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Epigenetic Inactivation of *SFRP1* and *SFRP2* Genes as Biomarkers of Invasive Bladder Cancer

Executive Summary

The epigenetic silencing of important tumor suppressor genes through promoter hypermethylation is becoming evident in many cancers. In bladder cancer, it has been proposed that this mechanism causes aberrant signaling in the Wnt developmental pathway through the silencing of important antagonists, the soluble frizzled-related protein (*SFRP*) gene family. A thorough study of such alterations could prove to be useful in determining appropriate therapy in bladder cancer patients and improving their prognosis.

Therefore, using a population-based case series, we sought to investigate three hypotheses, that (1) *SFRP* gene hypermethylation is associated with invasive bladder cancer, (2) smoking is associated with *SFRP* gene hypermethylation and (3) *SFRP* gene hypermethylation and *TP53* mutations act jointly as markers of invasive bladder cancer.

In our main results, we observed a significant association between the methylation of any *SFRP* gene and invasive bladder cancer ($p<0.003$). Furthermore, we found that methylation of an increasing number of SFRP genes was associated with higher odds of invasive disease. The joint effect of *SFRP* methylation and *TP53* alterations (represented by immunohistochemical staining of p53) was significant; patients exhibiting both alterations showed a >7-fold odds of having invasive bladder cancer as compared to those without either alteration ($p=0.0001$). No conclusive relationship was found between smoking and *SFRP* methylation.

Our results suggest that epigenetic alterations of the *SFRP* genes are highly prevalent in bladder cancer and may be useful not only in the prediction of invasive disease, but also in the development of new cancer therapies.