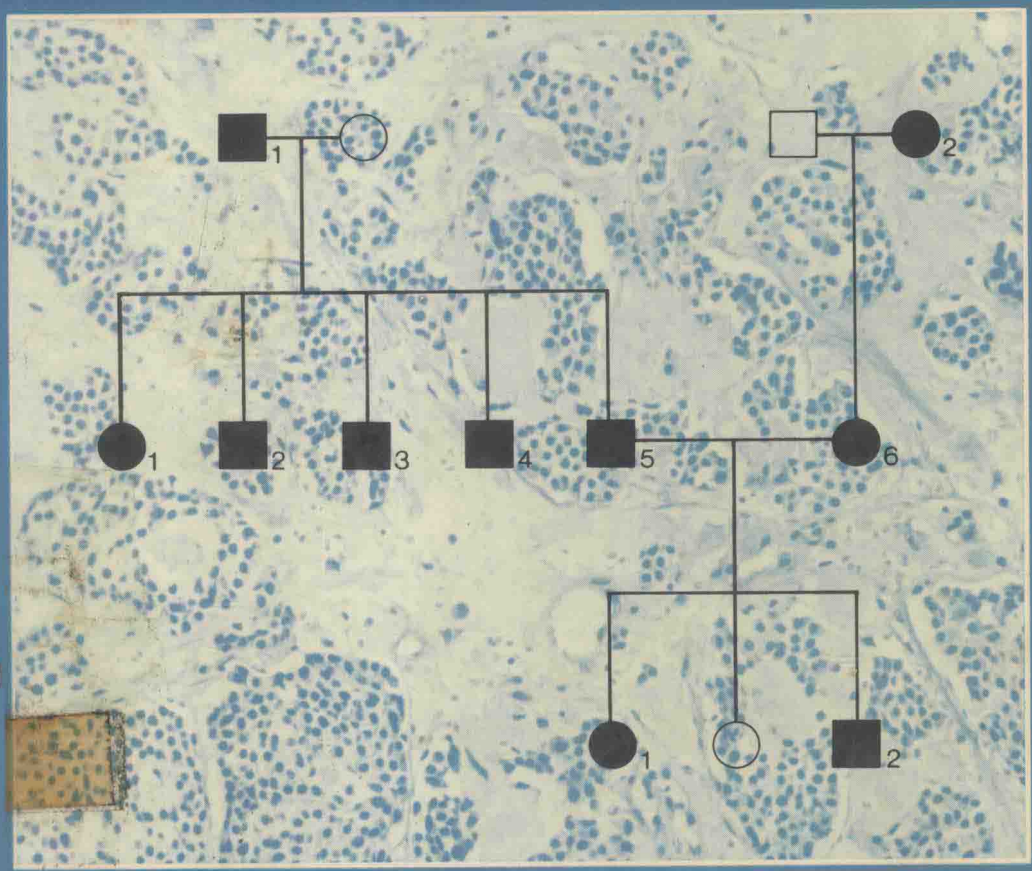
GENETICS IN MEDICINE AND SURGERY SERIES

GENETICS AND CANCER IN MAN

R. NEIL SCHIMKE
Foreword by Professor Alan E. H. Emery



CHURCHILL LIVINGSTONE

Genetics and Cancer in Man

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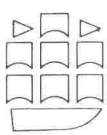

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Genetics and Cancer in Man

GENETICS IN MEDICINE AND SURGERY

General Editor

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The series is designed to provide trainee and practising doctors with easily accessible and authoritative information about genetic aspects of their specialties. Volumes describe what is known of the hereditary nature of various groups of disease and indicate how this knowledge can be applied in genetic counselling.

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To my wife Loretta,
who provides the support
and to my sons,
Douglas, Kevin and Todd
who make it worthwhile.

