PERSONS AT HIGH RISK OF CANCER
An Approach to Cancer Etiology and Control

PROCEEDINGS OF A CONFERENCE
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PREFACE

There is increasing recognition that the identification of high-risk groups provides a key to the ultimate reduction of cancer incidence and mortality through opportunities for surveillance, early detection and treatment, etiologic research and preventive measures. This volume is based on a conference convened by the National Cancer Institute and the American Cancer Society and held in Key Biscayne, Florida, December 10-12, 1974. The purpose of the conference was to define the present state of knowledge of risk factors in cancer and to explore ways of applying this information for the protection and further identification of high-risk groups.

We have tried to present in 32 chapters a comprehensive view of cancer risk factors. Following the format of the conference, the book is divided into six parts. The first two parts represent a survey of antecedent host and environmental factors that are known or suspected to increase a person's risk of developing cancer. Consideration is given both to causal factors and to precancerous or precursor manifestations. The third part covers demographic features of cancer (e.g., age, sex, race, locale) that influence the distribution of risk factors, and facilitate their identification and modification by control programs. The utility of high-risk groups for surveillance and preventive measures is illustrated in the fourth part, while strategies to enlarge and sharpen our knowledge of risk factors are presented in the fifth. The final part consists of reports from two groups meeting during the conference to identify special opportunities for work in the areas of cancer etiology and control.

Contributions to the delineation of high-risk groups may come from the clinic, the laboratory, or field studies. To promote interchange at the conference, 90 participants were invited from various fields, including epidemiology, genetics, environmental and occupational health, chemical and viral carcinogenesis, immunology, and clinical oncology. The interaction among disciplines is reflected in many reports and discussion summaries concerned with cancer etiology. Although high-risk groups presently account for only a small portion of many cancers, they point the way to further research to elucidate risk factors of a fundamental nature that lie under the surface. Recent developments suggest that etiologic advances will depend heavily on laboratory studies to develop subclinical measures of risk and on increased collaboration between epidemiologists and experimentalists. Furthermore, the multifactorial nature of some high-risk groups will require sophisticated methods to identify interactions between environmental exposures or between environmental and host factors. At present,

epidemiologic studies of high-risk groups are often high-risk ventures: slow, complicated, tedious, expensive. More rapid progress will require not only greater training and research support of epidemiologists, but special efforts to strengthen the resources and freshen the tactics of cancer epidemiology.

Throughout the book attention is given to the potential and the limitations of high-risk groups in intervention programs to reduce morbidity and mortality from cancer. Before a major impact can be made on clinical and public health practice, it is clear that advances will be needed in risk identification. More effective criteria of risk are also needed; whereas the commonly used "relative risk" (ratio of cancer rates with and without the antecedent risk factor) is the key measure in etiologically oriented studies, the infrequently used "absolute or attributable risk" (percentage of the total cancer rate attributed to a risk factor) is more relevant to the feasibility of control projects. However, the two approaches should be closely linked. In particular, as we learn more about cancer risk factors through etiologic research, it will be possible to expand control programs and direct them with precision to segments of the population that are most likely to benefit.

Joseph F. Fraumeni, Jr.

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INTRODUCTION

Certain people are at high risk for cancer because of their genes. Since other reviews of genetic factors in human cancer are available [1-5], this chapter summarizes recent developments, with emphasis on the importance of genetics to clinical oncology and to the biology and prevention of cancer.

Genetic factors may be considered in three groups:

1) *Chromosomal,* with genetic imbalance because entire lengths of genetic material are absent or present in excess.
2) *Single-gene* locus, with disease arising from mutation either in one allele as in a dominant trait, or in paired alleles as in a recessive trait.
3) *Polygenic,* implying that many genes interact, perhaps with environmental factors, to cause disease, with no one factor or gene playing a major role. (This group is considered in Chapter 2 of this volume [6].)

CHROMOSOMAL DISORDERS IN CANCER

> Asymmetrical mitosis could be chiefly considered for the origins of tumors. . . . My theory is able to explain above all the defective histologic form and the altered biochemical behavior of tumor cells. Are there any means of reaching a trustworthy decision as to the worthiness of the views presented here? The most obvious would be to devote renewed attention to the counting of chromosomes, if possible with better techniques [7].

The author thanks Ms. S. Trimble and Dr. J.F. Fraumeni, Jr., for library and bibliographic support; Miss W. Wade and Mrs. J. Pearson for editorial and secretarial work; and Dr. J. Whang-Peng for helpful criticism of an early draft. Literature review ended December 1974.

For 60 years Boveri's hypothesis that malignancy was caused by chromosomal imbalance has awaited proof through better techniques for studying chromosomes. A quantum advance came with Caspersson's technique of labeling chromosomes with fluorescent compounds [8]. Until then, the 46 human chromosomes were classified solely by overall size and shape, with little to distinguish one from the other in the same group. At least four standard techniques for staining permit identification of each chromosome, and even parts of chromosomes, by the pattern of differential staining called banding [9]. Karyotypes with banding led to new insights into clinical conditions which were known to be associated with chromosomal anomalies but were poorly understood because of the limitations of techniques. Also, minute but consistent errors, not previously demonstrable, were reported.

Numerous reviews of cancer cytogenetics are available [10-15], but all antedate wide use of banding techniques. The following account deals first with recent findings in the cytogenetics of certain neoplasms, especially leukemia, then summarizes their meaning to cancer etiology; and finally, highlights advances in the interrelationship of chromosomes, cancer, and congenital defects.

The Leukemias

Chronic Myelocytic Leukemia (CML)

Most patients with CML have a small marker chromosome in the leukemic cells. When first discovered [16], this marker was correctly considered a G group chromosome that had lost part of its long arms. Specifically, it was thought likely to be chromosome 21, the same one that was trisomic in individuals with Down's syndrome. New techniques showed that the Philadelphia chromosome (Ph^1), as the marker in CML became known, was *not* the same one found in triplicate in Down's syndrome, but rather chromosome 22 [17]. Furthermore, often Ph^1 was not just a loss of the long arms of chromosome 22 but actually a translocation of this segment to the long arms of chromosome 9 [18, 19]. The possibility arises, to be resolved by further technical refinements, that minute parts of chromosome 9 or 22 are lost in translocation. In fact, if chromosomal loss is the basis of CML, then the deletion probably involves the long arms of chromosome 22, since translocation to 9 is not invariable; sometimes it is translocated to other chromosomes [20], sometimes just the long-arm deletion is seen [21].

Seventy to ninety percent of patients with CML have Ph^1 [22-24]; those without it have a different natural history and response to treatment, and perhaps etiology. Lately, a third group of about 30 CML patients have emerged [24, 25]. All are men who are older, survive longer, and have Ph^1; in addition, the Y chromosome is lost from the leukemic cell line. Since the Y chromosome