van de Water et al. documented that Dutch women 75 years and older with breast cancer who took part in a randomized trial of hormone therapy had a better prognosis than Dutch women with breast cancer who were not enrolled (1). The difference in prognosis between the groups was only partially attenuated when adjustment was made for measured differences in various tumor characteristics (eg, stage, grade), demographic characteristics, and the presence of comorbidity. The authors concluded that the difference in survival “hammers the external validity” of the trial, and that, in elderly women, “breast cancer trial results may not necessarily be extrapolated to the general breast cancer patient.”

Even if the findings in this study were to be true for all trials of treatment of breast cancer in elderly women, I suggest that this is not necessarily a threat to the external validity of such trials. What is relevant for generalizability is not only that the study participants and the general population from which they were drawn differ with regard to one or more characteristics, but that the presence or degree of treatment efficacy or safety differ according to those characteristics. Certainly there are some features of a malignancy that make it more or less susceptible to treatment, and there are some characteristics of patients that make them more or less susceptible to the development of the adverse effects of treatment (2). But, just because women with breast cancer enrolled in a trial have a relatively better prognosis than their counterparts in the population who are not so enrolled does not mean that the latter group would not have the same response to treatment (or lack thereof) that was observed in the trial.

Only by the documentation of the modifying influence of a tumor or personal characteristic on the efficacy or safety of a therapeutic intervention in a trial itself, one large enough to reliably identify such modification, can we obtain a basis for determining if there are patients to whom the overall trial results do not apply.

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References

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