demonstrating the greatest improvement in survival rates are acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and Wilms tumor. The typical definition of "cure" in childhood cancer includes completion of all therapy, clinical and radiologic evidence of no disease, and a period of 5 years since diagnosis.

Etiology

Often the first questions parents of newly diagnosed children with cancer ask is "How did my child get this, and did I do something to cause it?" Parents are also understandably concerned with the question of the likelihood that their other children will get cancer. Although there are numerous hypotheses concerning the origin of cancer, the most enduring theory is that some genetic alteration results in the unregulated proliferation of cells. Significant advances have been made in our understanding of cell proliferation, programmed cell death (apoptosis), genes that activate tumor growth (oncogenes), and genes that keep tumor growth in check (tumor suppressor genes). Cancer is the result of multiple genetic events but is not necessarily hereditary. Overall, the incidence of cancers caused by direct inheritance is low.

In the early 1970s, Alfred Knudson described the "two-hit hypothesis." This explanation of cancer inheritance is best described in retinoblastoma. Like most genes, the retinoblastoma gene *(Rb)* is present in two copies on each cell. It is a tumor suppressor gene, responsible for controlling cell growth. When just one of these copies is lost—the "first hit," the cell remains normal. However, when the second copy is lost—the "second hit," abnormal cell proliferation occurs and retinoblastoma develops (Knudson, Hethcote, and Brown, 1975). A child can inherit one altered copy of the retinoblastoma gene from a mother or father. Therefore, it takes only one more hit for retinoblastoma to develop. Perhaps the most well-known inherited cancer predisposition syndrome is Li-Fraumeni syndrome, which is mainly due to constitutional (in all cells) mutation in the tumor suppressor gene, *p53.* This syndrome is characterized by early incidence brain tumors, premenopausal breast cancer, soft tissue and bone sarcomas, leukemias, and lymphomas (Plon and Malkin, 2016).

Chromosome abnormalities have been identified in many