Foreword

'If the study of cancer is regarded as an important branch of general biology, both biology and medicine will profit.'
(Julian Huxley)

Though there have been considerable advances over the last few years in the treatment of various cancers, there is little doubt that the best approach to the problem would be through prevention. But this is only possible when the cause is known and can be avoided. There is general agreement that the more common cancers are largely due to environmental factors and the identification of such factors is an urgent problem facing medical research at the present moment. However there is increasing evidence that genetic factors are also important in aetiology. In the more common cancers this seems to be on a multifactorial basis but many relatively rare cancers are now known to be inherited as unifactorial traits. The elucidation of a genetic component in the aetiology of a particular cancer is important for reliable genetic counselling, and therefore for prevention, but may also contribute to our understanding of the molecular basis of neoplasia.

Professor Schimke has successfully marshalled a considerable amount of relevant information on this important topic. His extensive experience in clinical medicine combined with his professional interest in genetics means that he is uniquely qualified for this task. There is no doubt that this accomplished little book will prove of considerable interest and value to anyone concerned with cancer genetics, especially those who may be called upon to give genetic counselling.

1978 Alan E. H. Emery

Preface

This book can hardly be described as an exhaustive treatise on the subject. There are two reasons for this: 1) the data are simply not always available; and 2) it seemed appropriate to put what information was known in a form most useful to the practising physician, who after all compiles the family history and gets most of the initial queries about the possible inheritance of cancer. If clinicians find it of some help, my purpose has been accomplished.

I am indebted to Professor Alan Emery who encouraged me to undertake this effort. I am also grateful to the secretarial staff, both in Edinburgh and Kansas City for their help. I would like to especially thank Mrs Alice Algie who has laboured heroically over the years to decipher my progressively worsening penmanship.

1978 R. Neil Schimke

Acknowledgement

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Contents

1. The study of cancer genetics in man

The role of heredity in the aetiology of human cancer has long been a subject of dispute, save for a few rare conditions that are well known among clinicians. The usual problems that plague any genetic study in man are even more significant in cancer genetics. Malignancy in its various forms is a leading cause of human morbidity and mortality, and it is frequently more difficult to ascertain relevant genetic factors in common diseases than in those that are more rare. Man is genetically heterogeneous, his matings cannot be controlled, he has comparatively few offspring, there is a long generation time, and by and large, the most common forms of neoplasia occur in later adult life. This latter factor not only renders prospective studies more difficult, but also impedes the retrospective collection of adequate family data, since old records are frequently lost or destroyed. Then too, the environment and social habits change over the years, making difficult the chore of determining the relative importance of the external world in carcinogenesis and how the environment and man's genes might have worked in concert to produce disease, an interaction termed *ecogenetics*.

The foregoing difficulties and others have undoubtedly dissuaded many capable investigators from the study of cancer genetics in man, and instead, encouraged them to turn their attention to experimental animals. Such studies have contributed greatly to a fuller comprehension of the mechanisms of carcinogenesis. A host of proposed causal events have been advanced including somatic mutation, embryonic rests, native DNA instability, tumour genes, tumour viruses and numerous others, many of which are not mutually exclusive. It is likely that an animal model exists or can be developed to support any of these theories and that two or more theories might fit the same cancer model, especially since aetiological heterogeneity is to be expected. The applicability of any of these animal studies to man remains to be established, and in the final analysis, the best way to understand man is to study man, as pointed out by Slye (1928), fifty years ago in an article on cancer and heredity. She stated

> ... therefore since it is possible wholly to eliminate spontaneous cancer from families of mice by the appropriate genetic procedure, it might prove to be possible so to eliminate cancer from families of man. This does not mean that we can relax our vigilance against any forms of chronic irritations in any case, since we have not as yet even begun to apply the facts of heredity to the human species, and we have few adequate statistics of human heredity in relation to disease. But it does mean that we should begin to get correct scientific human statistics regarding diseases in man, based upon operation, biopsy, or necropsy in every case, and not upon opinion, so that we could make such application because in this procedure lies much hope ...

