# ADVANCES IN CANCER RESEARCH

VOLUME 23

# ADVANCES IN CANCER RESEARCH

*Edited by*

GEORGE KLEIN

Department of Tumor Biology
Karolinska Institutet
Stockholm, Sweden

SIDNEY WEINHOUSE

Fels Research Institute
Temple University Medical School
Philadelphia, Pennsylvania

*Consulting Editor*

ALEXANDER HADDOW

Chester Beatty Research Institute
Institute of Cancer Research
Royal Cancer Hospital
London, England



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## CONTRIBUTORS TO VOLUME 23

Numbers in parentheses indicate the pages on which the authors' contributions begin.

JOSEPH ALROY,* *Department of Pathology, Tufts University School of Medicine, Boston, Massachusetts* (23)

W. A. ANDIMAN, *Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut* (171)

A. FRANK, *Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut* (171)

HAROLD S. GINSBERG, *Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York* (91)

W. E. HESTON, *Laboratory of Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland* (1)

MIROSLAV HILL, *Department of Cellular and Molecular Biology and Equipe de Recherche No. 148 du C.N.R.S., Institute of Cancerology and Immunogenetics, Villejuif, France* (237)

JANA HILLOVA, *Department of Cellular and Molecular Biology and Equipe de Recherche No. 148 du C.N.R.S., Institute of Cancerology and Immunogenetics, Villejuif, France* (237)

FREDERICK B. MERK, *Department of Pathology, Tufts University School of Medicine, Boston, Massachusetts* (23)

G. MILLER, *Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut* (171)

MINAKO NAGAO, *National Cancer Center Research Institute, Chuo-ku, and Institute of Medical Science, University of Tokyo, Minato-ku, Tokyo, Japan* (131)

RICHMOND T. PREHN, *The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, Pennsylvania* (203)

* Present address: Rush Medical College and Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

TAKASHI SUGIMURA, *National Cancer Center Research Institute, Chuo-ku, and Institute of Medical Science, University of Tokyo, Minato-ku, Tokyo, Japan* (131)

RONALD S. WEINSTEIN,* *Department of Pathology, Tufts University School of Medicine, Boston, Massachusetts* (23)

C. S. H. YOUNG, *Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York* (91)

* Present address: Rush Medical College and Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

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# THE GENETIC ASPECTS OF HUMAN CANCER

W. E. Heston

Laboratory of Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland



## I. Introduction

This chapter is concerned with the genetic transmission of factors influencing the occurrence of cancer in man. It is not a complete review of the subject. Such a review would require a large volume with half a volume of references. Cancers that have received greater emphasis in this area of investigation are discussed, and an assessment is made of the kinds of evidence in support of genetic influences. Selected references are given.

An effort was made not to slight early investigations as is often done in reviews today. There was a peak of emphasis on the genetics of human cancer during the 1940s and early 1950s, stimulated in large part in the United States by a very informal Conference on Parental Influence in Relation to the Incidence of Human Cancer conceived and organized by Dr. C. C. Little and held as a part of the Fifteenth Anniversary Celebration of the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine, in 1944. It was concluded at this conference that evidence at that time on parental factors influencing occurrence of cancer in experimental animals, particularly mice, together with information already known regarding genetic influences in respect to cancer in man, made it imperative that geneticists extend their knowledge on the genetic influences in cancer in man, and place such knowledge in proper balance

with the increase in information on the chemical and physical agents and other nongenetic factors.

Several large studies were initiated soon thereafter. One on breast cancer was developed by Dr. Madge T. Macklin at Ohio State University. Another also on breast cancer was developed by Dr. C. P. Oliver at the Dight Institute of the University of Minnesota. Dr. Oliver later transferred to the University of Texas, where he developed a program in the same area; the Dight Institute program was carried on principally by Dr. Elving Anderson. At the same time a very significant program, principally on the genetics of gastrointestinal cancer, was being developed at the University of Utah by Drs. F. E. Stephens, Eldon J. Gardner, and Charles M. Woolf. This group had the advantages of access to the large polygamous families of the Mormons and the extensive family records in the Church's Genealogical Library in Salt Lake City.

