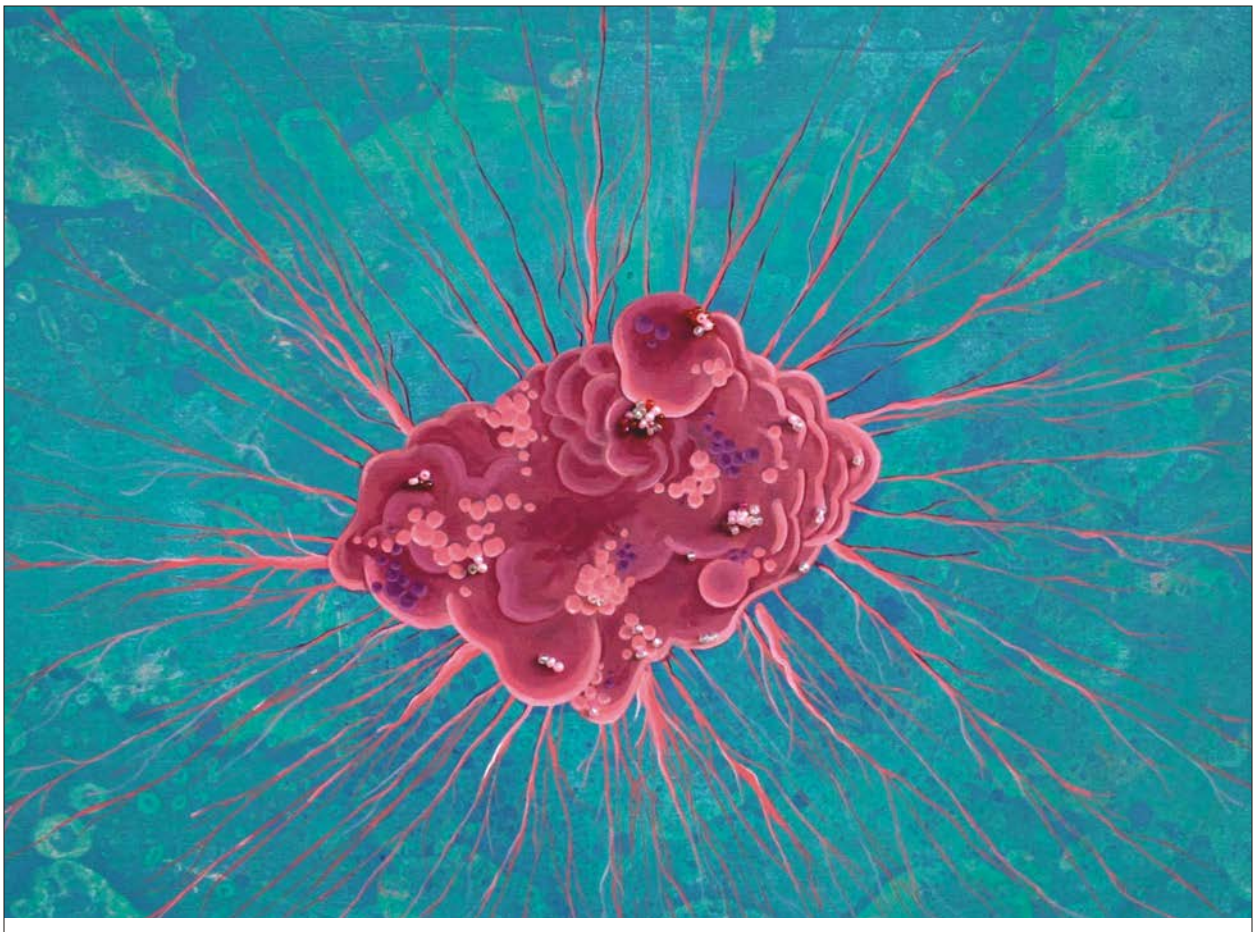

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Sporadic Breast Cancers Start With Ineffective DNA Repair Systems

Breast cancers that arise sporadically, rather than through inheritance of certain genes, likely start with defects of DNA repair mechanisms that allow environmentally triggered mutations to accumulate, according to researchers at the University of Pittsburgh School of Medicine, Magee-Womens Hospital of UPMC and the University of Pittsburgh Cancer Institute. The findings, reported this week in the early online edition of the Proceedings of the National Academy of Sciences, indicate that potent chemotherapy drugs that target DNA in later-stage cancers could be an effective way to treat the earliest of breast tumors.

Recent research has focused on familial breast cancers, in part because the predisposing genes have been well-characterized and women at risk can be identified, said Jean J. Latimer, Ph.D., assistant professor of obstetrics, gynecology and reproductive sciences at Pitt's School of Medicine. But these cases only comprise 15 percent of the 190,000 breast cancers that are diagnosed every year.

Research on sporadic breast cancer has involved the use of available cell lines derived from late-stage tumors, but most newly diagnosed tumors in the U.S. are stage I, the earliest form of invasive disease.

"Our team is able to grow stage I breast cancer cells - before they have spread to adjacent tissues and lymph nodes - allowing us to examine the mechanisms that underlie cancer development in people who didn't inherit a faulty gene," Dr. Latimer said. "The advent of innovative tissue engineering techniques has finally made it possible for us to culture these cells to determine what has gone wrong."

In earlier work, she and her colleagues found that breast tissue does not repair everyday damage to DNA as well as other tissues, such as skin. Ultraviolet light, for example, can cause mutations, but a sophisticated system of nucleotide excision repair (NER) proteins trolls the DNA strands to identify problems and initiate repair processes. The same system repairs damage caused by many environmental carcinogens, including tobacco smoke.

"Even in healthy breast tissue, this system is only about one-fifth as effective as it is in skin," Dr. Latimer noted. "This deficiency could set the stage for sporadic cancer development, with the risk increasing with age as DNA damage accumulates."

For the study, the researchers grew and assessed 19 sporadic, stage I breast tumors placed into culture directly from surgeries to test their NER pathways. In every case, there was a deficiency in repair capacity compared to disease-free breast tissue.

"That is a remarkably consistent feature for cancers that might otherwise seem random in their genesis," Dr. Latimer noted. "We rarely see a universal rule when it comes to breast cancer, but then until now, we have rarely studied stage I disease."

Some chemotherapy drugs work especially well on cells that exhibit reduced DNA repair, but they are typically given in later-stage disease. The new findings suggest, however, that these approaches could be effective in treating early stage disease, she noted.

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