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Boosting NAD(+) biosynthesis with NAD(+) intermediates has been proposed as a strategy for preventing and treating age-associated diseases, including cancer. However, concerns in this area were raised by observations that nicotinamide phosphoribosyltransferase (NAMPT), a key enzyme in mammalian NAD(+) biosynthesis, is frequently up-regulated in human malignancies, including breast cancer, suggesting possible protumorigenic effects for this protein. We addressed this issue by studying NAMPT expression and function in human breast cancer in vivo and in vitro. Our data indicate that high NAMPT levels are associated with aggressive pathological and molecular features, such as estrogen receptor negativity as well as HER2-enriched and basal-like PAM50 phenotypes. Consistent with these findings, we found that NAMPT overexpression in mammary epithelial cells induced epithelial-to-mesenchymal transition, a morphological and functional switch that confers cancer cells an increased metastatic potential. However, importantly, NAMPT-induced epithelial-to-mesenchymal transition was found to be independent of NAMPT enzymatic activity and of the NAMPT product nicotinamide mononucleotide. Instead, it was mediated by secreted NAMPT through its ability to activate the TGFβ signaling pathway via increased TGFβ1 production. These findings have implications for the design of therapeutic strategies exploiting NAD(+) biosynthesis via NAMPT in aging and cancer and also suggest the potential of anticancer agents designed to specifically neutralize extracellular NAMPT. Notably, because high levels of circulating NAMPT are found in obese and diabetic patients, our data could also explain the increased predisposition to cancer of these subjects.