Genetics and Cancer

JOHN M. MUELLER, M.D. AND ROBERT B. DIASIO, M.D., *Division of Medical Oncology*

The existence of a relationship between cancer and heredity has been recognized for years, but only recently has emerging knowledge in this area enabled physicians to detect and treat cancer earlier in affected individuals and to prevent its occurrence in others.

The genetics of human cancer can be divided into three categories: first, cancers inherited by direct gene transmission; second, familial disorders not characterized by malignant disease themselves but which predispose to an increased likelihood of developing cancer; third, cancers of one or more types occurring with an increased incidence within a family but with a mode of genetic transmission that may not be clear.

A relatively small proportion of cancers are inherited as a result of direct single gene transmission. One example is retinoblastoma, a highly malignant tumor of the eye which presents in early childhood, and which occurs in two different forms. The less common familial form of the disease is usually transmitted as a highly penetrant dominant trait, with affected individuals often having bilateral involvement and a somewhat earlier age of onset. The more common form is characteristically sporadic, with affected individuals having unilateral disease and a later age of onset.[1] As more affected persons will now reach adulthood and reproduce because of improved treatment, clarification of the mode of inheritance is mandatory to allow proper genetic counseling.

Multiple endocrine adenomatosis type II or Sipple syndrome consists of the association of medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid hyperplasia. This disorder appears to be inherited as an autosomal dominant but with incomplete penetrance. As with many inherited cancers, there is an increased incidence of bilateral organ involvement. Clinically, the patient may present with evidence of carcinoma in only one system; for example, medullary carcinoma of the thyroid may be present without a palpable thyroid nodule. However, appropriate testing may show occult disease in the other organs. An elevated serum calcitonin level may suggest an occult cancer in predisposed individuals[2]; therefore, diagnosis of any of the features of this unusual syndrome should lead to careful exclusion of the others, as well as to a search among close relatives for additional, possibly presymptomatic, cases.

Familial polyposis coli is an autosomal dominant disorder in which adenomatous polyps may be so numerous that they actually carpet the entire colon and rectum; Gardner syndrome is a distinct variant that includes associated sebaceous cysts and osteomas of bone. Early recognition of these disorders is critical since virtually 100% of affected persons will develop carcinoma of the colon by age 50 unless a prophylactic colectomy is performed.[3] A number of oncologists now recommend total colectomy as soon as the disorder is discovered in childhood unless it is possible to follow the affected child with regular sigmoidoscopies and barium enemas. The management of these families can be extremely difficult since it is essential both to stress the importance of regular examination and to avoid contributing to an obsessive cancer phobia.

Neurofibromatosis is an autosomal dominant disorder characterized by café au lait spots and multiple neurofibromas. The neurofibromas show a sarcomatous degeneration in about 10% of patients, and there is an increased risk of gliomas of the brain or optic nerve, meningiomas, acoustic neuromas, and pheochromocytomas.

Xeroderma pigmentosa is a rare disorder manifested by sun sensitivity and the development of freckles on sun-exposed areas which then become dry and scaly. Basal cell and squamous cell carcinomas of

Correspondence and reprint requests to Dr. Robert B. Diasio, Box 725, Medical College of Virginia, Richmond, Virginia 23298.

the skin later develop, and even if they are arrested, affected individuals have an increased risk of melanoma.[1] Xeroderma pigmentosa is transmitted as an autosomal recessive trait. The defect has been shown to be a specific deficiency in one of the several enzymes normally required to repair ultraviolet radiation damage to the DNA of epidermal cells.[4] When the precipitating causes of the problem are appreciated, the physician can teach affected individuals to protect themselves from the carcinogenic effects of ultraviolet radiation without undue disruption of a normal lifestyle.[5]

