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Response

Response to Pisano, Gastonis, Sparano, et al.

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We thank Pisano et al. (1) for their interest in our manuscript and for the opportunity to clarify our study's conceptual approach and outcomes. Our study was specifically designed to ascertain the breast tumor classification method that most accurately identifies women at highest risk of 5-year breast cancer mortality for use in studies of screening effectiveness (1). We calculated sensitivity, specificity, and positive predictive value (PPV) to evaluate each classification method using a binary outcome of advanced vs nonadvanced cancer. Among all cancers, American Joint Committee on Cancer (AJCC) prognostic pathology stage II or higher was overall the most accurate for predicting 5-year breast cancer death (sensitivity = 76.7%, specificity = 81.6%, PPV = 21.0%) while the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) method had high sensitivity (96.1%) but low specificity (41.1%) and PPV (9.1%). We also calculated the time-dependent area under the receiver operating characteristic curve using multiple categories for each classification method to predict 5-year breast cancer mortality (2). For AJCC staging systems, we used the 8 staging categories, IA through IV. For TMIST tumor classification, we constructed a 6-category variable: nonadvanced plus the 5 TMIST advanced categories ordered from worst to best survival observed in our study. We found AJCC prognostic pathologic stage had statistically significantly better discrimination for predicting 5-year breast cancer death than AJCC anatomic stage and the TMIST tumor categories when comparing the same women across tumor classifications. We also evaluated tumor classification methods by mode of detection. Using both the binary and area under the receiver operating characteristic curve outcomes shows that prognostic pathologic stage best predicts 5-year mortality overall and for screen-detected, interval, and clinically detected cancer. Notably, our results were consistent when predicting 10-year breast cancer death and across racial and ethnic groups.

We appreciate that TMIST investigators chose an endpoint for a different reason than our study—to identify cancers generally considered for chemotherapy treatment with the hypothesis that women undergoing digital breast tomosynthesis would have a lower proportion of TMIST advanced cancers than the digital mammography arm, and thus fewer women undergoing digital breast tomosynthesis may require chemotherapy. Avoiding chemotherapy is an important outcome in addition to reducing breast cancer mortality. It will be of interest to see if TMIST results support this hypothesis because we were surprised to find 3 of 5 TMIST advanced cancer subcategories have very high 5-year survival (≥95%), possibly because women received chemotherapy. Had the TMIST investigators used prognostic pathologic stage II or higher to determine enrollment sample size, TMIST would have required a larger sample size than the 165 000 planned enrollment given the prevalence of prognostic pathologic stage II or higher is 18% of our study screening population compared with the TMIST advanced cancer prevalence of 56%.

AJCC prognostic pathology stage II or higher is a clinically meaningful intermediate outcome to evaluate screening programs given it is an accurate predictor of 5-year breast cancer mortality. We suggest AJCC prognostic stage II or higher should be the primary outcome for studies of screening program effectiveness when the primary goal is to assess the ability to reduce breast cancer mortality (3).

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Author contributions: Dr Miglioretti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Kerlikowske, Bissell, Lee, Miglioretti. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Kerlikowske, Bissell, Lee. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Bissell, Miglioretti.

Data Availability

Please see Kerlikowske et al, *J Natl Cancer Inst*. 2020 Nov 10: djaa176. doi: 10.1093/jnci/djaa176, which states: Available after study aims of funded grants are addressed and following approval by the BCSC Steering Committee (http://breastscreening.cancer.gov).

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