Carbone Cancer Center:

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MADISON, Wis. – A new study by UW Carbone Cancer Center researchers has found that dense breasts and inflammation are associated with poor prognosis in breast-cancer patients, and suggests that an FDA-approved drug may improve prognosis for those patients with dense breasts.

These symptoms have long been known as risk factors for developing breast cancer, but their relationship to the disease has not been clear.

“In this study we were able to analyze the inflammatory component and the extracellular matrix, or the region surrounding the cancer cells, and identify how they affect the progression of breast cancer,” said Dr. Karla Esbona, a clinical and translational researcher at the UW School of Medicine and Public Health, and lead author of the study. “We found that there is definitely something going on between the extracellular matrix, specifically the collagen in it, and its interaction with immune cells.”

Breast density is a clinical feature determined by mammogram and is related to the density of collagen in breast tissue. Inflammation is an immune response mediated in part by macrophages, a type of immune cell that can access the extracellular matrix and the growing tumor. Some macrophages negatively affect the tumor, but some can promote its growth.

Using early-stage breast cancer biopsy samples from 371 patients, Esbona and colleagues observed a number of features, including total collagen, how the collagen appeared structurally, macrophage presence and location and the

inflammation marker COX-2. They were able to correlate these biological features with clinical features such as tumor grade, recurrence and overall survival.

They found, for example, that higher COX-2 levels and higher numbers of pro-tumor macrophages in the extracellular matrix led to poorer overall survival. They also found that, while total collagen deposition in the extracellular matrix did not have any effect on survival, if collagen fibers were aligned with each other and crosswise to the tumor boundary, patients had poorer overall survival.

“This study provides an overall model for how these biomarkers relate to breast cancer,” Esbona said of the study, published Feb. 8 in the American Journal of Pathology. “It’s not just collagen, it’s not just the immune component and inflammation. I analyzed everything together and determined how each of these variables contributes to breast cancer progression.”

The next step will be to use these markers to inform a clinical trial they already have underway, which will involve women with mammographically dense breast cancer. This trial was based on their conclusions from a previous pre-clinical study in a mouse model of breast cancer.

In that study, the researchers used mice that are genetically prone to develop breast cancer, and have either dense or regular mammary tissue. If the FDA-approved COX-2 inhibitor, celecoxib, was given, tumors shrank and the chronic inflammatory response significantly decreased – but only in the mice with dense mammary tissue. In the human clinical trial, women with dense breasts and a biopsy showing early-stage breast cancer will be given celecoxib for two weeks before surgery to remove the tumor.

“We’ll compare the biopsy sample from before celecoxib treatment to the surgical sample, and measure the same cancer-related markers we identified in this study,” Esbona said. “Because we expect this drug to be most effective on women with dense breasts, we hope to see some of the results we saw as favorable in our biomarker and pre-clinical studies, namely, reduced COX-2 levels, lower marks of cell proliferation and more favorable collagen signatures.”

If the human clinical trial mimics what they saw in mice, celecoxib treatment could become part of a breast-cancer treatment plan or possibly a preventive strategy for women with dense breasts.

Esbona, who now is a scientist in the department of pathology and also manages the Translational Research Initiatives in Pathology (TRIP) Laboratory, conducted much of this work while a graduate student with Dr. Patti Keely, who passed away in 2017 after a third battle with cancer.

“One of Patti’s wishes was to have research move from the lab all the way to the clinic, which this work is doing,” said Dr. Suzanne Ponik, a senior scientist in Keely’s lab and co-author of the pathology study. “She wanted her work to carry on through her students and scientists, too.”