Polyamines (putrescine, spermidine and spermine) are small organic polycations that play an indispensable role in key cellular processes such as the regulation of growth, differentiation and macromolecular functions. Elevated levels of polyamines have been shown to be one of the major factors involved in carcinogenesis. In this study, specific silencing of three genes of polyamine (PA) biosynthesis pathway, ornithine decarboxylase (ODC), S-adenosylmethionine decarboxylase (SAMDC) and spermidine synthase (SPDSYN) gene expression was achieved using RNAi technology in oral (KB) and breast (MCF 7 and MDA MB 231) cancer cell lines. For optimizing the effective small interfering nucleic acid (siNA), three variant of ODC siNA [siRNA, LNA modified siRNA and siHybrid (RNA and DNA hybrid)] were used and a dose- and time-dependent study was conducted. The most effective silencing was observed at 50 nM concentration after 48 h of incubation. Then, the PA biosynthetic genes were targeted individually and in combination. The transfected cells were analyzed for the mRNA expression of target genes, polyamine levels, cell growth inhibition, cell morphology, apoptosis and cell migration. RNAi-mediated reduction in the expression of polyamine biosynthesis genes resulted in distorted cell morphology, reduced cancer cell viability and migration characteristic. The most promising results were observed with treatment of siSPDSYN and siODC simultaneously in MDA-MB231 cells with 87% cell growth inhibition. On analyzing the expression profile of cell cycle and apoptosis related genes, it was observed that RNAi against polyamine biosynthetic genes down-regulated the expression of CDK8, CCNE2, CCNH, CCNT1, CCNT2, CCNF, PCNA, CCND1, CDK2, and up-regulated the expression of E2F4, BAX, FAS, TP53, CDKNA, BAK1, CDKN1B, ATM, GRANB, ATR genes when compared with control-transfected cells. A cancer targeting siRNA delivery PEG PLGA nanoparticle was also developed by conjugation with MUC1 aptamer. The Apt conjugated siRNA PEG-PLGA nanoparticle could successfully encapsulate, protect and specifically deliver siRNA to MCF 7 cancer cells. Thus, targeting polyamine biosynthesis in oral and breast cancers could be a promising strategy for breast cancer therapy.