



Figure 4. The Early Role for Abnormal DNA Methylation in Tumor Progression

This is depicted in the classic model (Kinzler and Vogelstein 1997) for genetic alterations during the evolution of colon cancer. The altered DNA methylation is shown to occur very early (*red arrow*), as discussed in the text, during conversion of normal to hyperplastic epithelium. This places it in a strategic position (*left bottom black arrow and left bottom box*) for channeling stem cells into abnormal clonal expansion (see Fig. 5) by cooperating with key genetic alterations. These epigenetic abnormalities also have marker connotations, as shown in the bottom left black box. The abnormal DNA methylation continues to accrue during progression from noninvasive to invasive and ultimately, metastatic tumors (*right bottom arrow and right box*). This has connotations for cancer treatment and for markers of prognosis.