BACKGROUND: The inactivation of the tumor suppressor gene BRCA1 is a predisposing factor for a breast/ovarian cancer development. Formation of cancer-specific alternative splicing variants with aberrant biological properties can represent additional mechanism decreasing the overall BRCA1 activity in DNA double strand break (DDSB) repair. In this study, we analyzed BRCA1 alternative splicing variants BRCA114-15 and 17-19 ascertained previously during the screening of high-risk breast cancer individuals. METHODS: We established a stable MCF-7 cell line-based model system for an in vitro analysis of BRCA1 variants. Using this system, we analyzed the impact of BRCA114-15 and 17-19 variants on DNA repair kinetics using comet assay and confocal immunomicroscopy. The capacity of DNA repair was assessed directly by an in vitro NHEJ assay and indirectly by a mitomycin C sensitivity test. The proliferation activities were determined by a clonogenic assay and growth curves. RESULTS: Overexpression of BRCA114-15 and 17-19 increases the endogenous level of DNA damage, slows down the DDSB repair, and decelerates the initial phase of radiation-induced foci formation and prolongs their persistence. Moreover, BRCA114-15 and 17-19 differentially influence the activity of HR and NHEJ and sensitivity of MCF-7 cells to ionizing radiation. CONCLUSIONS: The overexpression of BRCA114-15 or 17-19 impairs the DNA repair capacity in a dominant-negative fashion. We hypothesize, that BRCA114-15 and 17-19 impair the balance and communications between main DDSB repair pathways – HR and NHEJ. This leads to the loss of flexibility in DDSB repair and could contributes to the increased genomic instability. We conclude that alternative splicing variants BRCA114-15 and 17-19 negatively influence the BRCA1 functions in maintaining of genome homeostasis in MCF-7 cells.