INTRODUCTION

Carcinogenesis is generally recognized as a disease that progresses through several stages beginning with mutation of genomic DNA (initiation) followed by growth acceleration and further genetic damage (promotion) and, finally, development of malignant tumors (progression) [1]. With the latency period between stages ranging from years to decades, the science of cancer chemoprevention seeks to intervene using relatively nontoxic agents to prevent, delay or reverse one or more stages of carcinogenesis [2]. Intermediate biomarkers of cancer encompass the phenotypic, genotypic and molecular changes that characterize the multistage nature of carcinogenesis; their measurement is necessary for evaluating potential chemopreventive agents, elucidating mechanisms of action, selecting clinical trial cohorts and acting as surrogate endpoints for cancer incidence in human clinical trials. While the development of cancer biomarkers has advanced considerably in the past 25 years, researchers have yet to fully unravel the complex molecular, cellular, tissue, and epidemiological interactions that ultimately define the nature of carcinogenesis. Furthermore, indirect monitoring of carcinogenesis intervention is challenged by the proper identification, quantification, and validation of biomarkers, as well as establishment of relevance to clinical disease.

We currently present an overview of intermediate biomarkers that have proven useful in cancer chemoprevention strategies. However, continuous progress in cancer research along with recent advances in genomics and proteomics certainly assures some gaps in our knowledge of carcinogenesis will close. As a result, it is anticipated that new and perhaps more relevant biomarkers will be discovered in the near future.
INTERMEDIATE BIOMARKERS AS SURROGATE ENDPOINTS FOR CANCER INCIDENCE

The use of intermediate biomarkers as surrogate endpoints to cancer incidence in chemoprevention clinical trials is paramount to the successful integration of cancer chemoprevention into mainstream science. Currently, phase III chemoprevention trials depend on cancer incidence as the study endpoint for determining efficacy. As compared to traditional phase III trials, this leads to extremely expensive studies due to large numbers of subjects as well as longer follow-up periods [3]. The use of phenotypic and genotypic biomarkers as surrogate endpoints, however, holds promise that chemopreventive efficacy could be established within a period of three years with only a few hundred subjects [4].

Some criteria and issues surrounding intermediate biomarkers as surrogate endpoints for cancer chemoprevention have been reviewed by Kelloff et al. [4]. The NCI chemoprevention program has given priority to histological modulation of precancer (intraepithelial neoplasia; IEN) as well as specific and general genotypic changes corresponding to the carcinogenesis model for a targeted cancer type. To be useful, such endpoints must be determined easily with acceptable sensitivity, specificity and accuracy. The endpoint must also conform with the expected progression model for the specific cancer type and correlate with cancer incidence [4,5]. Validation of endpoint biomarkers is essential and would benefit by correlation with transgenic animal models which mimic the human neoplastic process, especially in determining mechanisms of action, dose selection, toxicity, pharmacodynamics, and long-term exposure risks with potential chemopreventive agents.

Prostate

Prostate cancer is the most common cancer in US males and is projected to account for 29% (180,400) of new cases of cancer and 11% (31,900) of cancer deaths in US men for the year 2000 [6]. Prostate cancer may develop over 20 years, as evidenced by prostatic intraepithelial neoplasia (PIN), and require an additional 10-30 years for progression to clinically significant carcinomas [7]. The slow growth of this disease is exemplified by a study of Yatani and colleagues who showed the prevalence of carcinoma in 20.6, 28.8, and 36.9 cases per 100,000 Japanese, German and African-Americans respectively, while the corresponding incidence of clinical cancer was 2.7, 21.1, and 67.1 per 100,000 [8]. Data also suggest that exogenous factors are significant contributors to disease as the rates of disease are nearly identical for US Caucasians and second-generation Japanese emigrees.

The primary biomarker for prostate cancer has been serum prostate specific antigen (PSA) levels, although it is not specific for neoplasia and it is