Hereditary Factors in Carcinoma

Henry T. Lynch

With 17 Figures

Springer-Verlag New York Inc. 1967
This monograph is dedicated to my
wife Jane, and my children,
Patrick, Kathleen, and Ann.
Acknowledgements

This monograph could not have been written without the constant help of my esteemed colleague, Mrs. Anne J. Krush, M.S., A.C.S.W. She assisted me with all of the chapters and played a major role in our original cancer genetics investigations. In addition, she has contributed a chapter on one of the pressing areas in oncology, namely, the attitudes and feelings of cancer patients toward their disease and the role they may play in delay in early cancer detection. Her insights into these problems have evolved over a period of 25 years as a medical social worker.

David E. Anderson, Ph.D., The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas, labored over the entire manuscript and made innumerable comments involving the development of ideas and concepts and technical accuracy on genetic matters. His own experience in the study of cancer genetics, particularly in the nevoid basal cell carcinoma syndrome and malignant melanoma, was relied upon heavily.

Margery W. Shaw, M.D., gave major assistance in our earlier work in cancer genetics and was instrumental in initiating our studies of Family G of Warthin. Her astute knowledge and experience in medical genetics helped us in formulating the original protocol for our study of “cancer families”, stressing at all times the need for rigid pathologic documentation.

Jane L. Johnson, B.A., provided inestimable technical assistance throughout the preparation of the entire manuscript. While her patience was frequently taxed by constant alterations and revisions of the manuscript, she demonstrated only the most sincere compassion, acceptance, and understanding.

Deva Lane and Betty Fraser provided genealogical assistance.

Additional technical assistance was rendered by Susan Naman, Frances Barclay, Jo Carpenter, Marilyn Rippetrop, Rose Reynolds, Laurel Batson, George Pfau, and Christopher Krush.

Countless physicians provided assistance by permitting the study of their patients, and in many cases by offering their private clinical facilities for our use. We thank these individuals deeply.

Finally to the many patients and their relatives who were investigated in these studies, we offer thanks which words could not possibly fully express.
Preface

The writing of this monograph was stimulated on the one hand by experience gained in the study of “cancer families”, and on the other, by the frequent perplexed and bewildered comments made by numerous physicians who have expressed amazement that we could think that “cancer is hereditary”.

In reviewing the world literature it became immediately apparent that no compendium on the subject of cancer genetics was available to the physician or research scientist. Therefore this monograph has been written for the following reasons: 1) To illuminate the problem for those who may have missed or ignored the evidence supporting a genetic etiology for certain malignant neoplasms; 2) to supply useful information to all practicing physicians regarding genetic risks to their patients; and 3) to provide new thoughts on the subject for use by cancer investigators. Finally, our paramount hope is that information gleaned through the reading of this monograph may contribute to the early diagnosis of cancer in members of high risk “cancer families”.

Houston, Texas, December, 1966

Henry T. Lynch
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CHAPTER 1
HISTORY OF CANCER GENETICS IN MAN
Henry T. Lynch, M. D.

An intensely controversial area in medicine as well as in genetics has been the question of a hereditary etiology for malignancies in man. Much of this controversy has stemmed from the myriad problems posed in gathering accurate data on such a complex problem as cancer and particularly in such a poor research subject as man himself. The obvious inability to control matings in man, long generation interval, small number of offspring, difficulty in collecting valid data through more than two generations, problems in population mobility, outright refusal to give authorization to obtain data and/or refusal to submit to physical examination in many cases, and finally, repression and suppression of vital information by some individuals because of fear and anxiety about one of mankind's most dreaded diseases, have only compounded an already difficult problem.

