# What Causes ER-Positive Breast Cancer to Spread to the Brain?

Diana Cittelly, PhD, studied how certain proteins in the brain drive metastasis in the presence or absence of estrogen.

August 11, 2026 By Greg Glasgow and University of Colorado Cancer Center

---

New research by University of Colorado Anschutz Cancer Center member Diana Cittelly, PhD, may help to explain a persistent puzzle in breast cancer metastasis — why estrogen receptor-positive (ER-positive) breast cancer can sometimes spread to the brain. Even though this type of brain metastasis is fairly common, it hasn't been studied as much as other types.

"If you think about brain metastases in breast cancer, people often think that triple-negative breast cancer and HER2-positive breast cancer are the ones that go to the brain," says Cittelly, associate professor of pathology in the CU Anschutz School of Medicine. "It is true that fewer patients with ER-positive breast cancer develop brain metastases, but if you look at the population of patients living with brain metastases from breast cancer, almost 50% of them have ER-positive breast cancer. It's a smaller fraction, but it's within a much larger group of people. It also is somewhat difficult to study because the biology of how those metastases develop is different from triple-negative and HER2-positive."

## The FGFR1 connection

Cittelly found that the group of ER-positive breast cancers able to grow in the mouse brain, have extra copies of a gene called FGFR1. This gene was known to help cancer cells survive and grow, especially after they become resistant to hormone-blocking treatments. However, Cittelly and her group found that the FGFR1 gene needs to be activated when metastatic cancer cells arrive at the brain. FGFR1 can be activated by two proteins: FGF2 and NCAM1, which are presented by brain support cells called astrocytes. This activation of FGFR1 in the brain, is critical for brain metastasis initiation.

"We found that FGF2 was much higher in the brain of younger animal models than the older ones," says Cittelly, who published the results of her research in May in the journal Nature

Communications. “There is also more estrogen in the younger animal models, so in younger mice the metastases will grow a lot because they are fed by estrogen and by FGF2. But it turns out that brain FGF2 decreases with aging, so we were puzzled, because we could see that the metastases are still happening in the older mice, even those lacking ovarian estrogen.

“We thought an additional driver must be activating FGFR1 in older mice,” Cittelly says. “FGFR1 and NCAM1 have been described in the brain for other functions, which is why we thought this could be a mechanism worth investigating. We found that when you have a lot of FGF2, FGF2 is the preferred ligand, because it has higher affinity for FGFR1. But when FGF2 decreases, NCAM1 becomes the predominant ligand. Thus, we demonstrated for the first time that a NCAM1 activation of FGFR1 is a mechanism that is relevant for brain metastases and that the cancer cells are utilizing a pathway previously unrecognized.”

## To inhibit or not to inhibit

Cittelly’s research found that using drugs that inhibit the action of FGFR1 inhibitors worked well when used early in the metastatic process, and not so well when metastases are already big and growing, which is the stage at which they are usually detected in patients. The problem she says, is that the inhibitors currently under development are very toxic, making a cost-benefit analysis very important when it comes to using them in treatment.

“If a patient has an FGFR1 amplification in their primary tumor, this probably will call for more close surveillance, because those patients are more likely to develop brain metastases,” she says. “Probably an oncologist would want to do more surveillance to make sure that the metastasis is caught earlier, so that other more direct treatments can be used to treat the metastases. But if a patient already has one metastasis, they are at higher risk of developing more new metastases. That may be a population where you could use an FGFR1 inhibitor to prevent new secondary metastases from happening.”

## Next steps

Cittelly says the next step in her research is to understand more about how the FGFR1-positive breast cancer cells are able to survive in the brain after they become independent from the early activation by FGF2 and NCAM1.

“We know the receptor is there, but we don’t know how the cell is able to survive in this microenvironment long-term,” she says. “What is changing in that cell that is allowing it to stay there? We are trying to get funding to study the epigenetic adaptation that the cells are acquiring

that allows them to overcome the FGFR1 dependence.”

This article was originally published July 31, 2026, by the University of Colorado Cancer Center. It is republished with permission.

---

© 2026 Smart + Strong All Rights Reserved.
http://beta.docker.cancerhealth.com/article/causes-erpositive-breast-cancer-spread-brain