Another program deserving special mention was the one in Denmark involving the University Institute of Human Genetics under the direction of Dr. Tage Kemp, the Danish Cancer Registry under the direction of Dr. Johannes Clemmenson, and the University Institute of Pathologic Anatomy directed by Dr. Julius Engelbreth-Holm. Extensive studies on genetics of leukemia and of breast cancer were carried out there. Productive programs were carried out elsewhere by other investigators, one of whom was Dr. R. P. Martynova in U.S.S.R. She deserves special mention not only because of the early work she did on the genetics of breast cancer in women, but also for her signal role in keeping the genetics of cancer alive in the U.S.S.R. during the Lysenko era.

These programs, which utilized for the most part comparison of incidence of cancer in relatives of cancer probands with that in relatives of control probands, established that genetic factors were involved in many kinds of cancer in man and could be demonstrated provided enough data were collected. The studies also defined some of the limitations of this approach. These studies are reviewed because of their own merit and so that today we may distinguish between new discoveries and extension or confirmation of observations made at that time.

The concept of human cancer as a somatic mutation disease does not receive special emphasis here, but not because somatic mutation is not involved. It surely is, as some form of change in the genetic material of the cell, but the subject has recently been covered thoroughly by Knudson (1975). Furthermore, no attempt has been made to give a complete review of cytogenetics and cancer. This subject has been covered thoroughly in a recent volume edited by German (1974).

Some attempt is made to forecast what future investigations might

reveal from what is being discovered in experimental animals. Of principal interest here is that many kinds of cancer in experimental animals are now known to be induced by viruses, and that many of these viruses are endogenous. These are of particular concern to the geneticist because of evidence that they are transmitted vertically as a part of the host genome, much as genes are transmitted. If viruses are involved in the induction of cancer in man, and they most surely will be shown to be involved, the geneticist must take a very active role in their discovery.

## II. Cancer of the Breast

Studies to date indicate an inherited influence in the etiology of breast cancer that is especially prominent in the case of premenopausal cancer.

From a large proband study of cancer in Holland, Wassink (1935) observed that when the proband had cancer of the breast there was a significant increase of cancer among female relatives owing to an increase in the homologous form of cancer. This was followed by Martynova's (1937) rather extensive study in the U.S.S.R. From her data on 201 breast cancer family histories, she concluded that hereditary factors play a definite role in predisposition to cancer of the breast in women. She also concluded that predisposition to cancer of the breast is in some way connected with predisposition to cancer in general.

Jacobsen (1946), working at the University Institute of Human Genetics in Copenhagen and in collaboration with the Danish Cancer Registry, compared relatives of 200 breast cancer probands with like relatives of 200 controls and found what he termed an indubitable excess incidence of breast cancer among the female relatives of the breast cancer probands with exception of grandmothers. He interpreted these results as indicating that the hereditary predisposition was a major factor in the development of breast cancer.

It was noted that the curve of the age distribution at the first manifestation of the disease in the 200 breast cancer probands had two peaks, at ages 45–49 and 60–64. It was further observed that probands with stronger evidence of hereditary influence were in the early age group. This is comparable with the difference between pre- and postmenopausal breast cancer described recently by Anderson (1972).

In 1955, Woolf reported on his study of breast cancer in the Utah population. He selected 216 patients who had died from breast cancer as probands and collected cancer data on their relatives. The number of deaths from cancer in these relatives was compared with an expected number based on proportionate mortality rates from the general popula-

tion. Also, by the sequential analysis method he compared the frequency of cancer in the families of the breast cancer probands with the frequency in a control sample. In addition to data on mothers and sisters of the probands, he also collected data on fathers and brothers since he was interested in whether his data would confirm Martynova and others who considered that susceptibility to cancer of the breast was only one manifestation of susceptibility to cancer in general or confirm Penrose *et al.* (1948) and others who considered the predisposition to be organ specific.

Female relatives of the breast cancer probands had a higher incidence of cancer of the breast than the female relatives of the control probands and higher than expected from the general population, confirming that there was an inherited predisposition. The fact, however, that the frequency of other types of cancer in all four groups of relatives was no greater than in the control sample indicated that the inherited predisposition was organ specific.