It is not surprising then that much of the pioneering work concerning the heredity of malignant neoplasms has been at the infra human level, and most often with mice. 8, 45, 54, 82, 86, 93

The systematic study of cancer genetics in humans is a relatively recent discipline. The history of investigations in this area has been reviewed by Clemmesen, 17 Jacobsen, 49 and Woolf. 109 It is believed that hereditary factors in malignancy in man were conjectured by physicians as early as the seventeenth century and possibly even earlier. 109 The question, "Is cancer hereditary?" was included in a questionnaire sent to all English physicians in 1802 but apparently no results emerged from this inquiry. 17 In the 19th century many publications dealt with studies of multiple family members affected with cancer, but careful controls were never utilized. Bashford 6 in 1908 raised many questions concerning the etiology of carcinoma and demonstrated remarkable insight in demanding that environmental and cultural factors be weighed heavily when interpreting genetic factors. For example, in considering racial differences in skin cancer, he stated, "...The extraordinary frequency of cancer of the skin of the abdomen in Kashmiris as compared with Europeans would at once suggest some racial difference were it not that we know the causative factor in this case to be one of custom. The Kashmiris wear a charcoal oven against the abdominal wall and Europeans
do not. Many other instances could be quoted, all pointing to the same direction." Bashford attempted to analyze family histories for the presence of malignancies and was disturbed by their incompleteness. He finally proposed a dichotomy between "inherited constitutional conditions" and "acquired constitutional conditions" predisposing to malignancy and concluded that the role of the latter was more important and that "... we shall more profitably spend our time if we frankly seek to ascertain how they are acquired, than if we continue to preach the doctrine that they are inherited ...".

Waaler was one of the first investigators to study a relatively large population of cancer patients and to use controls (spouses) as well as mortality statistics for comparison. In addition, he studied separately the various sites of malignancies and stressed the importance of sound diagnoses as a basis for statistical computations. He proposed the role of both exogenous and endogenous factors in the etiology of carcinoma.

Hereditary factors in cancer of specific sites such as breast, stomach, colon, and prostate, as well as the leukemias and lymphomas were systematically investigated through the use of large numbers of probands, their relatives, and comparable controls. These studies assumed increasing importance through the 1930's, 40's, and 50's, and each suggested a role for hereditary factors in the etiology of specific types of malignancies though modes of inheritance could not be identified. However, varying empiric risk figures were found for relatives of cancer probands. Probably the most "famous" family for "site specific" occurrence of a malignancy was the family of Napoleon Bonaparte. Napoleon died in 1821 from carcinoma of the stomach and it is alleged that his three sisters, his brother, his father, and his grandfather, all expired from gastric malignancies.

TWIN STUDIES

Twin studies, one of the most valuable and tried methodologies in genetics in general, have been utilized in the study of cancer genetics. The first large cancer twin study was that of Macklin in which she combined her own series of twins with published cases. Her finding an excess of concordance in monozygous twins over that in dizygous twins must be evaluated from the standpoint of the well known tendency to publish
concordant twin pairs. However, in further analysis of her data, the most striking difference between the zygosity groups favored concordance for site specific lesions. The largest twin series studied for cancer was that of Harvald et al. They traced nearly 7,000 sets of unselected twins from the Danish twin registry and found the incidence of cancer in twins to be no higher than the expected rate. In addition, concordance rates for cancer in general and for cancer of specific sites did not differ between the 1,528 dizygous pairs. These data do not support the conclusions of Macklin.

In spite of the attention given to and the theoretical expectations from twin studies, their usefulness in better comprehending genetic factors in carcinoma has been limited. For example, modes of inheritance are not identifiable through twin studies. Oliver has proposed that the best use of the twins would be through longitudinal studies. "... twins are of little use for a one shot study. Most of the twins were too young for study or had become lost to follow up. After one twin develops cancer, one cannot in justice conclude that the cotwin will remain free of the disease unless the study is carried on for a number of years." Osborne and De George also question genetic conclusions derived from twin studies "based upon the conventional concordance-discordance type of cancer studies in twins to the single born."

