It is accepted that cancer results from the accumulation of mutations in genes controlling cell birth or cell death. Also, the microenvironment, including stromal and vascular endothelial cells, is important for the growth and persistence of the cancer cell. This entire constellation of the abnormal molecular biology of cancer cells and their microenvironment is the signature of cancer. However, we still do not understand the mechanisms leading to the origin of cancer cells sufficiently well to have an impact on cancer mortality. The most critical point of cancer development is the transition from a normal target cell to a cancer cell. However, the mechanisms establishing tumor cellular identity, which play an essential role in allowing cancers to arise, have received little attention. Recently, it has been hypothesized that cancer cells are cellular states arising as a result of external perturbations, implying that mutation would not be a direct cause for cancer origin, and that generation of cancer cells would be strongly dependent on cell-cell interactions and environmental variation. From this perspective, there are three key questions for understanding the cancer initiation process. What are the cues instructing a target cell to switch from a normal to a cancerous fate? What is the molecular nature of the cancer cell switch? When, during normal cell development, does this switch take place? This last question is critical because, to find the players of the normal/cancer switch mechanism, one has to know when/where to look. The mechanisms initiating cancer must integrate developmental cues (different between cancer types) with the universal requirements for the creation of a tumor mass. Although it is generally believed that the decision to become a cancer cell must be made once the normal cell has adopted a cell fate compromise in the majority of cancers, recent data suggest that this timing of cancer initiation is not a universal feature shared by many oncogenes. Actually, several recent papers have found that oncogenes contribute to cancer development not only by inducing proliferation, but mainly via developmental reprogramming of the epigenome. Indeed, using stem-cell restricted transgenic expression systems, it has been shown that the expression of the oncogene in the reprogramming-prone stem/progenitor cells is capable of programming the development of all the cells that compose the tumor mass. Overall, these results not only highlight a previously unrecognized role for oncogenes in cancer, but also provide evidence for a previously unmodeled process for tumorigenesis in which the programming of the malignant phenotype has already taken place at the stem cell stage, thus uncovering a new role for oncogenes in the timing of cancer initiation. In this context, mutations that activate oncogenes would have a driving role in the reprogramming process, but may act as passenger mutations (or have a secondary, different role) thereafter. These findings lead to new questions. First, is the decision to initiate cancer made at one time point during the differentiation process, or are a series of consecutive decisions required to switch to a cancer-cell fate? and, are all these decisions cell-autonomous? What is the nature of the (epi)genetic pathway downstream from the cancerspecific initiation gene defect(s)? If we learn how to stop cancer development by manipulating the cancer-initiation program then, someday, understanding the initiation of cancer will also be useful for cancer therapy.