Abnormal expression of cell adhesion molecules such as E-cadherin, beta and gamma catenin are associated with various carcinomas. We hypothesize that loss of E-cadherin, beta- and gamma-catenin may play an important role in the pathogenesis of bladder and renal cancers. We tested this hypothesis through analysis of E-cadherin, beta- and gamma-catenin in human bladder and renal cancers. Human bladder and renal cancer specimens were analyzed for E-cadherin, beta- and gamma-catenin expression. The mechanisms of inactivation of these genes were analyzed by CpG methylation of promoter regions and mutational analysis. Normal and bladder cancer samples from 51 patients were compared in terms of E-cadherin gene expression and methylation status by immunohistochemistry, methylation-specific polymerase chain reaction (MSP), and bisulfite genome-sequencing techniques. Ten different CpG sites (nt 863, 865, 873, 879, 887, 892, 901, 918, 920, and 940) in the promoter region were studied. Thirty-five of 51 (69%) bladder cancer samples lacked E-cadherin expression, whereas only six of 51 (12%) normal bladder samples lacked E-cadherin immunoreactivity. MSP analysis of bladder cancer samples suggested that 43 of 51 (84%) showed methylation of the promoter region, whereas only 12 of 51 (24%) normal bladder samples showed hypermethylation. Sodium bisulfite genome-sequencing analysis revealed that of 10 CpG sites, two sites (nt 892 and nt 940) showed 100% methylation in all the cancer samples analyzed. Other CpG sites were partially methylated (47–91%). Normal tissue showed only 12% methylation (range, 1–33%) on various CpG sites. Similarly, 67% (23 of 34) of renal cancer samples lacked E-cadherin expression, with an associated increase in methylation, compared with normal tissue. E-cadherin gene promoter was methylated in all renal and bladder cancer cell lines and was accompanied by a loss of E-cadherin gene and protein expression. Also supporting these data, E-cadherin-negative renal and bladder cancer cell lines restored expression of the E-cadherin gene after treatment with the demethylating agent 5-aza-2' -deoxycytidine. On an SSCP analysis for beta-catenin in human bladder cancer, abnormal bandshifts were detected in some high grade carcinomas with intracellular beta-catenin accumulation. Further sequencing revealed three mutations [AGT (S) to ATT (I), TCT (S) to CCT (P) and TCT (S) to TGT (C)] within the consensus motif for GSK-3beta phosphorylation. Loss of E-cadherin, intracellular accumulation of beta- and gamma-catenin are important events in both human and renal cell carcinomas, therefore, can be biomarkers for these cancers.