Many early studies of cancer genetics in humans were epidemiological in nature and tended to emphasize common neoplasms. Later approaches focused

on a number of simply inherited entities in which malignancy was a conspicuous feature. The composite view, and one supported by many workers in the field, suggests that there are a few neoplasic conditions with great heritability but that genetics plays a minor role in the aetiology of most cancers in man. Thus it has been suggested that familial aggregation of common cancers is either statistical artifact or is related to reporting bias. For example, Woolf and Isaacson (1961) have mathematically advanced the concept that given a sufficiently large population, one would expect to uncover families containing more than one member with a specific cancer, but this discovery would provide no support for a genetic aetiology for the cancer. The results of such studies have not been as clear as predicted from the theoretical model and even these investigators concluded that there seem to be as yet poorly understood predisposing factors in some families that increase the risk of malignancy three to ten fold over that of the general population.

Other workers notably Knudson, Strong and Anderson (1973) have emphasized aetiologic and genetic heterogeneity and have suggested that, in addition to the simply inherited cancer syndromes, there exists a subset of patients with common neoplasms whose cancer or perhaps more accurately, cancer predisposition, behaves for practical purposes as a simply inherited trait. In other words, the population may actually consist of a large number of individuals with no or perhaps only a minimal risk of cancer and a small group with a large risk. A statistical survey of such a population might easily conclude that it was homogeneous in regard to those factors which cause cancer and that the average risk was in fact small. What appears superficially to be a normal population distribution, perhaps with a slight skew, may be found upon closer study to consist of a number of distinct curves, whose additive effective may closely mimic a normal distribution. For example, carcinoma of the colon may be randomly distributed in the general population, but it is well known that it develops as a regular accompaniment of a number of heredity polyposis syndromes and in individuals in these families the risk of carcinoma behaves like a Mendelian dominant. The existence of polyposis families does not preclude the existence of non-polyposis families whose risk of malignancy is also Mendelian in expectation (see Chapter 6), but they are not easily identified because exactly what the defective gene does is not known since it is not related to the development of premalignant polyps.

Even interpretation of the pedigree data in a given family might engender difficulty. If we assume that all the individuals, depicted by shaded symbols in Figure 1.1 have carcinoma of the colon and all clear symbols are unaffected then we easily might conclude, assuming that there is no common environmental factor, that the disease in this family is polygenic with an unfortunate particular aggregation in one branch. The risk to the proband of developing the disease would be quite small; i.e., 1 or 2 per cent, based on a survey of the entire family and assuming low heritability; i.e., 20 per cent or less, for colon cancer. If, on the other hand, the affected individuals in this pedigree suffered from the Marfan syndrome, a well known autosomal dominant noncancerous condition, the risk to the proband would be 50 per cent, a figure more than 25 times that expected from a polygenic model. In such a pedigree

the remainder of the presumably unaffected family would be disregarded for counselling purposes with the assumption being made that a new mutation had occurred in the grandfather of the proband. The important point to recognize here is that prior knowledge of the existence of a condition known as the Marfan syndrome along with precise information regarding its genetics allowed for an accurate appraisal of the counselling risks. Non-polypotic colon carcinoma likely has more than one cause, and it is conceivable that a proportion of such cases may be simply inherited. Study of large families as well as study of large populations tends to obscure aetiologic, which in this context may be considered genetic, heterogeneity. To return to the example of the Marfan syndrome, careful scrutiny of patients classed as having this disease has revealed a number who actually had a closely simulating disease, homocystinuria, which is inherited differently and has different molecular pathology. At an even grosser level if one looked at a population with dislocated ocular lenses, a feature seen in both

