Race and Subset Analyses in Clinical Trials: Time to Get Serious About Data Integration
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Colorectal cancer mortality rates have decreased in the last two decades primarily because of improved population screening rates and enhanced multimodality treatment of the disease (1). Because the decline in mortality rates among African American patients has not been as substantial as in white patients of European descent, the disparity in stage-specific survival between African Americans and whites continues to widen (2,3). Multiple factors contribute to the lower survival of African American patients, including reduced access to quality primary care that can lead to less preventative care, higher rates of comorbidities, diagnosis at later stages of disease, and lower utilization of potentially curative treatment after diagnosis (4–7). Unfortunately, there has been a paucity of integrated data at both the individual and population levels to develop effective policies to close the gap.

In this issue of the Journal, Yothers et al. (8) sought to determine whether black (African American or of African ancestry) colon cancer patients with stage II and III disease treated in an equivalent manner within the setting of clinical trials achieved similar cancer-specific and overall outcomes compared with white patients. The authors examined the overall survival, recurrence-free survival, and recurrence-free interval of 13,393 whites and 1218 blacks from the Adjuvant Colon Cancer EndpointT (ACCENT) collaborative group database. The strength of this study was the uniform collection of individual patient level data from participants in 12 adjuvant phase III clinical trials in North America from 1977 to 2002. The results of the study showed that under standardized treatment conditions, black patients still had statistically significant worse overall and recurrence-free survival compared with white patients, whereas both patient groups had a similar recurrence-free interval. Based upon these findings, the authors conclude that the worse survival of black patients is likely because of factors unrelated to response to adjuvant treatment, such as racial differences in comorbidities, general life expectancy, or potentially in care for recurrent disease. It is worth noting that despite the addition of a more contemporary cohort of patients, the results of this study are almost identical to those published in this Journal by Dignam et al. (9) more than a decade ago, which included only the first five National Surgical Adjuvant Breast and Bowel Project (NSABP) colon cancer trials (C-01 through C-05). Moreover, data within this study precede the adoption of biologic therapies for the treatment of advanced colorectal cancer and include outcome data from 5-fluorouracil (FU)-based therapies, which were broadly applied to patients without consideration of the molecular mechanisms driving disease progression. We now understand that colorectal cancers are of a heterogeneous nature (10–12) and should be treated as such. Therefore, studying the poorer overall and recurrence-free survival of African Americans compared with whites among a uniformly treated population without reference to the underlying heterogeneity in tumor biology limits interpretation of the study findings.

Nevertheless, it is useful to examine what additive information is gleaned from each of the endpoints in this article (8). This study demonstrates a non-statistically significant 8% increase in the hazard of recurrence for blacks compared with whites (hazard ratio = 1.08, 95% confidence interval = 0.97 to 1.19, \( P = .15 \)) (8). The authors conclude that this supports either no difference in response to therapy or at best a very small difference. This conclusion has some caveats. Given the higher competing causes of death for black patients before potential recurrence (as evidenced by the poorer recurrence-free survival), recurrences that may have manifested will never occur, which biases the results toward the null hypothesis. More importantly, despite a very large sample size, the study still only included 1218 black patients, and of these, a little less than one-third had recurrence events. Given the heterogeneity in both tumor biology of colon cancer [eg, microsatellite instability (MSI) (13–15)] and host factors [such as the lower frequency of the methylenetetrahydrofolate reductase (MTHFR) codon 677 TT genotype among African Americans (16), which is associated with an increased response to 5-FU-based therapy (15)], it is premature to conclude that biology plays no role. Indeed, studies in the metastatic setting suggest lower response rates to chemotherapy among African Americans (17,18) and lower toxicity with 5-FU chemotherapy among African Americans in both the adjuvant and metastatic settings (18,19). These observations highlight the importance of continued rigorous collection and integration of both tumor and host factors that affect treatment efficacy in a clinical trials setting.

The statistically significant lower recurrence-free survival for black patients, when placed against the non-statistically significant cancer recurrence risks, strongly argues (as the authors have) for higher rates of death before recurrence for black patients as the driving factor. Although toxic deaths from therapy could theoretically be contributing, this is a relatively rare occurrence with 5-FU-based adjuvant therapy and indeed, as mentioned above, African Americans may actually suffer lower toxicities to therapy compared with whites. One likely answer, as seen in the breast cancer literature, is the higher rates of baseline comorbidities among African Americans, leading to increased competing causes of death (20). This conclusion is also supported by the lack of survival differences by race in the Department of Defense system.
where, presumably, lifestyle and baseline health status are more uniform across racial and ethnic groups (21). Unfortunately, detailed comorbidity information is only sporadically collected in cancer clinical trials. We argue that if clinical trials are going to continue to be used to examine racial and ethnic differences in outcomes, then it is crucial to collect detailed comorbidity as well as other sociodemographic factors in a prospective fashion. Data on how well comorbidities are controlled and managed beyond the active treatment phase should be considered in the final analysis. Lack of these data underscores the need for a medical home for all cancer survivors, especially the under- and uninsured, who are less likely to have access to quality primary care.

