Breast cancer risk prediction models improved by adding multiple biological markers of risk

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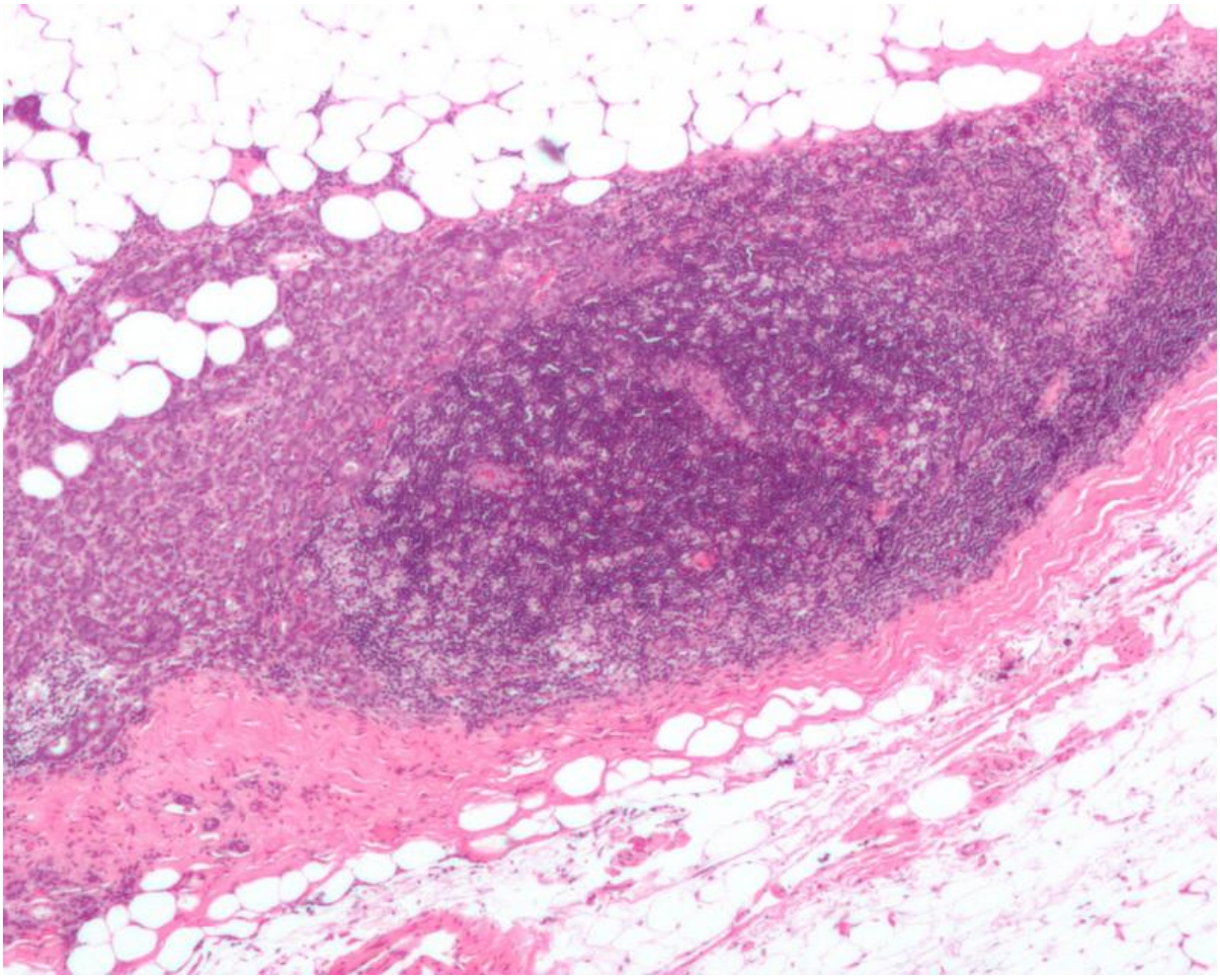

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Adding biological markers of risk to breast cancer risk prediction models currently in use in the clinic appears to improve risk prediction, especially for postmenopausal women not using hormone therapy (HT), according to research presented here at the AACR Annual Meeting 2016, April 16-20.

Improved ability to identify a woman's breast cancer risk could help more precisely tailor the use of chemopreventives and screening recommendations.

"Risk prediction models are a type of statistical model that can provide insight into whether an individual is at low, medium, or high risk for a specific disease given their individual risk factor profile," said lead author of the study Xuehong Zhang, MD, ScD, assistant professor of medicine at Harvard Medical School and associate epidemiologist at Brigham and Women's Hospital in Boston. Breast cancer risk prediction models, such as the Gail and Rosner-Colditz models, have been used to estimate women's risk of breast cancer in order to tailor chemoprevention and screening recommendations.

"To date, these models generally have included only traditional breast cancer risk factors such as age, family history of breast cancer, reproductive factors, body mass index (BMI), and alcohol intake, and their ability to discriminate between women with vs. without breast cancer has been limited. However, neither model as initially developed included multiple biological markers of risk," Zhang said.

"We conducted the first comprehensive evaluation of the independent and joint contribution of several biological markers of risk in the two validated breast cancer risk prediction models [Gail and Rosner-Colditz models] using data from up to 10,052 breast cancer cases and 12,575 controls of European ancestry from the Nurses' Health Study (NHS) and NHS II," he added.

The biological markers of risk the researchers assessed were a genetic risk score, mammographic density, and levels of the endogenous hormones testosterone, estrone sulfate, and prolactin; each of these markers has been associated with breast cancer risk in multiple studies.

"A genetic risk score can summarize in a single number an individual's genetic predisposition to a certain disease outcome [e.g., breast cancer in this study] based on multiple risk alleles," Zhang explained. He and colleagues calculated a breast cancer genetic risk score based on 67 single-nucleotide polymorphisms (SNPs) identified from a recently published meta-analysis of nine genome-wide association (GWAS) studies.

After stratifying the data by menopausal status, the researchers assessed how the newly added biological factors improved risk prediction for developing invasive breast cancer and estrogen receptor- and progesterone receptor-positive disease (ER+PR+) over a five-year period. They measured improvement by calculating the area under the curve (AUC), adjusting for age.

The units of AUC span from 50, meaning that a model's ability to predict risk is no better than a coin toss, to 100, meaning that the model's ability to predict risk is perfect, Zhang explained.

Of the women whose data were used in this study, about 45 percent were premenopausal, 25 percent were postmenopausal and not using HT, and 30 percent were postmenopausal, using HT at blood draw. For postmenopausal women not using HT, adding genetic risk score, percent mammographic density, and hormone levels to the Gail model improved the AUC by 10.8 units, from 55.2 to 66; for the Rosner-Colditz model, the corresponding AUC improved by 6 units, from 60.2 to 66.2.

To predict the risk of developing ER+PR+ breast cancer in

postmenopausal women not using HT, adding the biological factors improved the AUC by 11.7 units and 9.4 units for Gail and Rosner-Colditz models, respectively.

"Based on 1999-2010 data from the U.S. National Health and Nutrition Examination Survey [NHANES], over 90 percent of postmenopausal women are not using HT, thus the larger improvements we saw for this subgroup would apply to the majority of postmenopausal women in the U.S. An important next step in this research will be to validate these initial findings in other study populations," Zhang said.

More information: Kyriaki Michailidou et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk, *Nature Genetics* (2013). DOI: 10.1038/ng.2563

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