

Multi-center study sheds light on understudied breast cancer type

October 14 2022



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A multi-center analysis of patients with invasive lobular carcinoma, or ILC—the second most common histological subtype of invasive breast cancer in the U.S.—showed that, despite its prevalence, ILC is detected

later and has worse outcomes than the predominant subtype of invasive breast cancer, known as invasive ductal carcinoma (IDC), or no special type.

Published today in the *Journal of the National Cancer Institute*, the study of more than 33,000 [patient records](#) from three large [cancer](#) centers—UPMC Hillman Cancer Center, Cleveland Clinic Cancer Center and The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James)—shows that ILC and IDC are biologically distinct, highlighting important differences between the two diseases and the need for specific detection and treatment options for the lobular subtype.

"Lobular [breast](#) cancer makes up about 10% to 15% of breast cancer cases, but it has historically been neglected by the [research community](#), so we really don't know that much about it," said co-lead author Steffi Oesterreich, Ph.D., co-leader of the Cancer Biology Program at UPMC Hillman and professor at the University of Pittsburgh School of Medicine's Department of Pharmacology & Chemical Biology. "There has been increasing awareness that ILC and IDC are distinct, but this large multi-center study provides compelling evidence that these are two different diseases that require different management."

Co-senior authors Megan Kruse, M.D., a breast medical oncology specialist at Cleveland Clinic, and Nicole Williams, M.D., a breast medical oncologist at OSUCCC—James, worked with Oesterreich to analyze records from patients treated at the three cancer centers for ILC or IDC between 1990 and 2017.

"These findings likely indicate that detection of lobular breast cancer is delayed," said Kruse. "When these tumors are finally detected, they're larger and they've already moved to the lymph nodes, indicating the

cancer is spreading. We need to put more effort into improving early detection of ILC by developing new imaging technologies or other methodologies."

The idea for the study was sparked one evening as Oesterreich was washing dishes and listening to a recording of a Lobular Breast Cancer Alliance conference call that she'd missed. When Susan MacDonald, a lobular breast cancer advocate from Cleveland, mentioned that Cleveland Clinic researchers were beginning a project to analyze the center's breast cancer registry, Oesterreich's ears pricked up.

"I thought, 'Wow, we have been doing the very same thing at UPMC. It would make sense to collaborate and work together,'" said Oesterreich.

ILC's key feature is loss of a gene called E-cadherin that helps cells stick together. As a result, lobular cancer cells grow in lines, producing tumors that look more like [spider webs](#) than the familiar round lumps of IDC, explained Oesterreich. These web-like tendrils make ILC difficult to spot on mammograms until the cancer has grown and often advanced.

The analysis found that ILC cells were lower grade than IDC, meaning that they looked more similar to normal cells. However, ILC tumors were diagnosed twice as often at stage III or IV— advanced stages in which cancer cells have spread beyond breast tissue to the lymph nodes or metastasized to other parts of the body. Lobular tumors were also larger in size than their ductal counterparts.

The researchers restricted the next part of their analysis to patients with tumors bearing estrogen receptors and lacking the HER2 receptor. They found that patients with lobular cancer had worse disease-free survival and overall survival. ILC patients also had more [disease recurrence](#) than those with IDC, and recurrences tended to occur later.

"In other words, more tumors are coming back, and they're coming back later for patients with ILC," explained Oesterreich, who also holds the Shear Family Endowed Chair in Breast Cancer Research and is co-director of the Women's Cancer Research Center, a partnership between UPMC Hillman and Magee-Womens Research Institute. "This suggests that tumor cells hibernate somewhere in the body until they are reawakened. We need to find where these cells hang out and why they reawaken."

A commercially available advanced genomic test called Oncotype DX was used to predict risk of recurrence and response to chemotherapy for patients with early-stage estrogen-receptor-positive, HER2-negative breast cancer.

The analysis found that there was a significant association between the Oncotype DX score and cancer recurrence for patients with IDC. Very few ILC cases were classified as high-risk, despite more late recurrences, highlighting the need for specific molecular tests that improve predictions for lobular breast cancer.

"Lobular breast cancer and ductal breast cancer are two distinct diseases. Our study shows that lobular breast cancers are diagnosed at a more advanced stage and have increased chance of recurrence. However, invasive lobular cancer was less likely to be classified as high-risk by a commonly used genomic test," said Williams. "Despite their differences, these cancers are often treated the same. We hope these findings will spark research aimed at developing new diagnostic tools and drugs to improve outcomes for patients with lobular breast cancer."

Other researchers who contributed to the study were co-first authors Azadeh Nasrazadani, M.D., Ph.D., and Jian Zou, M.S., both of Pitt or UPMC; Neil Carleton, B.S., Yujia Li, B.S., Kathryn Demanelis, Ph.D., George Tseng, Ph.D., Adrian V. Lee, Ph.D., all of Pitt or UPMC;

Tiffany Onger, M.D., and Matthew D. Wright, M.D., both of Cleveland Clinic; and Bhuvanewari Ramaswamy, M.D., of The Ohio State University Wexner Medical Center.

More information: Clinicopathological features and outcomes comparing patients with invasive ductal and lobular breast cancer, *Journal of the National Cancer Institute* (2022).

Provided by University of Pittsburgh

Citation: Multi-center study sheds light on understudied breast cancer type (2022, October 14) retrieved 22 June 2024 from <https://medicalxpress.com/news/2022-10-multi-center-understudied-breast-cancer.html>

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