S9. Can a Marker be a Surrogate for Development of Cancer and Would We Know it if it Existed?

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Carcinogenesis proceeds through a very long preclinical period, during which time a number of genetic changes in multiple biologic pathways occur. Chemoprevention attempts to arrest or reverse this process, and over a thousand agents demonstrate potential activity. In the hope to make drug evaluation faster and cheaper, extensive effort has been made to identify and validate surrogate endpoint biomarkers (SEBMs). The intellectual framework underlying validation of SEBMs has served well for AIDS and cardiovascular research, but success in cancer has been elusive. Unfortunately, despite much work, to date there are no validated prehistologic biological or molecular intermediate markers for sporadic cancers. As long time proponents of chemoprevention and development of biomarkers, we now question if this framework is applicable given the biological realities of carcinogenesis. Several factors account for difficulties encountered in SEBM development, but the common thread is the complexity of the underlying biology of carcinogenesis. When disease incidence is very low, as for individual cancer sites, the predictive marker or test must have an unattainably high sensitivity and specificity to be of any use. Compared to cancers, cardiovascular disease is very common, and validation of markers has been successful largely because the disease incidence is high. The ability to account for even a majority of cancer risk or drug effect with a single or small group of markers is called into question as activity on alternate pathways degrades the marker sensitivity and specificity. Compared to carcinogenesis, the link between lipid levels and coronary artery disease seems straightforward and reasonably uniform across populations. In contrast, while carcinogenesis is commonly portrayed as a linear progression of disruption from normal tissue to invasive cancer, the reality is considerably more complex. In fact many independent pathways lead to cancer, and many points of disruption along these pathways interact to produce cancer. Thus the emergence of even a small set of highly reliable, universal, predictive or prognostic biomarkers appears unlikely without a drastic shift in our understanding of the underlying biology. Although recent successful chemoprevention trials have proven validity of the concept of chemoprevention, the current strategies to develop SEBMs are flawed, and need to be reassessed in light of the difficulties faced over the last 20 years.