Foreword

Cancer is the second leading cause of death in the United States, accounting for 22.4% of all deaths based on 1992 statistics. Cancer deaths in general are increasing in the industrialized world at rates that cannot be explained by population demographics alone [1].

Many laboratory studies and most epidemiological data suggest that approximately three-fourths of all cancer deaths are attributable to so-called lifestyle factors (diet, tobacco, and alcohol use) and occupational exposures. The existence of major lifestyle determinants represents the potential for intervention and prevention of many cancers, including cancers of the breast. Breast cancer is a major affliction of women in affluent, Western industrialized nations. In the United States, breast cancer is the highest incidence cancer in both black and white women, and will result in an estimated 46,300 deaths this year.

Cancer chemoprevention is the intervention with chemical agents (drugs) that either abolish or delay the development of those processes which begin with normal-appearing tissues and progress to metastasis. Testing candidate chemopreventive drugs differs substantially from testing chemotherapeutic drugs. Efficacy testing (Phase II) of chemotherapeutic drugs involves cancer patients and uses reduction in disease and/or improved mortality as study endpoints. Chemopreventive agents, on the other hand, are tested on basically healthy individuals who may or may not be at increased risk for cancer, and uses the reduction of cancer incidence as the endpoint. Since an individual cancer may develop over decades, clinical trials are large, long and, as a result, expensive [2,3].

Surrogate endpoints, particularly intermediate biomarkers, may help circumvent the length and expense involved in chemoprevention clinical trials. Intermediate biomarkers are defined as morphological and/or molecular alterations in epithelial tissues associated with the early phases of carcinogenesis and are classified as histological, genetic, proliferation-related, and differentiation-related. Experimental studies on the development of intermediate biomarkers and their modulation by putative chemopreventive agents focuses on the reliability and predictive value of the individual markers as measured by such factors as specificity, sensitivity, and overall correlation with cancer endpoints. One of the benefits of intermediate biomarkers in chemoprevention clinical trials is the reduced time since the study endpoints are correlated with earlier stages in the carcinogenesis process. Efficacy trials will also require smaller study populations. As a direct result of these two considerations, chemoprevention trials should be lower in cost than other clinical trials. Finally, the results of efficacy trials for the modulation of biomarkers may serve as the rationale for performing further clinical trials with cancer incidence as the endpoint.

This special supplement to the *Journal of Cellular Biochemistry* is the fifth in a series to be published representing manuscripts from conferences sponsored by the National Cancer Institute (NCI). The purpose of these conferences is to bring together basic and clinical research scientists to design clinical trial strategies. The concept of intermediate endpoint biomarkers as surrogate trial endpoints was introduced in Supplement 16G, with the colon as the representative organ. Supplement 16H addressed chemoprevention of prostate cancer, the site of the highest incidence and the second highest cause of cancer deaths in US males. The design of chemoprevention trials for the prostate presents the additional problems of competing mortality in older study populations and the lack of dependable methods for detecting microscopic cancers. For this reason, the concept of biomarkers was expanded to include markers of progression. Supplement 16I addressed the chemoprevention of bladder cancer. Ten percent of the cancer deaths in the United States are attributable to cancers of the urinary tract; over 50,000 new cases of bladder cancer were diagnosed in 1992 [1]. Trials designed for chemoprevention of bladder cancers involve all the considerations enumerated previously as well as strong components of lifestyle factors (smoking in particular) and occupational exposures. The fourth supplement, 17F, dealt with the chemoprevention of upper aerodigestive tract cancers, as well as the design of Phase II clinical trials.

This supplement addresses the chemoprevention of breast cancer, the site of an estimated 183,000 new cases of cancer in 1993. The workshop addressed (1) the identification, detection and characterization of intermediate biomarkers, (2) candidate chemopreventive drugs, and (3) strategies for the design of Phase II clinical trials using surrogate endpoints.

REFERENCES

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