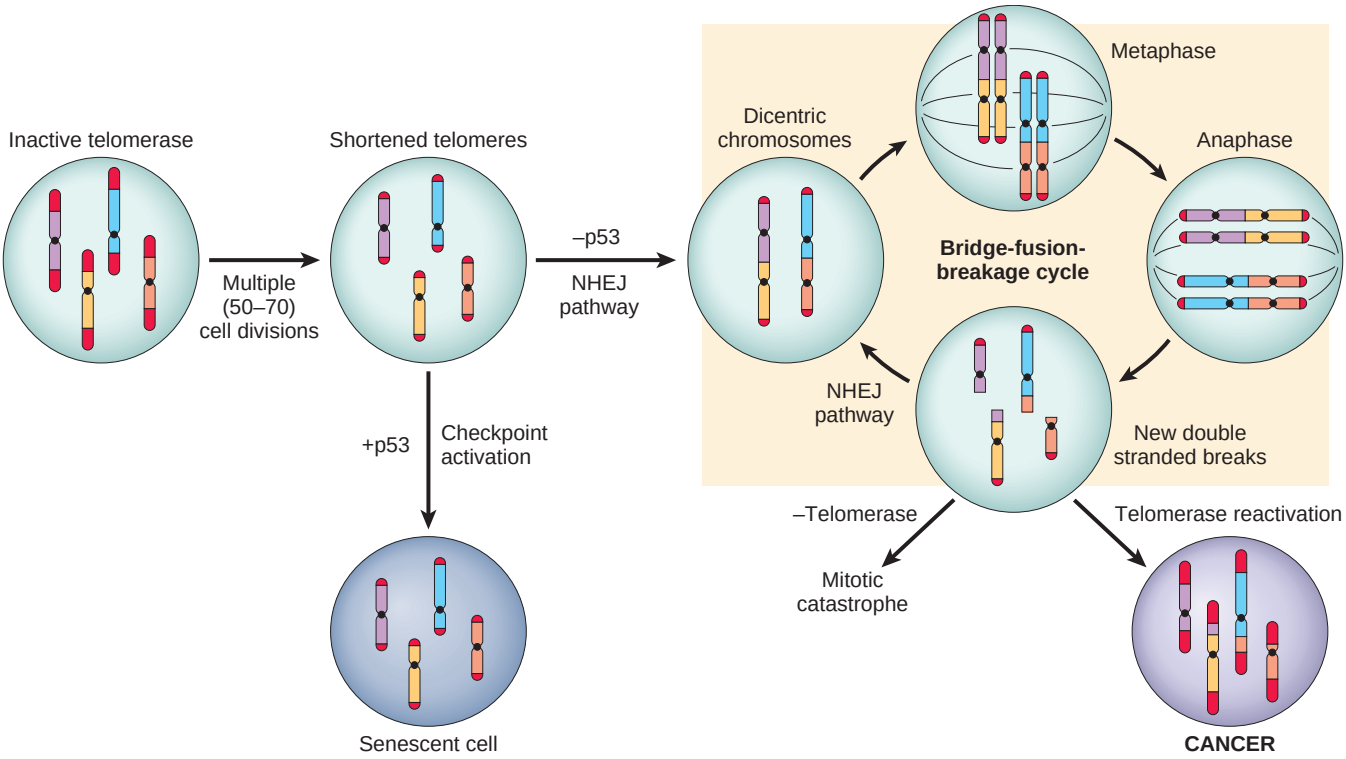

Figure 7-34 Escape of cells from senescence and mitotic catastrophe caused by telomere shortening. Replication of somatic cells, which do not express telomerase, leads to shortened telomeres. In the presence of competent checkpoints, cells undergo arrest and enter nonreplicative senescence. In the absence of checkpoints, DNA repair pathways, such as the nonhomologous end-joining (NHEJ) pathway are inappropriately activated, leading to the formation of dicentric chromosomes. At mitosis the dicentric chromosomes are pulled apart, generating random double-stranded breaks, which then activate DNA-repair pathways, leading to the random association of double-stranded ends and the formation, again, of dicentric chromosomes. Cells undergo numerous rounds of this bridge-fusion-breakage cycle, which generates massive chromosomal instability and numerous mutations. If cells fail to reexpress telomerase, they eventually undergo mitotic catastrophe and death. Reexpression of telomerase allows the cells to escape the bridge-fusion-breakage cycle, thus promoting their survival and tumorigenesis.

In a *symmetric division*, both daughter cells remain stem cells; such divisions may occur during embryogenesis, when stem cell pools are expanding, or during times of stress. In an *asymmetric division*, only one daughter cell remains a stem cell; in such circumstances, the non–stem cell daughter proceeds along some differentiation pathway, losing "stemness" but gaining one or more functions in the process. Such cells in "transit" to a differentiated state are often highly proliferative, but they eventually differentiate, stop dividing, and extinguish themselves.

The continued growth and maintenance of many tissues that contain short-lived cells, such as the formed elements of the bone marrow and blood and the epithelial cells of the gastrointestinal tract and skin, depends on a resident population of tissue stem cells that are capable of self-renewal. Following on this logic, because cancers are immortal and have limitless proliferative capacity, they too must contain cells that self-renew, so-called *cancer stem cells*. While the existence of cancer stem cells is accepted, there is ongoing debate about their identity and their numbers in particular cancers, due in large part to the difficulty in determining whether any particular cell is a cancer stem cell. Thus, the number of "stem cells" that are calculated to be present in a particular tumor can vary widely depending on methodology used to quantify stem cells, leading to uncertainty about whether cancer stem cells are rare or common in tumors.

Another open question is whether cancer stem cells arise from the transformation of tissue stem cells or from the conversion of conventional somatic cells to transformed cells with the acquired property of "stemness." The answer seems to be that both scenarios occur in different types of tumors (Fig. 7-35).

- In chronic myelogenous leukemia (CML), the *BCR-ABL* fusion gene that characterizes this tumor is present in a tumor cell subset that has all the properties of a normal hematopoietic stem cell. Thus, CML appears to originate from a transformed hematopoietic stem cell with an ingrained capacity for self-renewal. Similarly, certain epithelial tumors may arise from other adult stem cells, such as those that are present in colonic crypts.
- In contrast, studies of acute myeloid leukemia have shown that the cancer stem cells in this disease arise from more differentiated hematopoietic progenitors that acquire an abnormal capacity for self-renewal. How this occurs is unclear, but it is believed that certain mutated transcription factors, such as a PML-RARA fusion protein that is associated with acute promyelocytic leukemia (described later) may have important roles in acquisition of "stemness" (Fig. 7-35). Recall that expression of a small number of transcription factors can result in the epigenetic reprogramming of a

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