Re: Age-Specific Incidence of Breast Cancer Subtypes: Understanding the Black–White Crossover

In a recent article in the Journal, Dr. Clarke and colleagues (1) presented data from the California Cancer Registry on age-specific incidence of breast cancer subtypes investigating whether a black–white breast cancer incidence crossover exists at early ages. The authors categorized the breast cancers according to molecular phenotypes of hormone receptor (HR) expression (estrogen receptor [ER] and progesterone receptor) and protein overexpression (or DNA amplification) of HER2. The stratification of the subtypes produces four informative categories: HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2− (so-called triple-negative breast cancer [TNBC]). Their white and black HR+ breast cancer cohorts included 42,034 and 3,350 cases, respectively (1).

In agreement with previous studies (2,3), Clarke et al. found that in the entire cohort at younger ages, breast cancer incidence rates among blacks exceeded those for whites [figure 2A in Clarke et al. (1)]. The authors found that within the four molecular phenotypes, however, no such crossover occurs, but they did find that black women had higher rates of TNBC and lower rates of HR+/HER2− breast cancer relative to white women. This apparent difference-of-incidence crossover in the entire cohort but not in the subgroups is a reflection of a statistical effect known as Simpson’s Paradox (4–6). Described more than 100 years ago, the paradox refers to a correlation or effect difference present in multiple subgroups that appears to be reversed when the groups are combined. The data of Clarke et al. are amenable to the effect of Simpson’s Paradox given the relatively large differences in the number of the white and black subpopulations and the tendency for blacks to have higher-grade breast cancers and consequently, higher relative rates of TNBC and lower rates of HR+/HER2− breast cancers relative to whites.

The comparison of Clarke et al.’s data (1) using the California Cancer Registry with those of Anderson et al. (3) using the Surveillance, Epidemiology, and End Results (SEER) data (1975–2004) is particularly noteworthy when one characterizes their respective data among blacks and whites for HR activity alone. The SEER data utilized in the Anderson et al. paper (2,3) did not contain information on HER2 status. Figure 1 shows the incidence rate ratios for ER+ relative to ER− breast cancers derived from the Clarke and Anderson studies for white and black women. Given the differences in cohort populations and the expected difference in the absolute rate ratios, one can, nonetheless, appreciate that the rate ratios (ER+/ER−) are higher for whites relative to blacks and that the overall curves for each racial group are relatively parallel, suggesting similar effects within similar populations.

Epidemiological data, as presented by Clarke et al., are potentially susceptible to misinterpretation, a result of confounding, especially when arguing for molecular and biologic causes for relative incidence differences. We agree that molecular phenotyping needs to be considered when presenting observational studies and, as our clinical colleagues have demonstrated, needs to be integrated into diagnostic, prognostic, and treatment decisions. The importance of breast cancer molecular phenotyping may also need to be incorporated within a redefined staging system.

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References
Response

Schwartz et al. suggest that our observation (1) of the well-reported black–white crossover in age-specific breast cancer incidence disappearing after stratification by molecular subtype is an example of a Simpson’s Paradox. A Simpson’s Paradox can lead observers to incorrectly conclude that effects seen within subgroups reflect the true effect in the overall group. In such a situation, the observer must then carefully consider causality, confounding, and other knowledge about the subject matter to decide whether the subgroup or the overall population provides better information for answering the question under study (2).

We approached our analysis from a different perspective—namely, to ask whether the black–white crossover in overall breast cancer rates is also observed for breast cancer subtypes that are based on well-studied molecular subtypes defined jointly by hormone receptor and HER2 status. We concluded that the joint distributions of race/ethnicity and molecular subtype are more useful than race/ethnicity alone in understanding racial and ethnic differences in breast cancer occurrence. We further identified triple-negative (ie, hormone receptor–negative and HER2-negative) breast cancer as having very different age-specific incidence patterns compared with other subtypes, inferring etiologic heterogeneity. Schwartz and colleagues provide a graph of age-specific incidence rate ratios for estrogen receptor (ER)–positive vs ER-negative breast cancer among whites and blacks, which shows that the ratios are relatively consistent among races and suggests “similar effects within similar populations.” Using our own data, we extended that analysis by stratifying ratios further by HER2 status (Figure 1). The rate ratios for black and white women with HER2-positive cancers are similar across age groups, but for HER2-negative cancers the rate ratios increase slightly with age among black women and increase markedly with age among white women. This additional stratification by HER2 status shows that HER2-negative cancers may have


Notes

The authors declare no conflicts of interest.

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Advance Access publication January 25, 2013

Figure 1. Incidence rate ratios for hormone receptor (HRI)-defined breast cancer according to women’s age at diagnosis, race (non-Hispanic [NH] white, NH black), and tumor HER2 expression status. Figure created using data from Clarke et al. (1).
differential occurrence among white women, especially at older ages.

We see a clear and continuing trend toward more division of cancers (not just breast cancers) into subtypes defined by factors beyond the anatomical site at which they were diagnosed so as to enable targeted therapeutics, to better unravel etiology, or simply to improve upon traditional taxonomy and nomenclature. The comments of Schwartz and colleagues serve as a reminder that those efforts to subdivide tumors can create the statistical conditions for seemingly paradoxical, but by no means insurmountable, subgroup vs overall effects.

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Funding
This study was supported by the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program under contract HHSN261201000040C awarded to the Cancer Prevention Institute of California (CPIC). The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the SEER Program under contract HHSN261201000040C awarded to CPIC (formerly the Northern California Cancer Center), contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; the Centers for Disease Control and Prevention’s National Program of Cancer Registries, under agreement 1US8DP00807-01 awarded to the Public Health Institute.

Notes
The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. No authors report any financial conflict of interest. The study sponsors did not have any role in the design of the study, the analysis or interpretation of the data, the writing of the article, or the decision to submit the article for publication.

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DOI:10.1093/jnci/djt002

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Advance Access publication January 25, 2013