Significant variability exists in normal tissue reactions in patients with cancer receiving radiotherapy, with a subpopulation exhibiting increased toxicity to ionizing radiation. Genomic studies have proposed that single nucleotide polymorphisms in DNA repair genes, cytokines, and reactive oxygen species may play a role in clinical radiosensitivity. Additional research examining the association between genetic variants and radiation-induced inflammation and fibrosis may spur the development of targeted therapy in radiation oncology, which could increase cure rates and limit toxicity. As more people become long-term cancer survivors, oncology nurses must aggressively assess and manage late treatment side effects to optimize patient functioning and quality of life. The purpose of the current article is to describe the effect of ionizing radiation on normal and irradiated tissue, discuss genetic mutations that are proposed to influence radiosensitivity, and identify future areas of research on the association between genetics and radiation toxicity.