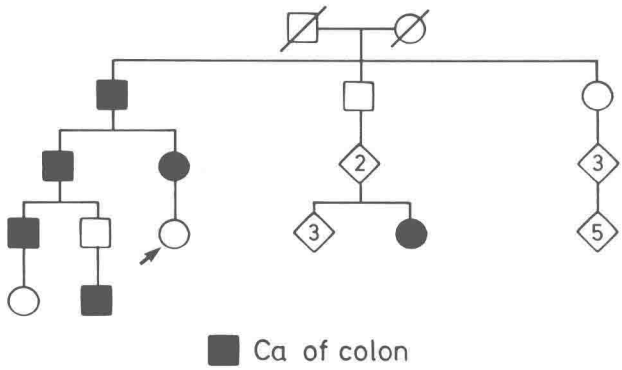

Fig. 1.1 Hypothetical kindred in which only colon cancer is under study.

the Marfan syndrome and homocystinuria, further heterogeneity would be found, with the majority of cases being traumatic, but with others due to sulfite oxidase deficiency (a recessive) and isolated genetic ectopia lentis (a dominant). Similarly, the bulk of colon cancer may not be genetic at all, but wholly environmentally induced. A subgroup may be multifactorial in aetiology, a term that implies that the genetic and environmental risks are so intertwined as to be inseparable. Another subpopulation may indeed have a cancer predisposition that behaves as a Mendelian dominant or recessive. Such subgroups have been uncovered in studies of families of various patients with breast cancer (Anderson, 1974).

The cancer risk in the environmental group may be exceedingly high if everyone in the family is exposed to the same oncogenic stimulus. In fact, this risk may be greater than maximum genetic expectations; i.e., >50 per cent, a situation that occurs for certain cancers in high incidence areas, like hepatoma in Africa or oesophageal carcinoma in the Middle East (Wynder and Gori, 1977). In the multifactorial group, the risk to first degree relatives of an affected individual may be no more than three to five times the age-adjusted population risk

or 1 to 2 per cent, assuming low heritability* of the particular cancer. If, however, heritability is high, say >80 per cent, then the risk for relatives would be substantially higher. For example, if under a multifactorial model such high heritability is assumed and, for example, the consultant has an affected parent and a sib, the cancer risk would be roughly 15 per cent. If both parents were affected, a not unique event by any means, and no sibs had cancer, the risk would be about 30 per cent. With two affected parents and an affected sib, the risk would be in excess of 40 per cent. These calculations are based on a disease frequency of 0.1 per cent with a heritability of about 80 per cent, the latter figure clearly beyond such estimates in most populations. However, they are developed to demonstrate that even with multifactorial inheritance, the risk of malignancy in some families may be of the same order of magnitude as with a unifactorial trait. Obviously, differentiation of multifactorial inheritance of a

Table 1.1 Environmental agents that have been strongly incriminated in the aetiology of site-specific cancers*

Cancer site	Environmental hazard
Liver	Arsenic, vinyl chloride
Nose, nasopharynx sinuses	Chromium, isopropyl oil, nickel, wood and leather dust
Lung	Arsenic, asbestos, chromium, cigarettes, coal products, dusts, iron oxide, mustard gas, nickel, petroleum, ionizing radiation
Bladder	Coal products, aromatic amines
Bone	Ionizing radiation; i.e., radium
Bone marrow	Benzine, ionizing radiation
Skin	Arsenic, ultraviolet irradiation

* Adapted from Wynder and Gori, 1977.

trait with high heritability from Mendelian dominant inheritance with incomplete penetrance might be quite impossible. It must be emphasized that these considerations are theoretical. From a practical standpoint, the consultant needs to know whether the risk is high or low and what can be done to minimize it.

