S11. How Should We Try to Move the Field of Chemoprevention Agent Development Forward in a Manner that is More Productive?

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A number of global changes are needed to move the field of cancer prevention forward. In the least, these include recognition and acceptance that: (1) No validated surrogate endpoints have been identified thus far for any human cancer. In referring to one's favorite marker, the term "surrogate" should be dropped and the less definitive term "biomarker" should be used; (2) Association between a biomarker and the risk of a cancer does not guarantee that drug-induced changes in that biomarker will produce a corresponding change in the true malignant endpoint. This is true for all types of preneoplastic biomarkers, whether they be molecular, biochemical, histologic or clinical (e.g., intraepithelial neoplasia (IEN)); (3) The greater the personal interest and time investment by an investigator to a biomarker, the more likely it is that belief will override proof. The standard of evidence for accepting "surrogacy" for a biomarker needs to be high and probably requires that a change in risk for the true endpoint occurs; (4) Changes in biomarkers should be used to guide drug development rather than substituting as surrogates for the true endpoint per se; (5) Development of more and convincing preclinical data in animal models that a biomarker and its modulation predict the true endpoint is necessary, since surprisingly little data exists at the current time. These cautions, however, belie the fact that drugs have already been approved for the treatment of IENs including actinic keratoses, adenomatous polys in FAP patients, and preneoplastic lesions of bladder cancer. Development of data further characterizing the biologic properties of IEN (or any biomarker) may lead to a prognostic subset of lesions in which modulation of key parameters could be used as acceptable evidence of efficacy. Alternatively, one could accept a lesser standard of evidence, as has already been done in several cases. We are in the process of developing guidelines for advancing drugs from preclinical testing to phase I, II, and III trials, with a major emphasis on the key phase II to III transition. This process involves assigning scores to various levels of evidence, such as consistency of preclinical evidence, observational data, secondary analysis of cancer endpoints in unrelated randomized trials, biomarker modulation in phase II settings, and toxicity. Using weighted criteria and an iterative process, numeric thresholds are proposed to guide whether a drug should be moved to the next phase of development or whether additional data needs to be developed before that decision should be made. The field of chemoprevention is at a critical juncture. Despite enormous amounts of basic laboratory data and epidemiologic observations suggesting that the approach should work, translation of the data to clinical benefit has not occurred, with most drugs turning out to be ineffective or too toxic for the prevention setting. We need to reexamine our basic premises and to reconsider our logic in the chemoprevention and biomarker development process.