CANCER FAMILIES

A pioneer study of cancer in families involving "all sites" as opposed to "specific sites" was that of Warthin in 1913. He identified families showing susceptibility to cancer of all anatomic sites as "cancer families" or "cancer fraternities." Warthin, a pathologist, was one of the first investigators to emphasize the critical importance of histologic documentation of malignancy in family studies. He censured several previous studies on human cancer genetics because they lacked pathologic verification. He further stated that, "... Practically all of the old statistical studies of neoplasms, particularly those of carcinoma, were based on mortality reports; or if not these, on morbidity reports based on clinical diagnoses. In very few instances only has the statistical study been carried out on the basis of records of a diagnostic pathological laboratory. Statistics of neoplasms from such a source must be of infinitely greater value than those founded on mortality statistics. In the records of the diagnostic laboratory the error is reduced to a minimum. In mortality statistics, on the other hand, the diagnoses are chiefly clinical and consequently subject to the
wide error, inherent in the clinical diagnoses of 'tumor,' 'neoplasm,' 'cancer,' and the like ..."

Warthin's initial study\(^{102}\) was based upon a review of medical records from 1600 cases of histologically proven carcinomas seen at The University of Michigan School of Medicine. Among these cases he found patients whose relatives were also affected with carcinoma through two or more generations. He presented data on four of these families and in one (Family "G") he continued the study through 1925.\(^{103}\) Hauser and Weller, colleagues of Warthin, updated this pedigree in 1936.\(^{42}\) This family is currently being investigated and updated by us\(^{57}\) and will be discussed in chapter 9.

In several of these "cancer families" Warthin found a high incidence of carcinoma of the uterine corpus in females, gastrointestinal carcinoma in males, and a high frequency of multiple primary malignancies in both sexes. The age of onset of the malignancies was significantly earlier than that found in the general population. In addition, a remarkably high incidence of tuberculosis was noted in patients with malignancies in these cancer families. These same features have been verified by Lynch et al.,\(^{58}\) in subsequent studies of "cancer families," with the exception of tuberculosis, which has not been found to be increased in frequency. This can be explained in part by the revolutionary antituberculosis chemotherapy in use since the 1940's.

A separate "cancer family" was reported by Savage in 1956.\(^{83}\) Interestingly, uterine corpus and gastrointestinal carcinoma and multiple primary malignancies were also prevalent in this kindred.

**MENDELIAN INHERITED CANCER DISORDERS**

Several precancerous and cancerous disorders in man provide indisputable evidence for the role of hereditary factors in their etiology. One of the best known and most documented of these conditions is familial polyposis coli. This disease was first described by Cripps\(^{21}\) in 1882. The familial nature of this condition had been stressed by Lockhart-Mummery in 1925\(^^{55}\) and was reaffirmed through continuing studies by Dukes.\(^{24}\) An autosomal dominant mode of inheritance was established by Cockayne in 1927.\(^{19}\)

Xeroderma pigmentosum was first described by Hebra and Kaposi in 1874.\(^{44}\) The hereditary basis was first studied by Siemens and Kohn in 1925\(^^{85}\) and later by Cockayne in 1933.\(^{20}\) The latter investigator, impressed with the high incidence of consanguineous marriages in the parents of probands,
ascribed an autosomal recessive mode of inheritance for the disorder. In a later study Macklin attributed inheritance of the disease to incomplete sex-linkage. However, subsequent studies have reaffirmed Cockayne’s original thesis of autosomal recessive inheritance.

Retinoblastoma is a rare tumor which occurs on a sporadic basis more frequently than it does on a familial basis. In a review of the hereditary aspects of this lesion in 1944, Griffith and Sorsby found a report of familial occurrence as early as 1897. They ascribed the mode of inheritance as being compatible with an autosomal dominant. The sporadic occurrence of this lesion is probably due to a high mutation rate for the gene or possibly to phenocopies.

Von Recklinghausen’s neurofibromatosis was described in 1882; however, the first description of its familial occurrence, according to Gates, was ascribed to Virchow who in 1847 recorded the condition in a father, son, and grandchildren.

Eldon Gardner in 1951 described a family who manifested polyps of the colon with a high rate of malignant transformation, osteomas, fibromas, and epidermal cysts. Subsequent studies of this and other families showed that this unusual combination of findings (Gardner’s syndrome) followed a classic autosomal dominant mode of inheritance. Actually, this condition was described in the literature as early as 1912.

The simultaneous occurrence of polyendocrine adenomatosis in a patient was first described by Erdieheim in 1903. The hereditary occurrence of polyendocrine adenomatosis showing autosomal dominant inheritance was described by Wermer in 1954.