Finally, the poorer overall survival for black patients at an even higher magnitude than the recurrence-free survival hazard (hazard ratio = 1.22 vs 1.14) (8) supports the authors’ conclusion that this is driven by a higher hazard of death after colon cancer recurrence for black patients. The reasons provided by the authors, including competing causes of death from comorbidities and lower receipt of palliative and, perhaps, potentially curative therapy for isolated liver and lung metastases, are plausible and supported by recent literature (22). However, within the last decade, several studies have documented the influence of tumor biology on response to treatment and survival outcomes (23). Despite decades of excellent work elucidating the molecular biology of colon cancer, we have only begun to scratch the surface (10,12). We know, for example, that the BRAFV600E mutation does not appear to influence recurrence-free survival in colon cancer but has a dramatic impact on overall survival, particularly in patients with MSI-low (MSI-L) and microsatellite stable (MSS) tumors (13). Possibly the most substantial impact on the advancement of personalized medicine in the treatment of advanced colorectal cancer has been the development and use of antiangiogenesis therapies like bevacizumab (24) and anti–epidermal growth factor receptor (EGFR) therapies (ie, cetuximab and panitumumab), as signaling through the EGFR has been identified as a primary mediator of tumor progression in a subset of colorectal cancers and is associated with poorer outcomes (25).

The use of these targeted therapies is leading to the further identification of population subsets that either benefit or do not benefit from these therapies (15,26). Similarly, colorectal cancer patients with tumors of the MSI-high (MSI-H) phenotype show no benefit from and, in some patients, have reduced overall survival following treatment with adjuvant therapy (14,27). Additional genetic and molecular alterations [eg, tumor protein p53 (TP53) mutations (28,29), BCL2-like 1 (BCL2L1) protein overexpression (30,31), and loss of the chromosomal 18q allele (32)] have also been shown to affect response to 5-FU-based therapy, with some specifically affecting patients with MSS stage III and IV colorectal cancers. The prevalence of these alterations is substantial within colorectal tumors and are very likely to have contributed to overall and recurrence-free survival outcomes following adjuvant treatment within the patients of the ACCENT trials. It remains to be seen whether the genetic and molecular alterations that drive colorectal cancer progression and affect response to standard therapy differ by race, but it is important that we do not exclude the possibility.

With the publication of this excellent study by Yothers et al. (8), we hope that we finally put an end to the publication of the “generic” cancer clinical trial racial analysis. The findings are clear and have been fairly consistent across numerous similar studies over the last decade: When treated equally, African Americans have similar colon cancer–specific survival but continue to have poorer overall survival compared with white patients. Germane to clinical trial analyses, if trials are going to continue to be used to examine racial differences in cancer outcomes, then we cannot continue to perform them as post hoc unplanned subset analyses; otherwise, the field will not advance. At a bare minimum, basic sociodemographic and detailed comorbidity information should be prospectively collected and integrated with detailed tumor and host biology data. In addition, primary care of cancer survivors must be improved and, it will be increasingly important to collect data on quality of surveillance after treatment so that differences in survival after recurrence can be better understood. To identify rare but potentially important genetic markers, which may differ by race, future studies need to be adequately powered to do so. As an example, this may require racial- and/or ethnic-specific enrollment targets, such that a trial could close to accrual for whites but remain open for African Americans until adequate accrual is reached; or trials should be opened to a large global community of different races/ethnicities. We have documented racial and ethnic differences in cancer survival by looking from 10000 feet over the past decade, but it is past time for us to get out of the clouds and collect and integrate data that advance the field.

References


Funding
This work was supported by the American Society of Clinical Oncology Career Development Award (to BNP), the National Cancer Institute (NCI) at the National Institutes of Health (NIH) (grant number F31CA136237 to BES), the Dr. Ralph and Marian Falk Medical Research Trust, and the University of Chicago Specialized Program of Research Excellence (SPORE) in Breast Cancer (NIH/NCI grant number 5P50CA125183 to OIO).

Notes
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Olopade is an American Cancer Society Clinical Research Professor. The authors declare no conflict of interest.

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