Immune deficiency disorders are associated with an increased incidence of cancer, particularly lymphoma. The prime examples are the recessively inherited syndromes such as X-linked agammaglobulinemia, ataxia telangiectasia, and Wiskott-Aldrich syndrome. Individually, each of these recessive syndromes is rare, and in the aggregate, affected homozygotes (or hemizygotes if the trait is X-linked) constitute only a small proportion of all patients who develop cancer. However, there is increasing evidence that heterozygous carriers of at least some of these recessive genes may also be predisposed to cancer. Carriers of rare recessive genes are, of course, much more numerous in the general population than are affected homozygotes; in fact, the rarer the recessive trait, the greater the relative frequency of heterozygous carriers in the population in comparison with affected homozygotes. Therefore, a small effect of cancer risk in heterozygotes could have much greater public health significance than would a major effect in homozygotes. Swift[6] has provided convincing evidence that heterozygous carriers of the genes for ataxia telangiectasia and Fanconi anemia have a three- to fourfold increased risk of developing cancer; he has estimated that at least 3% of all cancers arise in individuals who are heterozygous for one or the other of these two genes alone. At present, no laboratory test is available to identify carriers.

Detecting an increased familial risk of cancer and following the involved family members for evidence of developing neoplasia is an important activity for practicing physicians. The cancers may be always of the same organ, that is, a site-specific tumor may occur in familial aggregations, or they may be of multiple varied organs. The Table lists the site-specific malignant neoplasms with possible familial occurrence.[7]

There is considerable heterogeneity in the genetics of certain cancers, especially breast cancer.

Neoplasms with Possible Familial Occurrence

Breast	Lymphoma
Colon	Hepatocellular tumors
Stomach	Testicular tumors
Prostate	Neuroblastoma
Endometrium	Wilms tumor
Hodgkin disease	Burkitt lymphoma
Waldenström disease	Bronchogenic carcinoma
Multiple myeloma	Ovarian carcinoma
Leukemia	

Studies[8-10] have helped elucidate some of the risk factors. It is important to know whether the disease has occurred in two or more female first-degree relatives, whether the disease was pre- or post-menopausal in onset, and whether it was bilateral. In the premenopausal age group, the relative risk of breast cancer among family members of an affected individual is approximately three times that of controls, whereas in the postmenopausal age group, the risk is only slightly greater than that of controls. Relatives of women with bilateral disease have a fivefold risk compared to controls. The relatives of women with premenopausal and bilateral disease have a relative risk of developing breast cancer that is almost nine times greater than that of controls, while the relatives of patients with postmenopausal bilateral disease have a risk that is four times greater. The risk to other family members also depends upon the relationship of prior affected persons to the proband. For example, if prior disease involved a proband's mother, the proband's sisters will have a 30% incidence of cancer in the 20-to 29-year age group, a risk 47 times greater than that of the general population. Clearly, these facts imply a genetic factor in breast cancer which appears most consistent with polygenic inheritance of a predisposition. Physician recognition of and response to this inherited predisposition is important particularly in the high-risk situation. In one such family, for example, bilateral reduction mammoplasty with implantation of a subcutaneous prosthesis was recommended for a 19-year-old girl whose two sisters, mother, and maternal grandmother had had early onset of breast cancer.[11]

The concept of "cancer families" has been broadened to include kindreds displaying familial occurrence of diverse neoplasms even of dissimilar cell types.[12] The cancer family has the following characteristics: 1) an increased occurrence of adenocarcinoma primarily of colon and endometrium; 2) in-

creased frequency of multiple primary malignant neoplasms; 3) early age of onset of cancer relative to the usual age of onset of that cancer in the general population; 4) vertical transmission of cancer consistent with an autosomal dominant inheritance pattern. One such family has been described in Virginia.[13]

Environmental factors may also influence expression of the disease when there is a familial tendency to cancer. Studies by Tokuhata have confirmed an increased incidence of cancer of the lung in relatives of patients with lung cancer, and his data suggest that the combined risk of cigarette smoking and the familial host factor increase the liability of developing lung cancer in a synergistic rather than additive manner.[14]

The interrelationships between heredity and environment in the occurrence of cancer are complex and in many cases not completely characterized, but certain facts are clear. Specific cancers can be inherited directly. Certain diseases that predispose to cancer are inherited, and specific cancers or specific tendencies to develop a variety of cancers are inherited in families. Examples of each of these have been discussed. The long-range challenge to physicians is to recognize these situations and to study them thoroughly to further our understanding of the causes of cancer. More immediately, however, the alert physician who takes a detailed family history can recognize the increased risk of a particular malignancy and, by careful examination, testing, advice, and follow-up, can provide early treatment or even prevent the development of a potentially fatal malignancy.[11]

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