Later studies of Penrose *et al.* (1948), Anderson *et al.* (1958), Oliver (1959), and Macklin (1959) have been published with similar conclusions. Since Macklin's study was probably the most comprehensive, it will be discussed here. She collected complete data on mothers, grandmothers, aunts, and sisters of three groups of probands: (1) women with diagnosed breast cancer, (2) women with some cancer other than of the breast, and (3) women who had had no known cancer. Breast cancer occurred 2 or 3 times as frequently among relatives of the breast cancer probands as would have been expected from mortality rates or proportionate death rates. Among relatives of the probands with some other cancer, breast cancer occurred even slightly less frequently than expected, especially on mortality rates, thus failing to support any possible genetic relationship between breast cancer and other types. There was no difference between the frequency of breast cancer among relatives of the probands with no cancer and what would have been expected on mortality rates or proportionate death rates. From these data, Macklin concluded that there was some factor or factors that caused the relatives of breast cancer patients to have significantly more breast cancer than would have been expected if they had experienced the same risk as the population with which they were compared. She pointed out that these factors might be in the environment or the genes or both.

Macklin compared paternal aunts of the breast cancer probands with their maternal aunts and found no difference in frequency of breast cancer. She suggested that this would tend to rule out environmental factors and indicates the action of genetic factors, since it would be

unusual to find the same environmental factors influencing the fathers' mothers and sisters in the same way they influenced the mothers' mothers and sisters.

Comparison of paternal and maternal grandmothers of the breast cancer probands was of particular importance in view of the maternally transmitted mammary tumor virus (MTV) of the mouse. If there were a milk-transmitted breast cancer virus in women as in mice, one could expect a higher frequency of breast cancer in the maternal grandmothers than in the paternal grandmothers. From the fact that there was no difference between the two groups of grandmothers, she concluded that, if there is a milk-borne virus for breast cancer in women, it must be ubiquitous and some other agent is the deciding factor.

These are very significant observations in relation to our present knowledge of transmission of mammary tumors in mice (for review, see Heston, 1973). While Macklin did not rule out the possibility of a breast cancer virus transmitted from parents to offspring, if such a virus exists in women the best experimental model is probably not the strain C3H model, where the virus (MTV) is primarily transmitted through the milk. The best model may be the strain C3HfB model where the virus, in this case nodule-inducing virus (NIV), is transmitted through the male as readily as through the female and is not transmitted through the milk; or the strain GR model, where the virus is transmitted through the male as readily as through the female but can also be transmitted through the milk.

Present efforts are directed toward trying to find a virus in the milk of women, but this seems to be primarily because the milk is a convenient place to look for it. It must be pointed out that some suggestive, although far from conclusive, evidence for the presence of virus has been found. However, if any breast cancer virus in women is like NIV, it would not be expected to be in the milk, at least in detectable amounts.

There is considerable evidence that the mammary cancer virus in mice is transmitted as a provirus, i.e., that the viral information is integrated in the genome of the mouse. It may prove even to be transmitted as a dominant gene (Bentvelzen, 1972). Information thus far from studies of human breast cancer would suggest that if there is a breast cancer virus, it too is probably transmitted genetically and thus the virologists are going to need the assistance of geneticists in discovering it. Again one is reminded that geneticists made the original discovery in respect to the MTV in mice (Jackson Laboratory Staff, 1933; Korteweg, 1934).

In relation to some of the earlier observations of Jacobsen (1946) referred to above, Anderson (1972) separated his breast cancer probands

into premenopausal and postmenopausal cases. Breast cancer was increased about 3-fold in the relatives of the premenopausal group, but was not increased in the relatives of the postmenopausal group. He also noted a 5-fold increase in relatives of bilateral breast cancer patients; and in relatives of patients with both premenopausal and bilateral cancer the rate was increased 9-fold. He concluded that genetic factors must play a more important role in patients with early onset of multiple disease than in patients with late onset of a single tumor. The same situation could be expected if a vertically transmitted virus were a factor in inducing breast cancer. Anderson's observations are in line with those made in the mouse, where a strong genetic component or a strong viral factor, or both, results in early mammary tumors, the females often having multiple mammary tumors. It is thus in these patients with premenopausal and bilateral cancers that one would expect to have the greatest chance of demonstrating any breast cancer virus.

