S12. Do Surrogate Marker Results Transform to Clinical Prevention Success?

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Prevention trials are typically large, lengthy, and costly due to the slow process of cancer development and low incidence of cancer during the trial. Instead of using cancer incidence as an endpoint, surrogate endpoint biomarkers (SEBs) are often brought in as intermediate endpoints to increase the efficiency for prevention trials. The goals for prevention trials are (1) to screen out inefficacious agents, (2) to identify promising agents for further development, and (3) to yield a successful prevention strategy to be used in the population. Are SEBs capable of achieving these goals quickly and correctly? Can SEBs be helpful in the development of cancer prevention strategies? When and how can SEBs be best used for identifying cancer prevention agents? What are the triumphs and failures in using SEBs for cancer prevention? What are the roles of SEBs in developing targeted cancer prevention agents? To help answer these questions, we provide a literature review on the effort of using SEBs in cancer prevention. Lessons learned from the past and recommendations for the future development of cancer prevention agents will be given.

Specific examples of the development of SEBs will be reviewed. For example, cellular or molecular markers such as the PCNA or Ki-67 for proliferation, microvascular density for angiogenesis, apoptotic index for apoptosis, and RAR-beta for retinoid response have been proposed for screen cancer preventive activities of putative agents. Although these mechanism based endpoints are appealing for evaluating the efficacy of targeted agents, ample evidence indicates that targeted agents can work through alternative pathways, which render the limited use of these mechanism based SEBs. Carcinogenesis is also a complicated and a multi-faceted process. Looking for any single pathway through a specific cellular or molecular marker is likely to be too restrictive and may result in a false negative conclusion of rejecting promising agents. On the other hand, efficacy found on a single pathway may not be substantiated in terms of broader cancer prevention activities, which could result in false positive conclusions. Examining a narrowly defined single marker could run the risk of "barking up the wrong tree".

The most promising SEBs remain in the category of pre-cancer lesions including the intra-epithelial neoplasm (IEN). For example, colorectal polyp is considered as an endpoint to evaluate the efficacy of COX-2 inhibitors in patients with familial adenomatous polyposis – a nearly 100% risk of colon cancer. IENs are tightly coupling with cancer development and are often considered precursors of cancer. For example, cervical intraepithelial neoplasia (CIN) for cervical cancer, prostate intraepithelial neoplasia (PIN) for prostate cancer, aneuploid leukoplakia for oral cancer, and ductal carcinoma in situ (DCIS) for breast cancer. Advanced IENs are typically presented with advanced histology such as moderate to severe dysplasia or carcinoma-in-situ. They are in the direct causal pathway of cancer, hence, more relevant to be used as SEBs for cancer. SEBs can be particularly useful for phase II activity screening trials. They can also be used to fine-tune the optimal dose/schedule for the agent to maximize the benefit (efficacy) while reducing the risk (toxicity). The ultimate value of prevention agents, however, will need to be validated in phase III trials using cancer as endpoints.

To date, there are only a handful of agents approved by the US FDA to treat IENs and only one (tamoxifen) for reducing cancer risk. Recent efforts of applying karyometry for measuring the progression of IEN and using HPV infection as the SEBs for cervical cancer are encouraging. Several prevention trials, spun from the SEBs results but using cancer as the primary endpoints, are ongoing. The final verdict of using SEBs as successful tools for clinical cancer prevention is not in. However, with the increasing knowledge of biology, mechanism of drug effect, and omics, the prospect of using SEBs in cancer prevention trials is bright and promising.

To conclude, our answer to the posed challenge of using SEBs for developing successful clinical prevention strategies is "Cautiously Optimistic!"