Another Truism Bites the Dust

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Colorectal carcinoma is the second most common cause of cancer deaths in the United States (1), and on average approximately six people die every hour of every day as a result of this malignancy. Because these tumors are so frequent and so obvious on the mucosal surface of the large bowel, their morphogenesis has attracted great attention over the centuries (2). The evolution of understanding of the pathogenesis of colorectal cancer in recent years is nothing short of remarkable, especially during the era of molecular pathology. The article by Hawkins and Ward (3) in this issue of the Journal contributes to that evolution.

After considerable debate in the medical literature about the existence of de novo cancer and the classification of colorectal polyps and their relationship to cancer (4), the concept of the adenoma–carcinoma sequence emerged in the 1970s as the dominant morphogenetic explanation of colorectal cancer (5). The hyperplastic polyp was recognized as a frequently occurring lesion, but common knowledge held that its only importance resided in the need to distinguish it from the adenoma because the hyperplastic polypl was regarded as having no malignant potential or indication of risk for metachronous cancer (6). Although the concept of the adenoma–adenocarcinoma sequence is correct and explains most colorectal adenocarcinomas, it is now clear that morphogenesis is much more complicated than initially thought. Intraepithelial neoplasia (dysplasia) is recognized as the important histopathologic precursor (7) known to take several morphologic forms in addition to the polypoid adenoma. For example, intraepithelial neoplasia occurs as a premalignant lesion in chronic inflammatory bowel diseases, in hamartomatous polyps in Peutz-Jeghers syndrome and juvenile polyposis syndrome, in serrated adenomas and mixed adenomatosus–hyperplastic polyps, in flat and depressed adenomas, and in dysplastic aberrant crypt foci (8).

Molecular biology has contributed enormously to the understanding of the pathogenesis of colorectal adenocarcinoma and its precursors. Studies of rare familial syndromes as well as of ordinary tumors led to the recognition that alteration in the adenomatous polyposis coli (APC)/β-catenin pathway is the dominant molecular process involved in the adenoma–adenocarcinoma sequence, with familial adenomatous polyposis as the prototype. This molecular pathway is characterized by chromosomal instability with loss of heterozygosity, extensive karyotypic abnormalities, and altered total DNA content (9). Mutations and allelic losses of a plethora of genes characterize these tumors.

High levels of microsatellite instability (MSI-H) due to defective nucleotide mismatch repair characterize a second group of colorectal cancers for which the hereditary nonpolyposis colorectal cancer syndrome is the prototype. These cancers in both the inherited and sporadic settings are located frequently in the right or transverse colon, are poorly differentiated, have mucinous histology, and have histopathologic evidence of host immune response in the form of numerous intratumoral lymphocytes and peritumoral lymphoid nodules (10). Failure to repair mismatches in repeated nucleotide sequences within the coding regions of genes results in numerous and extensive mutations, but chromosomal instability with allelic losses of the type seen in microsatellite-stable cancers is rare in this tumor type. Another group of colorectal cancers is characterized by low levels of microsatellite instability (MSI) and has more heterogeneous pathologic features than MSI-H cancers (11).

Aberrant DNA methylation is an important molecular mechanism in colorectal tumorigenesis and is involved in the MSI-H pathway in sporadic tumors (12). Methylation of cytosines in cytosine–guanosine dinucleotide repeats located in the promoter region of a gene leads to transcriptional silencing without changes in nucleotide sequence. About half of human genes have these CpG islands, and aberrant methylation of numerous genes is evident in a subset of colorectal carcinomas with chromosomal instability and microsatellite stability (13). Methylation of the human mut-L homologue 1 (hMLH1) mismatch repair gene, however, results in tumors with MSI-H. In contrast to the adenoma–adenocarcinoma sequence attributable to alteration of the APC/β-catenin pathway, the precursor lesions of cancers with MSI and/or aberrant DNA methylation are not yet well defined. Rapid progression of cancers with MSI-H has been recorded, presumably leaving a small window of opportunity to find and study the precursors (14). A previous study (15) found that 5.8% of a large series of colorectal carcinomas had an adjacent serrated adenoma, and MSI was found in 37.5% of carcinomas associated with a serrated adenoma. In addition, patients with large or numerous hyperplastic polyps, termed “hyperplastic polyposis syndrome,” have a predisposition to right-sided colon carcinoma with MSI-H (16,17).

Hawkins and Ward (3) have taken a different approach to addressing the question of the precursor lesion to colon cancer with MSI. From a prospective series of 382 tumors, they identified a group of 29 sporadic cancers characterized by MSI and by loss of hMLH1 expression. They used a case–case match method with patients of a similar age and the same sex who had microsatellite-stable cancers of the same anatomic site. They then studied the frequency, classification, and molecular characteristics of synchronous lesions identified in the surgical resection specimens. Two patients in the study had hyperplastic polyposis syndrome. The authors found that the patients with...
cancer showing MSI had a markedly increased number of hyperplastic polyps (114 in 12 of 29 patients versus four in four of 29 microsatellite-stable control patients) and serrated adenomas (12 in six of 29 patients versus three in one of 29 microsatellite-stable control subjects). These numbers converted to an odds ratio of 4.0 (95% confidence interval = 1.1 to 14.2) for a patient with cancer showing MSI to have a serrated adenoma or hyperplastic polyyp and 3.7 (95% confidence interval = 1.0 to 13.1) for a hyperplastic polyyp. By contrast, conventional adenomas showed no differences in number or frequency between the two groups. Loss of hMLH1 expression in serrated adenomas and hyperplastic polyyps was frequent in the patients with cancer showing MSI and was associated with MSI and hMLH1 promoter methylation in informative lesions. This study suggests that hyperplastic polyyps and serrated adenomas are precursors to sporadic right-sided colon carcinomas with MSI.

The malignant potential of serrated adenomas had been identified in pathologic studies (14,18), but the potential for malignancy in hyperplastic polyps was much more in doubt. Genetic alterations of the type seen in neoplasms had been reported in hyperplastic polyyps (16,17,19). In addition, epidemiologic studies (20) had shown that the risk factors for adenomas and carcinomas were also risk factors for hyperplastic polyyps. The study by Hawkins and Ward (3) adds molecular pathology evidence, and these investigators have provided a model for progression.

The implications of the study for patient management are uncertain. This and other studies of hyperplastic polyyps suggest that not all of these polyyps are created equal. Rather, the right-sided hyperplastic polyyp and the large hyperplastic polyyp appear to be the ones of concern (3,17). The absolute and relative risks of colon cancer in patients with these lesions or serrated adenomas are unknown at present. It is therefore unclear how aggressively removal of these lesions should be pursued or if subsequent surveillance is justified when these lesions are found and removed. The relationship of aberrant crypt foci to these right-sided hyperplastic polyyps and serrated adenomas needs to be determined to understand the early molecular events. Finally, the implications for chemopreventive strategies need to be addressed. Adenomas are the target lesions in most clinical trials of chemoprevention agents, and the response or resistance of right-sided hyperplastic polyyps and serrated adenomas to various agents is as yet uncertain. This study leaves important questions unanswered, but the truism that hyperplastic polyyps lack malignant potential has bitten the dust as a result of the findings.

**REFERENCES**