The possibility of a genetic relationship between breast cancer and other forms of cancer suggested by the early works of Martynova (1937) and others is finding support in certain family studies reported recently. Li and Fraumeni (1969) described four families showing a concordance of soft tissue sarcomas, leukemia, breast cancer, and an apparent excess of multiple primary malignant neoplasms. Later Lynch *et al.* (1973c) reported a study of 34 families in which two or more first- or second-degree relatives had breast cancer. Of these 34 families, 11 had first- or second-degree relatives with associated soft tissue sarcomas, leukemia, or brain tumors, or combinations of these malignant neoplasms. In another study of 22 families, Lynch *et al.* (1973b) observed an association of gastrointestinal and breast cancer. Through three generations of two families reported by Lynch *et al.* (1974), there was an apparent association between breast and ovarian cancer.

One might expect the association between breast and ovarian cancer to be caused by hormonal factors. The administration of estrogen results in neoplasms in several organs of the endocrine and reproductive systems in mice. Woolley *et al.* (1952) induced adrenal, pituitary, and mammary gland neoplasms in certain hybrid mice by the hormonal imbalance resulting from early castration. In the absence of administered hormonal factors, one might expect such endocrine influences to be basically genetic.

Such associations of different forms of cancer presumably also could result from viral or genetic factors. A vertically transmitted virus with the oncogenic capacity of the polyoma virus (Stewart *et al.*, 1958) could result in such combinations. On the other hand, a single gene, like the $A^y$ or $A^{vy}$ genes of the mouse that increase the occurrence of hepa-

tomas, mammary tumors, pulmonary tumors, and leukemias (Heston and Vlahakis, 1968), if present in human beings could also result in such associations.

## III. Leukemia

### A. Studies on Inheritance

One of the most extensive proband studies on the genetics of leukemia was carried out in Denmark by Videbaek (1947). Data were collected on 209 leukemia probands and their 4041 relatives and on 200 sound control probands and their 3641 relatives with good agreement between the age distribution of the two groups of relatives. Videbaek reported among the relatives of the leukemia patients an excessive incidence of cancer, but this was due to high incidence of all forms of the disease. In the families of the 209 leukemia patient probands, however, 17 had at least one other verified case of leukemia whereas in the families of the 200 control probands there was only one case of leukemia. Thus, there was significantly more leukemia among the relatives of the leukemia probands than among the relatives of the controls.

From analysis of these 17 families and others from the literature making a total of 39, it was concluded that genetic factors had a role in the occurrence of leukemia, but the mode of inheritance could not be determined. It appeared that genes were controlling a predisposition to the disease, leaving open the possibility of the additional influence of chemical or physical carcinogens or viruses. There was no evidence of sex limitation or sex linkage and no evidence of extrachromosomal or maternal inheritance, as had been shown by that time for mammary cancer in mice. Genetically, leukemia appeared as an entity with the various types occurring among the relatives of the probands. Chronic lymphogenous leukemia, and probably also acute leukemia and chronic myelogenous leukemia, tended to occur earlier in the familial cases than in the sporadic ones.

These observations of Videbaek, with the exception of the increase in cancer in general in families of leukemia probands, might be expected from what we have observed of the occurrence of leukemia in certain inbred strains of mice and from the results of the classic studies of Cole and Furth (1941) and MacDowell and co-workers (1945). They demonstrated that genetic factors were involved in mouse leukemia, and these appeared to be multiple. Although Videbaek's observations were not confirmed by a more recent study of leukemia in man by Steinberg (1960), the excess of leukemia in sibships has been confirmed

for childhood leukemia by Stewart (1961) and Miller (1963). The frequency is about four times normal expectation.

