Epidemiologic studies of twins indicate that 20-40% of common tumors such as breast, colorectal, and prostate cancers are inherited. However, the effect of high penetrance tumor susceptibility genes such as APC, BRCA1, BRAC2, MSH1, MLH2 and MSH6 only accounts for a small fraction of these cancers. Low to moderate penetrance tumor susceptibility genes likely account for the large remaining proportion of familial cancer risk. Candidate tumor susceptibility genes have been identified based on the discovery of tumor-specific mutations, in vitro experiments, as well as animal models of cancer. Translational studies based on in vitro and in vivo discoveries have led to the identification of novel phenotypes and genotypes associated with cancer in humans. Case-control studies followed by validation studies and meta-analyses have unveiled several novel tumor susceptibility genes, several of which belong to genes encoding metabolizing enzymes and genes from the TGF-beta signaling pathway. Together with genome-wide association studies, candidate gene approaches are likely to fill a large gap in our knowledge of the genetic basis of cancer within the next decade.