Hypermethylation of hMLH1, HPP1, p14(ARF), p16(INK4A) and APC in primary adenocarcinomas of the small bowel.

Abstract:
Small bowel adenocarcinoma (SB-AC) is a very rare tumor entity. Epigenetic alterations, including hypermethylation of DNA mismatch repair genes and tumor suppressor genes, seem to be important for carcinogenesis in tumors of the gastrointestinal tract, but have not yet been investigated in SB-AC. In the current study, the prevalence of hypermethylation in a panel of genes involved in gastrointestinal carcinogenesis (hMLH1, HPP1, p14(ARF), p16(INK4A), APC) was determined in a series of SB-AC. Paraffin-embedded tumor samples from 56 patients with SB-AC who underwent surgical resection between January 1985 and December 2003 were investigated for hypermethylation by means of methylation-specific real-time PCR, and compared with our findings in a previously investigated series of 50 gastric adenocarcinomas. In comparison with adenocarcinomas of the stomach, SB-AC revealed a significantly higher rate of hypermethylation of HPP1 (86% versus 54%, p = 0.0003), p16(INK4A) (32% versus 10%, p = 0.0006), and a significantly lower rate of hypermethylation of APC (48% versus 84%, p = 0.0001). Hypermethylation of hMLH1 and p14(ARF) was present in 23% and 9% of SB-AC, respectively. Locally advanced tumor categories (pT3/4) showed a higher rate of hypermethylation of HPP1 (90%) than did early tumor categories (pT1/2 categories, 40%; p = 0.0036). This
was also reflected by the correlation between the HPP1 hypermethylation and high UICC stage (p = 0.02). No correlation was found between hypermethylation and other clinicopathologic parameters such as age, tumor grade and nodal status. Our findings suggest that hypermethylation of hMLH1, HPP1, p16(INK4A) and APC is frequent in primary adenocarcinomas of the small bowel. The differences in the hypermethylation spectrum of small bowel and stomach cancer indicate significant epigenetic differences between these tumors.