Progesterone Receptor in Estrogen Receptor–Positive Breast Cancer: The Association Between HER-2 and Lymph Node Involvement Is Age Related

To the Editor: Cui et al[1] discussed the biology and etiology of estrogen receptor (ER) -positive/progesterone receptor (PR) -negative breast cancers highlighting recent data on molecular crosstalk between ER and growth factor signaling pathways also demonstrating how PR might be a useful marker of these activities.

In their review, Cui et al missed our report on the negative association between PR and HER-2 in 1,104 women with an ER-positive breast cancer using semiquantitative immunohistochemistry with monoclonal antibodies NCL-ER-6F11/2 for ER, NCL-PgR-312 for PR, and CB11 for HER-2 (Novocastra Laboratories, Newcastle-upon-Tyne, United Kingdom). The negative association between PR and HER-2 is only seen after age 45; in younger women, HER-2 positive ER-positive breast tumors were as likely PR-positive with similar median PR levels as HER-2 negative tumors; patients with triple-positive cancer (that is, ER-, PR-, and HER-2–positive cancer) were younger than the others.[2] This suggests cross talk is age related and may explain why such breast cancers remain sensitive to antiestrogens in young women.[3]

In ER-positive breast cancers, PR-negative tumors are more aggressive than PR-positive cancers. Cui et al stated that the reason for the poor clinical course of PR-negative tumors is unclear. We previously reported that a negative PR in women with an ER-positive breast cancer predicts lymph node invasion independent of other predictors of lymph node invasion especially in younger women.[4]

Consequently, we repeated our analysis for a negative PR as a predictor for a positive lymph node status in ER-positive breast cancers taking tumor size and tumor grade into account in an updated cohort of 1,472 previously untreated and consecutive women with a unilateral invasive breast cancer that was surgically treated between 2000 and 2004 in one center. With multivariate logistic regression analysis using stepwise selection in the LOGISTIC procedure from the SAS software package version 9.1 (SAS Institute, Cary, NC), the following variables were first considered for inclusion in the model predicting the nodal status: PR (PR-positive *v* PR-negative), tumor grade (grade 3 *v* grade 1 and 2) and maximal tumor size (> 20 mm *v* $\leq$ 20 mm). After variable selection, the final model retained only variables having a coefficient significantly different from zero ($P < .05$; Wald χ^2 statistic).[5] As described in Table 1 and in agreement with previously reported findings from a recent paper[6] of Cui et al's group, this approach did not retain PR as a predictor for a positive lymph node status when the model was derived from all ER-positive breast cancer patients. In our analyses, considering women 50 years or younger at the time of breast cancer diagnosis, PR, tumor grade, and tumor size were all independent predictors for a positive lymph node status. In women older than age 50, only tumor size and tumor grade predicted a positive lymph node status.

In analyses of the prognostic effect of a negative PR in women with an ER-positive breast cancer, at least for its association with a positive lymph node and HER-2 status, younger and older women should be considered separately from each other and we believe this is an important addition to the data by Cui et al.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

In Reply: Neven et al highlight their recent studies on the relationship between progesterone receptor (PR) and HER-2 status in breast cancer. It is gratifying to note that they also found increased HER-2 positivity in estrogen receptor (ER) -positive/PR-negative tumors (11.5%) compared with ER-positive/PR-positive tumors (5.4%). A recent study using fluorescent in situ hybridization (FISH) measurement of HER-2 amplification, showed a similar 2.75-fold increase,[1] which is very similar to several other reports.[2]

Table 1. Predictors of Positive Lymph Node Status

Variables	All (N = 1,472)			≤ 50 Years (n = 458)			> 50 Years (n = 1,014)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
PR, −/+	—		—	0.547	0.300 to 0.997	.0490	—		—
Grade 1 to 2 *v* 3	0.628	0.494 to 0.799	.0002	0.569	0.373 to 0.866	.0086	0.696	0.517 to 0.938	.0172
Size > 20 *v* ≤ 20, mm	3.539	2.813 to 4.452	$< .0001$	4.745	3.117 to 7.224	$< .0001$	3.092	2.346 to 4.076	$< .0001$

Abbreviations: OR, odds ratio; PR, progesterone receptor.

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