Assessment of Exposure-Response (E-R) and Case-Control (C-C) Analyses in Oncology using Simulation Based Approach

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Objectives: Incremental median survival benefit with increasing drug exposure, as obtained by Kaplan-Meier estimation, suggests that increasing drug exposure could result in additional survival benefit for patients with low drug exposure. However, bias could be introduced due to unbalanced distribution of baseline risk factors affecting clinical response. Two ways have been attempted to correct the bias: multivariate Cox modeling and C-C analysis. This study is to evaluate 1) the performance of multivariate Cox modeling for E-R analysis when drug exposure is confounded with other risk factors and 2) the performance of C-C analysis at the presence of confounding risk factors when multivariate Cox modeling is not sufficient to correct the bias.

Methods: Seven true E-R relationship scenarios were created, with ECOG, tumor size at baseline, and drug exposure set as risk factors driving efficacy. For each scenario, 1000 virtual clinical trials were simulated. For each simulated virtual clinical data, multivariate Cox modeling and C-C analysis were conducted. Their performances were evaluated by comparing to the underlying true models. The 7 true E-R relationship scenarios are illustrated in Table 1.

Results: Multivariate Cox modeling can introduce bias for the estimation of E-R relationship, when the underlying model assumes a non-linear drug exposure effect on the hazard function (scenarios 3, 4, 6 and 7). For all investigated scenarios, C-C comparisons between Q1, Q2, Q3, Q4 and their corresponding matched control groups revealed the true underlying E-R relationships.
Conclusions: When drug exposure effect is non-linear, multivariate Cox modeling can introduce bias for drug exposure effect estimation. Even though the bias of drug exposure effect estimation could be addressed by implementing non-linear fit for the Cox model, this method has not been widely applied [1]. C-C analysis can correctly estimate the exposure-effect relationship under all investigated scenarios.