Progress in
Cancer Research and Therapy
Volume 3

Genetics of Human Cancer

Edited by

John J. Mulvihill, Robert W. Miller,
and
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National Cancer Institute
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER PROGRAM

THE NATIONAL FOUNDATION
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Foreword

The study of cancer genetics has come of age. At a time when major programs are underway to determine the environmental causes of cancer, it is important to review the genetic factors that interact with the environment to produce cancer.

Genetics is the study of inherent variability among living things. In human cancer, the science of genetics concerns differences in susceptibility and resistance to cancer, the reasons for this heterogeneity among humans, and the application of this knowledge toward cancer control.

Although an increasing number of known and potential environmental carcinogens have been identified, scientists still are unable to explain many of the differences in cancer occurrence among people: why some heavy smokers apparently are resistant to the development of lung cancer; why cancer occurs more often in some families than in others; or why some vinyl chloride workers develop angiosarcomas, but others do not.

As scientific and public interest begins to shift from a strictly environmental focus on the causes of cancer to the interactions between the individual and his surroundings, it is appropriate that the National Cancer Institute and the National Foundation–March of Dimes highlight the wide scope of information on genetics resulting from the varied interests and special perspectives of prominent experts in medical genetics, molecular biology, cellular genetics, and epidemiology.

In two cancer-related diseases, xeroderma pigmentosum and ataxia telangiectasia, specific defects in DNA repair were identified by applying laboratory tools developed in microbial systems to the study of rare patients in whom clinicians had noted an unusual sensitivity to environmental agents. The advent of new technology from molecular biology and biochemistry, combined with additional clinical and epidemiologic study of persons at high risk of cancer, may help scientists extend their knowledge of other genetic–environmental interactions and clarify fundamental mechanisms of carcinogenesis.

Frank J. Rauscher, Jr., Ph.D.
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Preface

The major purpose of this volume is to summarize and evaluate the recent dramatic advances that have occurred in basic and medical genetics as they relate to oncology. The developments described in this volume should stimulate greater cooperation between geneticists and oncologists. Indeed, the recent establishment of 17 research centers for cancer and 10 for genetics in the United States provides vast resources for expanding collaboration.

The recent development of banding techniques and the visualization of sister chromatid exchanges (i.e., the interchange of identical genetic material between duplicated sections of chromosomes) opened an epoch in cytogenetics. These procedures show great potential in revealing the pathobiology of cancer development in man.

Mendelian genetics has contributed new insights into the fundamental mechanisms of carcinogenesis through investigations of patients with rare single gene traits predisposing to neoplasia. Typical are studies of cancer associated with various birth defects and immunologic deficiencies; chromosomal fragility, as in the Fanconi and Bloom syndromes; a possible excess of cancer among heterozygous carriers of genes which, in the homozygous state, predispose to malignancy; defects of DNA repair in xeroderma pigmentosum and ataxia telangiectasia; and the common embryologic origins of seemingly diverse disorders, such as neurofibromatosis, neuroblastoma, multiple endocrine adenomatosis, and perhaps small cell carcinoma of the lung. Also, the products of some genes associated with malignancies, such as *ABO, HLA,* and aryl hydrocarbon hydroxylase inducibility, may help identify persons at high risk of cancer for prevention, screening, early detection, and further research.

With regard to polygenic or multifactorial inheritance in human cancer (i.e., the interaction of many genes and environmental agents with no single factor playing a dominant role), empiric risk data have detected relatives markedly predisposed to cancer, and an interdisciplinary approach to "cancer families" has revealed subclinical laboratory manifestations of susceptibility.

Population genetics and epidemiology have provided etiologic clues from studies of special populations, such as inbred groups and twins, and of international and ethnic variations in cancer.

Laboratory geneticists have turned their tools to the cancer problem by hybridizing cells among species, hybridizing nucleic acid from viruses and human tumors and observing cells *in vitro* from persons prone to cancer.

These observations on patients, populations, cells, and DNA have been melded into theories and hypotheses of carcinogenesis to be tested by further investigations;

examples include the proposed mechanisms of double mutation or premutation to account for dissimilarities in familial and nonfamilial forms of cancer.

These proceedings are based on a conference cosponsored by the Epidemiology Branch of the National Cancer Institute and the National Foundation–March of Dimes.

The attendance of official delegations from collaborative efforts of the U.S.–Japan Cooperative Cancer Research Program (Analytical Epidemiology Committee) and the U.S.–U.S.S.R. Joint Working Group on Mammalian Somatic Cell Genetics Related to Neoplasia indicated the broad international appeal of this topic.

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Ethnic Differences in Cancer Occurrence: Genetic and Environmental Influences with Particular Reference to Neuroblastoma

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There are marked geographic differences in cancer rates (21), even within the United States (36). Much of the variation is believed to be environmentally induced. There are, however, important differences which appear to be genetically influenced. The marked excesses or deficiencies of certain tumors in an ethnic group may fall in this category. In seeking ethnic differences in cancer occurrence it is important, as always in etiologic studies, to purify the diagnoses as fully as possible. Otherwise, key clues to etiology may be overlooked, as when registry or death certificate data are coded routinely according to anatomic site, and not by histologic type.

BLACKS

Ewing's Tumor

When all forms of bone cancer are grouped together, important ethnic differences in occurrence are obliterated. Thus, Higginson and Muir (21) found virtually no difference in the incidence of bone cancer in the U.S. population including all races as compared with U.S. blacks alone.

In 1965 we acquired death certificates for all children in the United States under 15 years of age who had died of cancer since 1960. We recoded the diagnoses according to histology, and were surprised to learn that Ewing's tumor is virtually absent in blacks (Fig. 1) (14,17,43). The finding was confirmed by data from other sources (32), including the histologically sophisticated Armed Forces Institute of Pathology (24). The rates for osteosarcoma exhibited no such difference between whites and blacks.