EVALUATION OF SURROGATE ENDPOINTS THROUGH DIRECT AND INDIRECT CAUSAL EFFECTS

Koji Oba[1] and Tosiya Sato[2]

[1] *EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[2] *Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan*

A surrogate endpoint is often used to evaluate the effects of exposure or treatment on the most clinically relevant endpoint, true endpoint, in medical research. For example, a surrogate endpoint is useful for a study of a chronic disease (e.g. coronary heart disease) because the occurrence of the true endpoint may take a long time. Proportion explained (PE), which is meant to indicate the proportion of the treatment effect mediated by the surrogate, is an appealing quantity for the evaluation of surrogacy. However, PE may be invalid in the presence of confounders between surrogate endpoint and true endpoint even in the setting of randomized clinical trials, because the surrogate endpoint is a post-treatment variable. In this paper, we propose the modified PE which is a proportion of the average causal indirect treatment effect explained via surrogate endpoint in the total effect. In this context, we use a natural direct and indirect effect which can be described as the effect of changing treatment while the surrogate endpoint still arises randomly from its conditional distribution given treatment set to the same baseline value throughout. We illustrate the performance of the modified PE and the original PE in a large antihypertensive randomized clinical trial, Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial.