**Lay Description of Important Outcomes**

• Recent studies have shown that a specific protein called ERα, which is associated with breast cancer, might be involved in the spread of cancer cells from the breast to other parts of the body, a process known as metastasis. This protein has been detected in tumors that have spread and appears to be linked to cancer spreading to the bones. However, the exact ways in which ERα helps breast cancer cells survive and grow in different organs like bones, lymph nodes, or lungs are still not completely clear. Interestingly, our recent research has discovered a new role of ERα in working with RNA, in addition to its well-known action on DNA. This breakthrough, coming after three decades of studying its DNA-related functions, is reshaping our understanding of how ERα contributes to tumor formation and metastasis and offering completely new ways of drugging breast cancer metastasis.

• Our research has shown that ERα helps breast cancer cells produce certain proteins that allow them to adapt and survive in challenging environments as the tumor progresses and spreads as metastasis in other organs.

 • We have also found that the ability of ERα to interact with RNA is associated with resistance to drugs, a crucial factor in cancer cells spreading to distant sites.

• Additionally, we have discovered that ERα influences the production of proteins in breast cancer by interacting with another protein called a translation factor. This translation factor can be targeted by a drug named Zotatifin, which is currently undergoing testing in phase II clinical trials for metastatic breast cancer. These findings open up possibilities for further clinical trials focused on treating metastatic breast cancer. Our research results can also aid in developing new markers to identify breast cancer patients at high risk of developing metastasis and who could benefit from treatment with Zotatifin.