It is probably impossible to estimate how many patients with common cancers actually have their disease on a primary genetic basis. A study of more than 4000 clinic registrations in two US metropolitan centres revealed that nearly one-half of the families evaluated had no significant cancer history, whereas about 7 per cent were deemed cancer prone as evidenced by the presence of cancer in three or more first degree relatives of the index case (Lynch, *et al.*, 1974). This figure of 7 per cent probably represents a minimal estimate of heritable cancer as it likely excludes the well known but quite rare simply inherited

* Heritability is defined as that proportion of the total variation of a phenotype due to genetic factors. The greater the value, the more important the genetic role. It is calculated from the incidence of a condition in relatives and in the several populations and as such is a rough, but useful estimate.

tumour-associated syndromes, such as neurofibromatosis. The heritable proportion may be quite variable depending upon the type of cancer in question; i.e., 5 to 10 per cent for colon cancer vs. 25 to 35 per cent for embryonal neoplasms (Knudson and Strong, 1973). Even within a diagnostic category, heritability estimates may be different; i.e., there seems to be a larger genetic component in chronic lymphocytic leukaemia as contrasted with the chronic myelocytic variety. The results of large-scale screening techniques for early detection of cancer have not justified early optimism. Perhaps such procedures, which are both expensive and time-consuming should be reserved, or at least applied more liberally, to that sub-population shown either to be at substantially increased genetic risk for development of cancer or in whom the environment has been strongly incriminated (Table 1.1).

THE ORIGIN OF HERITABLE TUMOURS IN MAN

Even in those families in which the genetic risk of malignancy is high, as in familial dominantly inherited retinoblastoma, some puzzling features remain. For example, monozygotic twin concordance, while significantly higher than that for dizygotic twins, is frequently far less than the 100 per cent theoretically expected, even when sophisticated ophthalmologic equipment able to detect old 'burned out' tumours (spontaneous remissions) is used for evaluation of probable genetic carriers of the trait. Similarly, the genetic interpretation applied to a family containing two affected sibs and unaffected parents or one with an affected child and an affected collateral relative with an unaffected common relative is complex, and has led to postulation of non-penetrance of the heritable mutant gene, to theories of gonadal mutation and to the concept of premutation. This latter theory, first offered by Auerbach (1956) and more recently mathematically refined by Knudson (1973), adopts the premise that the development of all malignancy requires two mutational events. In the case of heritable tumours, the first event or premutation is germinal and the second (telomutation) is somatic (Hermann, 1976). Lack of penetrance (skipped generations) and less than expected twin concordance in familial tumours could be explained by the absence of a second or somatic event required to initiate oncogenesis. This theory also accounts for the observed fact that familial tumours have a greater tendency to be multifocal or in the case of paired organs to be bilateral, since the relevant tissues would already harbour the germinal mutation and only one rather than two events would be necessary for tumorigenesis. An earlier average age of onset would also be expected and in general this holds true for familial tumours. One would also postulate that most familial tumours would be inherited as dominant disorders, and this also appears valid based on present evidence. Sporadic or non-familial tumours would tend to be unifocal since two separate somatic events would be required for frank tumour development. Implicit in this two-mutation or two-hit hypothesis is that carcinogenesis is related to discrete changes occurring at random and that they occur at a constant average rate. While these two assumptions are difficult to prove, the model at the very least offers a unique departure for study of the mechanism of hereditary malignancy in man.

SITE-SPECIFIC NEOPLASIA AND CANCER FAMILIES

The pedigree in Figure 1.1 was used to illustrate pitfalls in assessing genetic factors in colon carcinoma. Since only colon carcinoma was being studied, it is obvious why the heritability could be debated in terms of a polygenic vs. a unifactorial model. If the Figure were redrawn to include cancers of other sites (Fig. 1.2), one would be forced to conclude that a cancer diathesis was present in the family, which for practical purposes, behaves like a highly penetrant autosomal dominant trait. A number of family members appear to be at risk for cancer at a number of sites of which the colon is only one.

