## HOXA9 regulates BRCA1 expression to modulate human breast tumor phenotype.

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**Public Summary:**
BRCA1 is a tumor suppressor implicated in both familial and non-familial breast cancer. BRCA1 expression is often reduced in non-familial breast tumors, but the molecular basis for this is unknown. In this study, we identified homeobox A9 (HOXA9) as a gene frequently reduced in human breast cancers and tumor cell lines, and noted that reduced HOXA9 levels associated with tumor aggression, metastasis, and patient mortality. Experiments revealed that loss of HOXA9 promoted breast cell growth and survival, and perturbed tissue organization. Restoring HOXA9 repressed breast tumor cell growth and survival, and inhibited the malignant phenotype of breast cancer cells. Studies demonstrated that HOXA9 restricted breast tumor behavior by directly modulating the expression of BRCA1. Consistently, HOXA9 expression correlated with BRCA1 in patient specimens and with tumor aggression in patients lacking estrogen receptor/progesterone receptor expression in their breast tissue. These findings indicate that HOXA9 restricts breast tumor aggression by modulating expression of the tumor suppressor gene BRCA1, which we believe provides an explanation for the loss of BRCA1 expression in non-familial breast tumors in the absence of BRCA1 genetic modifications

**Scientific Abstract:**
Breast cancer 1, early onset (BRCA1) expression is often reduced in sporadic breast tumors, even in the absence of BRCA1 genetic modifications, but the molecular basis for this is unknown. In this study, we identified homeobox A9 (HOXA9) as a gene frequently downregulated in human breast cancers and tumor cell lines and noted that reduced HOXA9 transcript levels associated with tumor aggression, metastasis, and patient mortality. Experiments revealed that loss of HOXA9 promoted mammary epithelial cell growth and survival and perturbed tissue morphogenesis. Restoring HOXA9 expression repressed growth and survival and inhibited the malignant phenotype of breast cancer cells in culture and in a xenograft mouse model. Molecular studies showed that HOXA9 restricted breast tumor behavior by directly modulating the expression of BRCA1. Indeed, ectopic expression of wild-type BRCA1 phenocopied the tumor suppressor function of HOXA9, and reducing BRCA1 levels or function inhibited the antitumor activity of HOXA9. Consistently, HOXA9 expression correlated with BRCA1 in clinical specimens and with tumor aggression in patients lacking estrogen receptor/progesterone receptor expression in their breast tissue. These findings indicate that HOXA9 restricts breast tumor aggression by modulating expression of the tumor suppressor gene BRCA1, which we believe provides an explanation for the loss of BRCA1 expression in sporadic breast tumors in the absence of BRCA1 genetic modifications.