Letters to the editor

The potential and perils of observational studies

The Epidemiological Strategy and Medical Economics (ESME) program aims at making use of real-life data on patients with metastatic breast cancer (MBC) treated in the French network of cancer centers. We applaud this initiative which has the potential of generating crucially important information on the treatment and outcome of patients with MBC. We take issue, however, with the analyses presented by Delaloge and colleagues to compare HER2-negative MBC patients receiving paclitaxel plus bevacizumab with those receiving paclitaxel alone [1]. A comparison of treatments actually given to patients does not generally provide reliable information on the benefits and harms of the various treatments under consideration. Regardless of how well the data were collected, how many patients were included, or to what extent the statistical models were adjusted for known prognostic factors, the biases inherent in such comparisons are likely to dominate true treatment differences. We are particularly worried about such biases in the current study in view of the highly discrepant findings obtained from previously published randomized trial analyses. Before practice-changing recommendations can be made, an in-depth reanalysis is warranted in order to identify the sources of these discrepancies. Insight could be obtained by restricting the observational data analysis to those patients who would have been eligible for a randomized trial (and thus for whom there are no contraindications to receive bevacizumab), by studying rates of treatment crossover in the randomized trial and observational data analyses, and by ensuring that treatment crossovers are handled in the same way [2].

The authors have used propensity score methods to alleviate concerns about model extrapolation due to patients in the paclitaxel group having very different patient characteristics, on average, from those in the combination group. However, these methods cannot salvage bias when—as is certain to be the case—both groups also differ in terms of unmeasured prognostic factors. Some statistical methods have been proposed to analyze real-world, nonrandomized data by making use of instrumental variables [3]. For instance, when centers or clinicians have definite preferences for certain treatment options, then comparisons of results between centers or clinicians can be informative [4, 5]. If such differential preferences existed in the present context, additional analyses along the instrumental variables principle could deliver a more complete 'sensitivity' analysis.

In fairness, the authors of the article have taken great care to qualify their results. They go as far as to state "Our data cannot therefore support extension of current use of bevacizumab in MBC" [1]. Such a statement is likely to puzzle many readers, who are likely to wonder why a survival hazard ratio of 0.67 (i.e. a 33% reduction in the risk of death, or a prolongation of survival by ~8 months) does not lead to a practice-changing recommendation. The reason is that this hazard ratio is almost surely biased to an extent that cannot be known or inferred from the information presented in the article. It seems unfortunate to publish such encouraging results, and at the same time to disqualify them as being so biased as to have no proper interpretation.

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Disclosure

M.B. is Associate Editor for Biostatistics at *Annals of Oncology*. The authors have no financial relationships with any organizations that might have an interest in the submitted work.

Funding

The authors received no financial support from any organization for the submitted work.

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doi:10.1093/annonc/mdw539
Published online 13 October 2016