Receptors, Associations, and Risk Factor Differences by Breast Cancer Subtypes: Positive or Negative?

Leslie Bernstein, James V. Lacey, Jr.

Correspondence to: Leslie Bernstein, PhD, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, 1500 East Duarte Rd, Bldg 173, Duarte, CA 91010 (e-mail: lbernstein@coh.org).

As classification of breast cancer subtypes has evolved from a dichotomy based on estrogen receptor (ER) status to groups based on gene expression profiling, epidemiologists have attempted—first using ER, then ER and progesterone receptor (PR), and most recently, using ER and PR combined with HER2—to determine whether risk factors could explain the heterogeneous nature of breast cancer. These approaches approximate but cannot directly reproduce the molecular taxonomy identified by Perou et al. (1)
because population-based epidemiological studies frequently only have data on these three receptors and rely on archived results collected from many laboratories. Thus, epidemiological studies tend to classify subtypes as luminal A (ER- or PR-positive and HER2-negative), luminal B (ER- or PR-positive and HER2-positive), triple-negative (ER-, PR-, and HER2-negative), and HER2 overexpressing (ER- and PR-negative and HER2-positive). Tumors that express ER or HER2 respond more favorably to antiestrogens and trastuzumab treatments, respectively, whereas triple-negative breast cancers are more difficult to treat, often present as interval cancers in breast cancer screening programs (2), have high risk of early recurrence (3), and comprise a large portion of breast cancer among women with a BRCA1 mutation (4,5). Hence, determining whether these subtypes are etiologically distinct could stimulate the development of novel targeted approaches to prevention.

In this issue of the Journal, Phipps et al. (6) report on the risks of triple-negative breast cancer and ER-positive breast cancer in an analysis that combined the Women’s Health Initiative (WHI) clinical trials with its observational study component. Among 155,723 postmenopausal women who were aged 50–79 years at recruitment and were followed for a median of 7.9 years, Phipps et al. identified 307 women with triple-negative breast cancer and 2,610 with ER-positive breast cancer. The main results for ER-positive breast cancer reflect the expected associations for this subtype (7,8): an inverse association with later age at menarche, a positive association with nulliparity and late age at first birth, and a modest inverse association with increasing parity among parous women. Triple-negative disease was not associated with age at menarche or age at first birth, was inversely associated with nulliparity, and was suggestively positively associated with increasing parity. No association was noted for either subtype and breastfeeding history or use of oral contraceptives, although women with at least 10 years of oral contraceptive use had reduced risk of ER-positive breast cancer. These results on nulliparity for triple-negative breast cancer are consistent with some studies [eg, (9)] and discordant with others [eg, (10)], and Phipps et al. suggest reasons for some of these differences. Clearly, the age distribution and racial–ethnic composition of study populations are important because triple-negative breast cancer occurs more frequently among younger women and African American women (9,11,12) and the penetration of risk factors may vary by age, menopausal status, and race.

All previous studies cited by Phipps et al. suffer from small numbers of triple-negative cancers, as does their own analysis, despite the fact that it was based on the large WHI studies. Other analyses are beginning to tackle the sample size problem. The Journal recently published an article describing data from 10,900 ER-positive breast cancer patients, 3,895 ER-negative breast cancer patients, and 17,399 control participants contributed to the Breast Cancer Association Consortium (BCAC) by 12 population-based studies, perhaps the largest study to date of ER-negative disease (13). Early age at menarche, nulliparity, and late age at first birth were all associated with increased risk of ER-positive but not ER-negative breast cancer. Among the four studies with HER2 data available, neither nulliparity nor late age at first birth was associated with risk of triple-negative breast cancer. These results did not confirm the nulliparity finding of Phipps et al.

One view of the current literature is that most of the well-established reproductive risk factors for breast cancer are more strongly associated with ER-positive breast cancer than with more refined subtypes that include PR and HER2. This observation raises two issues of immediate importance for studies of receptor subtypes and, particularly, triple-negative disease. First, because most epidemiological studies to date rely on subtype classifications based on assay results collected from a wide variety of laboratories, are results for receptor status consistent, valid, and reproducible enough to detect potential differences in risk factor associations? And, are these receptor-defined subtypes etiologically relevant? With regard to ER status, the answer appears to be “Yes” to both questions. The differing age patterns of breast cancer incidence by ER status have been well defined (14), and at least some confirmed susceptibility loci from genome-wide association studies demonstrate statistically significant heterogeneity and are more strongly associated with ER-positive than with ER-negative breast cancer (15). Studies that compared ER assay results abstracted from pathology reports with immunohistochemistry (IHC) performed in a central laboratory showed strong agreement (>85%) between the two (κ statistics for chance corrected agreement, 0.64–0.70) (16,17). Results for PR (80.5% agreement; κ = 0.60), ER-negative/PR-negative (κ = 0.69), and ER-positive/PR-positive (κ = 0.62) were generally similar (10). These data suggest that conclusions based on results from outside laboratories are reasonably reliable for ER status and ER-positive/PR-positive and ER-negative/PR-negative subtypes. Although misclassification will occur, its impact on risk factor estimates for reproductive factors did not alter conclusions in one study (10).

Adding HER2 to this mix complicates the misclassification problems. The majority of HER2 testing by community-based laboratories is done by IHC, which is cheaper, faster, and easier to perform than the fluorescent in situ hybridization (FISH) assay (18). But IHC has downsides: it performs better in fresh tissue and is affected by tissue fixation methods, reagents used, assay protocols, antibody sensitivity, and scoring system (18). Lack of reproducibility of IHC results between community-based laboratories and central laboratories is of great concern (19,20). For clinical trials, interlaboratory agreement for FISH assays has shown high concordance ranging from 92% (20) to 99% (22). FISH may indeed be more reliable, reproducible, sensitive, and accurate than IHC, but its adoption outside the large pathology centers has been limited (19). The ongoing debate about the best method of testing for HER2 and interpretation of results has recently been discussed in this Journal (23). Until those issues are resolved, errors in HER2 classification added to those for ER and PR can make interpretation of epidemiological associations more difficult and may contribute to inconsistency of results across studies.

Another key question is what should epidemiological studies do to narrow the gap between what is known about the potential etiologic differences among breast cancer subtypes and how those subtypes might ultimately be used to guide strategies for the prevention of breast cancer? Continued accrual of large samples of breast cancer patients and control participants, especially by large-scale consortia that can identify precise differences between smaller subgroups of patients, remains essential. It is equally important for investigators conducting individual studies to anticipate what
types of new markers or new subtypes might emerge in the future. The analysis by Phipps et al. used WHI data that have been collected continuously since 1993, and the pooled analysis within BCAC drew on studies that began many years ago. It will be interesting to see whether nulliparity has the paradoxical effects on risk of triple-negative breast cancer vs ER-positive breast cancer observed by Phipps et al. when HER2 test reliability improves. A remaining ongoing challenge is the epidemiologist’s ability to collect biospecimen results in the presence of rapidly changing technology or, alternatively, to collect specimens and organize large-scale testing for proven and new markers in ways that minimize the types of misclassification error that have complicated the analysis of HER2 in current epidemiological studies. Meeting that challenge successfully could accelerate the translation of new biomarkers in ways that bring targeted prevention, detection, and treatment of breast cancer closer to reality.

References

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Affiliation of authors: Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA (LB, JVL).