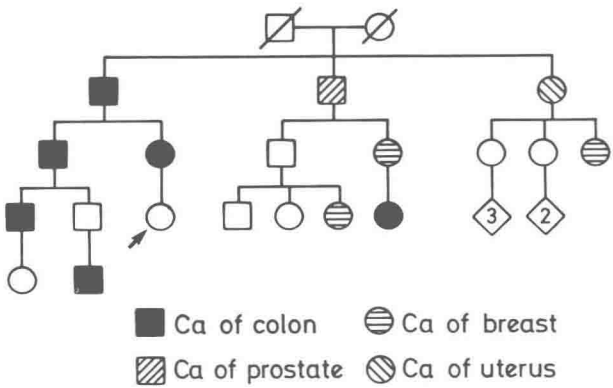

Fig. 1.2 The same kindred as in Figure 1.1 showing tumours at sites other than colon.

Lynch and Krush (1973) have studied a number of cancer-prone families in detail and have reached some general conclusions. First of all, in these families the cancer predisposition appears to segregate as an autosomal dominant disorder with high penetrance and variable expressivity. Secondly, of the family members who are at risk, more than 40 per cent have developed tumours by age 40. Third, multiple primaries occur quite frequently in affected individuals and these are often at apparently discordant sites. Fourth, the various family members need not have the same tumour, and in fact it seems apparent that in general this phenomenon of discordant site-specific tumours within such a family may be comparable to the tendency of a single individual in the same

Table 1.2 The spectrum of tumours seen in the cancer family syndromes

Type I	Type II
Endometrium	Breast
Ovary	Sarcomas
Breast	Embryonal neoplasms
Prostate	Brain tumours
Colon	Acute leukaemia
Stomach	Adrenal cortex
Skin	Hodgkins disease
Melanoma	Thyroid
Pancreas	Bladder cancer

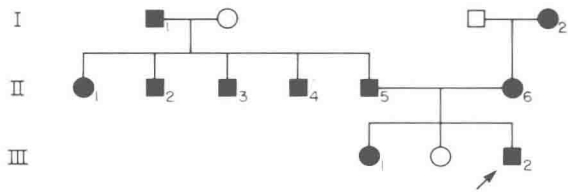

Fig. 1.3 A cancer family seen at Kansas University Hospital with multiple members affected. This kindred probably best corresponds to the Type I family (Table 1.1). All affected members are deceased. The family was ascertained through the proband who died of metastatic melanoma.

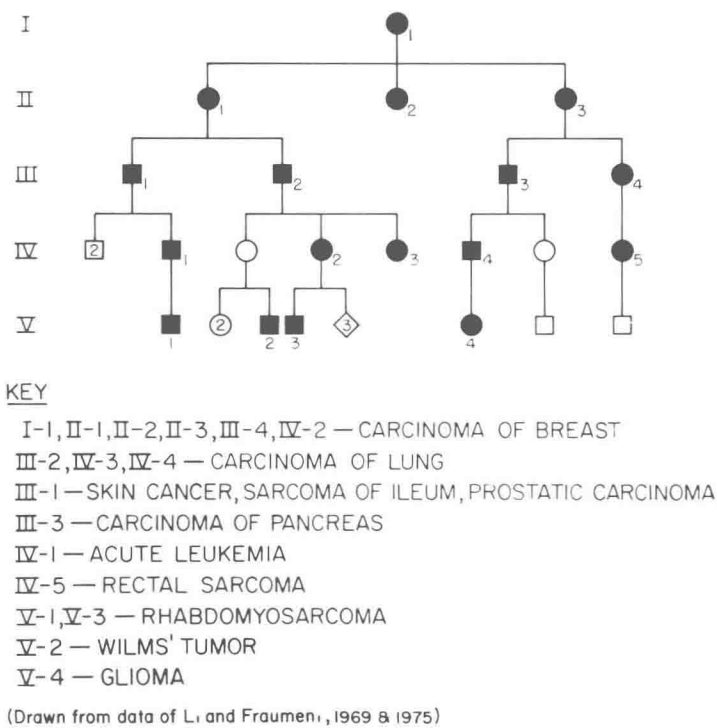

Fig. 1.4 A cancer family pedigree of the breast carcinoma-soft tissue sarcoma type.