Cell fate depends on genetic, epigenetic and environmental inputs that are interconnected, making it difficult to disentangle their respective contributions to cell fate decisions, and epigenetic reprogramming is a major contributor to tumor plasticity and adaptation. Although cancer initiation and progression are generally associated with the accumulation of somatic mutations, substantial epigenomic alterations underlie many aspects of tumorigenesis and cancer susceptibility, suggesting that genetic mechanisms alone may not be sufficient to drive malignant transformations. However, whether purely non-genetic reprogramming mechanisms are sufficient to initiate tumorigenesis irrespective of mutations is unknown. Here, we show that a transient perturbation of transcriptional silencing mediated by Polycomb-Group proteins is sufficient to induce an irreversible switch to a cancer cell fate in Drosophila. This is linked to the irreversible derepression of genes that can drive tumorigenesis, including JNK and JAK-STAT signalling pathways and zfh1, the fly homolog of the ZEB1 oncogene, which we show to be a necessary driver of the cancer fate. These data show that a reversible perturbation of Polycomb-Group protein levels can induce cancer in the absence of driver mutations and suggest that this is achieved through epigenetic inheritance of altered cell fates.