Hereditary multiple exostoses, according to Solomon, was first reported in a family by Bayer in 1914. The first major paper on the hereditary aspects of the disorder was that of Stocks and Barrington in 1925. However, examples of dyschondroplasia were unfortunately included in their analyses. The mode of inheritance for this disorder is consistent with an autosomal dominant.

The multiple nevoid basal cell carcinoma syndrome was first described by Straith in 1939 and later by Binkley and Johnson in 1951. The description of the inheritance of this disorder as an autosomal dominant with reduced penetrance of the gene was first given by Gorlin and Goltz in 1959.
Finally, a syndrome consisting of medullary thyroid carcinoma with amyloid and occasionally associated with pheochromocytoma was recently described by Hazard and associates in 1959. The mode of inheritance is consistent with an autosomal dominant in some families.

A review of each of these disorders is presented in Chapter 2. Undoubtedly, many more cancerous and precancerous conditions showing classic mendelian inheritance will in time be demonstrated.

**CYTOGENETICS**

Cytogenetics and its association with malignancies in man began to receive serious attention following the pioneering cytologic work of Makino and Nishimura in 1951, Hsu in 1952, Ford and Hamerton in 1956, Tijo and Levan in 1965, and Moorhead and associates in 1960. However, as early as 1890, von Hansemann suggested that cancer might be related to alterations of the chromosome set. According to de Grouchy, Boveri in 1914, and Winge in 1930, demonstrated abnormalities in the chromosomal constitution of malignant cells. Further details on the historical aspects of human cytogenetics have been reviewed by Hirschhorn and Cooper. Thus far, malignant neoplasms have been found to occur with increased frequency in several cytogenetic disorders, including Down's syndrome, Klinefelter's syndrome, Turner's syndrome, and other somatosexual disorders (see Chapter 5).

Recent studies by Sawitsky, et al. on Bloom's syndrome and Swift and Hirschhorn on Fanconi's anemia have shown a high frequency of chromosomal aberrations (chromosomal breakage and rearrangement). Each of these autosomal recessive disorders have an increased predilection for malignant transformation, most frequent of which is leukemia (see Chapter 2). The "cause" of such chromosomal changes is not clear. It is suggested that "... detailed examinations of the earliest preneoplastic stages will settle the controversy as to whether the observed chromosome changes are the cause or only the sequence of the neoplastic transformation."

A chromosomal abnormality involving a deletion or translocation of the long arms of chromosome 21 (Ph for Philadelphia) was first described in 1961 in a patient with chronic myelogenous leukemia. Subsequently, this chromosome abnormality has been well documented in numerous other patients with chronic myelogenous leukemia. Two recent studies of identical twins showed one twin to have chronic myelogenous leukemia and
Blood Group Antigens

The Ph\textsuperscript{1} chromosome, while the normal twin lacked the abnormal chromosome.\textsuperscript{36,48} These findings suggest that the Ph\textsuperscript{1} chromosome may be acquired. Inheritance of a small acrocentric chromosome (probably \#21), where the short arms were missing, was found in a family with chronic lymphocytic leukemia. This abnormal chromosome was designated Ch\textsuperscript{1}.\textsuperscript{39}

Chromosomal variations in solid tumors range from hypodiploid to extreme hyperploidy. In one study of 18 human solid tumors, no diploid metaphase was observed and no two tumors were found to have a similar chromosome constitution.\textsuperscript{111} Many processes are involved in the production of abnormal karyotypes in solid tumors. These include somatic chromosome aberrations, reduplication of the entire chromosome complement, nondisjunction, translocation and fusion with loss of centromere fragments.\textsuperscript{22,56} Marker chromosomes may result from these processes.\textsuperscript{5,22}

Hauschka\textsuperscript{41} suggests that chromosome studies of malignancies be coordinated with biochemical and virology studies in order to more fully appreciate initiating factors in the production of abnormal karyotypes in tumor tissue. Such approaches as these could supply vital clues to the etiology of carcinogenesis.

