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Single Hormone Receptor–Positive Breast Cancer—Signal or Noise?

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Canonical predictors for the prognosis of breast cancer include estrogen receptor (ER), progesterone receptor (PR), and ERBB2 (formerly HER2) receptor. In most cases, positive ER status is auspicious, but there are exceptions (young women, black women, and *BRCA2* mutation carriers). The simplest designation, hormone receptor–positive cancers, includes tumors that express ER and/or PR (hormone receptor–negative cancers express neither). A complementary classification scheme groups patients into 4 categories based on gene expression profiles, 2 of which are hormone receptor positive (luminal A and luminal B). Luminal B tumors are less likely to express PR than luminal A tumors, they may be ERBB2 positive, they have a worse prognosis, and they are more likely to be treated with chemotherapy. Both luminal A cases and luminal B cases are candidates for tamoxifen or other hormone therapy.

Li and colleagues[1] address the 4 different combinations of ER and PR and breast cancer survival using a large population-based cancer registry, the Surveillance, Epidemiology, and End Results (SEER) database. They abstracted data from 823 399 patients with breast cancer diagnosed from 1990 to 2015 with known ER and PR status. Eighty-six percent were concordant for receptor status; 67.2% of all patients expressed both ER and PR, and 19.0% expressed neither receptor. A small proportion were discordant: most were ER positive/PR negative (12.2%), but some were ER negative/PR positive (1.6%). The 20-year breast cancer–specific survival was similar in all 4 subgroups; however, there were small differences in survival, which in a large data set become significant. As described in eTable 1 of the Supplement,[1] the highest 20-year survival was seen among patients with the ER-positive/PR-positive subtype (76.5%), followed by patients with the ER-positive/PR-negative subtype (69.8%), those with ER-negative/PR-positive subtype (68.5%), and those with ER-negative/PR-negative subtype (67.6%).

Some have argued that the ER-negative/PR-positive subtype is biologically implausible given the coexpression and pathways of the ER and PR in breast cancer,[2] and other studies have been unable to reproduce the ER-negative/PR-positive subtype using alternative techniques.[3] The question is whether the group of ER-negative/PR-positive cancers is a legitimate subgroup or is an artifact resulting from misclassification. Perhaps the best evidence that it is a meaningful category comes from the survival difference reported by Li and colleagues[1]: 68.5% for women with the ER-negative/PR-positive cancer vs 76.5% for women with the ER-positive/PR-positive cancer (hazard ratio, 1.61; 95% CI, 1.55-1.67). Adjustment for clinically significant variables was made, but data on tamoxifen use were unavailable. A patient with an ER-positive/PR-positive tumor is more likely to be prescribed tamoxifen than a patient with an ER-negative/PR-positive tumor. Also, the patients with the ER-negative/PR-positive subtype are more likely to be luminal B than are those with the ER-positive/PR-positive subtype. Data on ERBB2 status were lacking for most patients.

Other evidence from the study by Li et al[1] comes from the difference in tumor characteristics. If the pathologists misclassified ER status when they assigned an ER-negative/PR-positive subtype to a patient with ER-positive/PR-positive subtype, then the patients with ER-negative/PR-positive subtype should resemble the ER-positive/PR-positive subtype in terms of clinical outcomes. There were clear differences in the 2 groups in terms of age, race, tumor size, lymph node status, and distant metastasis. Is it possible that some patients with ER-negative/PR-negative tumors were in fact misclassified as having ER-negative/PR-positive tumors? In eTable 1 in the Supplement,[1] we see that for most variables the ER-negative/PR-positive phenotype distribution was intermediate between the patients with the ER-positive/PR-positive and the ER-negative/PR-negative subtypes,

suggesting a mixture of the 2. The 10-year survival of ER-negative/PR-positive breast cancer was 75.0% and was between that for ER-positive/PR-positive (86.0%) and ER-negative/PR-negative (72.0%) breast cancer; this is consistent with the premise that the patients with ER-negative/PR-positive tumors may have a 20/80 mix of ER-positive/PR-positive and ER-negative/PR-negative subtypes. It turns out that the same mix can account for many of the differences in eTable 1.[1] One exception is age at diagnosis, which was shown to be significantly lower among patients with ER-negative/PR-positive tumors compared with patients with all other hormone receptor subgroups. Given the distribution of the prevalence of ER status and PR status among the cohort, misclassification would need to occur in 0.5% of ER-positive cancers and 6.4% of PR-positive cancers, the latter of which seems unlikely.

In the study by Li and colleagues,[1] a finding against the case that the ER-negative/PR-positive subtype is a real category is the decline in proportions from 4.5% to 1.0% from 1990 to 2015. Nowadays, only 1% of breast cancer cases are categorized as ER negative/PR positive, and the problem is not so large as it once was. It is unlikely that cancer types are evolving in response to a changing environment. Classically, ER positivity and PR positivity are not dichotomous variables; rather, they are based on cutoffs of the proportion of positive-staining cells. Where there is a gray zone, there is bound to be misclassification. In the case of hormone receptor status, technologies and protein expression cutoff values varied during the study period (1990-2015). Over the next decade, we will perhaps see the proportion of ER-negative/PR-positive cases decline from 1% to an even smaller fraction.

There are limitations with SEER data. ERBB2 status is available from 2010 onward in the SEER database, and it is unclear to what extent this influenced the results by Li and colleagues.[1] Furthermore, it is unclear to what extent antiestrogen therapy is used among patients with ER-positive/PR-negative and ER-negative/PR-positive subtypes, with some studies showing effectiveness similar to that in patients with the ER-positive/PR-positive subtype.[4] Data on hormone therapy are unavailable in the SEER database.

How might the results by Li and colleagues[1] affect treatment decisions? If the ER-negative/PR-positive subtype represents a mixture of the ER-positive/PR-positive and ER-negative/PR-negative subtypes, then we should observe a marginal survival benefit with hormone therapy. In a meta-analysis[5] of adjuvant tamoxifen trials, a reduced risk of breast cancer recurrence was observed for tamoxifen use vs placebo among patients with ER-poor/PR-rich cancer; however, the difference was not statistically significant. In contrast, if the ER-negative/PR-positive subtype is a valid category, then we might consider the use of alternative therapies, such as antiprogesterone therapy. Denosumab is an anti–receptor activated nuclear factor–κβ ligand monoclonal antibody that suppresses progesterone-mediated receptor activated nuclear factor–κβ signaling. Randomized clinical trials of adjuvant denosumab treatment in breast cancer are underway, and preliminary findings have so far shown improved disease-free survival.[6] It will remain a challenge to personalize treatment for ER-negative/PR-cancer considering that this subtype now constitutes only 1% of all breast cancers.

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