Chronic inflammation has emerged as one of the hallmarks of cancer. Inflammation also plays a pivotal role in modulating radiation responsiveness of tumors. As discussed in this review, ionizing radiation (IR) leads to activation of several transcription factors modulating the expression of numerous mediators in tumor cells and cells of the microenvironment promoting cancer development. Novel therapeutic approaches thus aim to interfere with the activity or expression of these factors, either in single-agent or combinatorial treatment or as supplements of the existing therapeutic concepts. Among them, NF-κB, STAT-3, and HIF-1 play a crucial role in radiation-induced inflammatory responses embedded in a complex inflammatory network. A great variety of classical or novel drugs including nutraceuticals such as plant phytochemicals have the capacity to interfere with the inflammatory network in cancer and are considered as putative radiosensitizers. Thus, targeting the inflammatory signaling pathways induced by IR offers the opportunity to improve the clinical outcome of radiation therapy by enhancing radiosensitivity and decreasing putative metabolic effects. Since inflammation and sex steroids also impact tumorigenesis, a therapeutic approach targeting glucocorticoid receptors and radiation-induced production of tumorigenic factors might be effective in sensitizing certain tumors to IR.