**BLOOD GROUP ANTIGENS**

Some of the early workers in the field of blood groups and malignancies were Buchanan, Higley,\textsuperscript{10} Alexander in 1921,\textsuperscript{2} and Johannsen in 1925.\textsuperscript{51} Aird and associates in 1953\textsuperscript{1} were the first investigators to demonstrate an association between gastric carcinoma and blood group A. Subsequent investigators confirmed this statistical association and additionally found an association of group A with pernicious anemia.\textsuperscript{11,16,81} Blood group A has also been found to be statistically associated with carcinoma of the genital tract,\textsuperscript{77} tumors of salivary gland tissue in general,\textsuperscript{14} and with mucinous secreting tumors in particular.\textsuperscript{78} An excess of blood group A has been noted in patients with multiple primary malignant neoplasms.\textsuperscript{27} Xeroderma pigmentosum, on the other hand, has shown a statistical correlation with blood group O.\textsuperscript{25}

The meaning of these associations (of blood groups with malignancies) is not clear. Buckwalter and associates comment on this as follows: "The full implications of the observed association remain to be realized. Interested clinical and basic scientists alike have regarded this association as perhaps
the frontier of a new field of investigation, development of which may lead to an understanding of fundamental considerations having to do with the cause of gastric cancers, cancers in general, and the broader aspects of heredity and disease.\(^{11}\)

**CANCER RESISTANCE**

The phenomenon of "cancer-resistance," with the exception of skin cancer, has received very little attention in humans, though it has been intensively studied in chickens\(^{89,105}\) and mice.\(^{15}\) In the case of squamous and basal cell carcinomas of the skin, overwhelming evidence has indicated the carcinogenic role of sunlight exposure and the "protection" provided by pigmentation of the skin.\(^{53}\) These observations date to at least 1894.\(^{97}\) Knox and associates\(^{53}\) comment about skin cancer-resistance and how this is afforded by pigmentation as follows: "The only obvious difference in light, as compared to dark skin is the amount and distribution of melanin pigment. In negro skin, melanin is present throughout the epidermis, including the stratum corneum. In light skin, the melanin content is small and is found almost exclusively in the basal layer; therefore, the melanin would appear to offer little protection to the epidermis... Pigment is the chief factor in natural protection."

Studies of cancer-resistance in humans have been primarily concerned with negative associations between carcinoma and other clinical disorders such as atherosclerosis\(^{52}\) and diabetes mellitus.\(^{34}\) However, data on cancer-resistance, particularly in the case of atherosclerosis, is controversial.\(^{34}\)

Recently, Lynch et al.\(^{59}\) reviewed the world literature on osteogenesis imperfecta and found a marked paucity of malignancies in this autosomal dominant disorder. Furthermore, in a study of 7 families with this condition, not a single malignancy was found in affected individuals, though it was found in relatives who were not affected with osteogenesis imperfecta.\(^{60}\)

In summary, it is seen that in reviewing the history of cancer genetics in man, the most striking observations which have emerged are the skepticism and vacillation concerning the importance of hereditary factors. They were prevalent at the turn of the century, lasting through the 1940's and 1950's and even somewhat into the present decade. On the other hand, the biological counterpart of the problem at the infra human level gathered momentum and impetus based on facts of heredity and carcinoma
gained through meticulous controlled matings, backcrosses, etc. Acknowledging the obvious complexities involved in studying heritable factors of malignancies in man, it seems likely that clear-cut demonstration of these phenomena in animals should cement the inevitability of hereditary etiology for at least some human malignant neoplasms. Such, of course, is the case for several classically inherited syndromes, i.e. neurofibromatosis, nevoid basal cell carcinoma syndrome, Gardner's syndrome, xeroderma pigmentosum, and others.

With advances in medical genetics, epidemiology, and allied sciences additional knowledge will undoubtedly be obtained regarding the role of hereditary factors in malignant neoplasms. In order that emerging concepts from this work may be meaningful and useful, investigators must always keep in mind the importance of environmental factors which are constantly impinging upon man's genome. In the end analysis, it is our fervent belief that insight acquired concerning the "concert" of this interaction will supply vital clues to carcinogenesis and advance cancer control.
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