A classical approach to the identification of genetic factors is the comparison of concordance in identical or monozygous twins with that in fraternal or dizygous twins. Since nongenetic factors would be about as nearly alike in the dizygous twins as in the monozygous twins and since the latter would be identical genetically except for mutations occurring after the splitting of the zygote, a greater concordance would be expected between the monozygous pairs if genetic factors were involved. MacMahon and Levy (1964) have reported a concordance rate of about 25% for childhood leukemia among monozygous twins while in the literature only three concordant sets were described as dizygotic and none was well documented. If a twin child falls ill with leukemia the monozygous mate has one chance in four or five of also developing the disease and usually within weeks or a few months.

Although the data from twins are strong evidence for genetic factors in childhood leukemia, Clarkson and Boyse (1971) have suggested as an alternative explanation the possibility that high concordance in the monozygous twins may be due to fusion of placentas with common circulation permitting the formation of hematopoietic chimerism. They are suggesting that the neoplastic change may occur before birth and that many cases of concordance may represent only one occurrence of leukemia, not two. They further point out that whether or not this is the case might be shown through cytogenetic studies.

This evidence for inherited influences, especially in childhood leukemia, is in line with the high incidence and early appearance of leukemia in certain inbred strains of mice where the genetic influence is strong, but it is also generally true in mice where a potent leukemia virus is involved.

The significant demonstration by Gross (1951) of a vertically transmitted leukemia virus in the mouse eventually led to the concept of genetically transmitted C-type leukemia viruses put forth by Huebner and his associates (Huebner and Todaro, 1969) as their oncogene theory. This postulates, like the provirus theory of the transmission of the B-type mammary tumor virus, that the C-type oncogenic RNA viral information is transmitted as DNA in the host genome. Actual identificaton and location of the locus or loci has come forth from works of others, particularly Rowe and associates (1972). From rapidly accumulating information on leukemia viruses in mice and other experimental animals, it appears likely that a leukemia virus will eventually be found in man. If so, it probably also will be genetically transmitted, and thus here geneticists working in collaboration with virologists will again be able

to make a real contribution to our understanding of the transmission of the disease.

## B. Chromosomal Aberrations and Leukemia

In the 1930s, Dr. Warren H. Lewis was observing that neoplastic cells had more chromosomal morphologic irregularities than did normal cells. He asked the basic question whether these changes were the cause of the neoplasia, the result of the neoplastic change, or a manifestation of a basic factor causing both the neoplasia and the chromosomal changes. We still do not have the final answer to his question although certain chromosomal traits are found to be of value in diagnosis and in determining cancer risks.

Dr. Lewis' basic observations stimulated a vast number of karyotypic studies of tumors of all kinds, which for the next two decades were relatively unproductive. The changes did not appear to have much uniformity in their patterns of manifestation or in their causation. The picture changed in 1960 when Nowell and Hungerford reported that a minute chromosome replaced one of the smallest autosomes in cells of seven patients with chronic granulocytic leukemia which they had studied. This minute chromosome was not seen in cells of four cases of acute granulocytic leukemia in adults or of six cases of acute leukemia in children. There were no other frequent or regular chromosomal changes in the cells of the chronic granulocytic leukemia patients, and all patients had many cells with a normal karyotype. Thus, a chromosomal marker for chronic granulocytic leukemia, that was to be confirmed many times, had been identified. This minute chromosome is now commonly referred to as the Philadelphia chromosome ($Ph^1$) (Sandberg *et al.*, 1964).

This observation of a definite chromosomal change associated with a particular kind of neoplasm has given a renewed stimulus to cytogenetic studies of neoplasia, particularly the leukemias and other reticulum cell neoplasms. The observation that Bloom's syndrome is associated with increased susceptibility to acute leukemia is of particular interest to the geneticist because the syndrome itself is inherited through an autosomal recessive gene (Sawitsky *et al.*, 1966). The syndrome is characterized by photosensitive telangiectasia of the face. Data indicate that one of eight persons with the syndrome will develop leukemia during the first 30 years of life. It is thought that the causation of leukemia is related to the observation of excessive chromosomal breakage and rearrangement in cultured cells from patients with the syndrome.

Similarly, the recessively inherited Fanconi's aplastic anemia (Bloom