SESSION 4

Problems and Promise of Surrogate Markers in Tumor Prevention

S8. Problems With Using Biomarkers as End Points

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Investigations employing surrogate cancer end points are especially attractive because they may be smaller, shorter, and cheaper than comparable studies with explicit cancer outcomes. A surrogate end point will be defined here as 'valid' if the effect of an intervention on (or the association of an exposure with) the surrogate is concordant with is effect on (or association with) incident cancer. A broad range of histologic, cellular, and molecular markers could serve as surrogate end points. For many potential surrogate end points – epithelial cell proliferation will be taken as an example – inferences are problematic because of the existence of alternative causal pathways to cancer that bypass the surrogate end point. Furthermore, in such circumstances, a surrogate found to be valid for one intervention or exposure may not be valid for another. Additional complications arise when a single biomarker (a pro-inflammatory cytokine, for example) has distinctly contradictory effects on carcinogenesis. Thus, in evaluating potential surrogates, an understanding of the causal structure underlying the interrelations of exposures, surrogate, and cancer is essential. Three questions can help to shed light on this structure: (1) What is the relation of the surrogate end pont to cancer? (2) What is the relation of the intervention (or exposure) to the surrogate? (3) To what extend does the surrogate end point mediate the relation between intervention (exposure) and cancer? Data pertinent to one or more of these questions may derive from animal experiments, human metabolic studies, observational epidemiologic investigations (including ecologic studies), and randomized trials. Inferences to cancer from such downstream markers as colorectal adenomatous polyps and persistent human papillomavirus infection of the cervix, are strong, through not absolutely unassailable. For these markers, offsetting alternative pathways are unlikely to be of importance. Measurement error is a consideration in evaluating surrogates. Error in surrogate measurement will attenuate associations between intervention (exposure) and the surrogate and between the surrogate and cancer; such error will also lead to an underestimate of the extent to which the surrogate mediates the intervention (exposure)-cancer connection. In summary, surrogate end point markers can be valuable in elucidating underlying biologic processes and can play an important role in Phase 2 studies. For all but the very-close-to-cancer markers, considerable caution is warranted in extrapolating from surrogate effects (associations) to cancer.