Cancer of Endocrine Glands and Target Organs: Genetic Considerations*

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ABSTRACT

The pathogenesis of cancer in general is influenced by many factors, genetic and environmental. Epidemiological studies demonstrate familial aggregation of cancer in a significant proportion of cases. Many of these familial cancer syndromes contain endocrine hormone-related components. The etiology of endocrine-related cancers is complex, as is that of other cancers. Tumors of endocrine glands and target organs are subject to the same influences as other cancers; an additional variable is that of hormone-responsiveness.

The existence of familial cancer was recognized as early as the last century, but the concept of inherited susceptibility was only introduced in 1931 by Warthin, who used the term “cancer family” or “cancer fraternity” to denote families with an excess of specific types or groups of neoplasms.95 Recent studies have confirmed the non-random distribution of cancer in the population, and numerous familial clusters determined by genetic factors, environmental factors or a combination of the two have been recorded.4,36,39,47,54,56,75,88 Intrafamilial or sib-sib concordance for certain types of childhood cancers have been reported, and the occurrence of malignancy in one child is known to increase the risk in siblings to approximately twice that of the general population.47,51,54,62

General Considerations

The term “cancer family” was originally applied by Warthin to families in which affected patients developed cancer of the thyroid or cancer of the uterus and lip.95 Lynch et al, however, have redefined the criteria for the designation Cancer Family Syndrome to include carcinoma of the colon in association with endometrial carcinoma or other adenocarcinoma, an excess of multiple primary malignancies, early age of onset and autosomal dominant mode of inheritance.4,54,75 Studies of cancer families demonstrate a variability in the associated tumors found in different families and among the members of the same family.4,54 A genetic susceptibility predisposing a specific group of organs or tissues to malignant transformation has been postulated.4,56
More than 150 single gene defects are associated with human cancer. Some conditions are expressed solely through the development of neoplasia in one or more organ systems; in others, non-neoplastic features may predominate early in their course. A number of genetically determined premalignant conditions have been described, some characterized by clinically definable phenotypes, reliable biochemical markers or immunological abnormalities. In some instances the familial aggregation follows a mendelian pattern of inheritance; in others the mode of determination remains unclear. At the cellular level, the importance of chromosomal abnormalities has been documented through cytogenic studies of natural and experimentally-induced tumors. Moreover, all phenotypic characteristics of cells, including those resulting in malignant transformation, are genetically determined.

Most human cancers have been reported as dominantly inherited conditions characterized by a high risk for the specific tumor, an earlier than usual age of diagnosis and a multiplicity of primary tumors. The prototype of these disorders is hereditary retinoblastoma, for which Knudson has proposed a two-mutation model, which might also apply to other autosomal dominant cancers. According to his hypothesis, a germinal mutation conferring susceptibility is transmitted from parent to offspring; an additional somatic mutation is necessary for the expression of the cancer. The germinal mutation alone, therefore, is not sufficient to produce neoplasia. Indeed, five to ten percent of obligate carriers develop no tumors. Age-specific analysis of retinoblastoma carriers implies that only one mutation, in addition to the germinal one, is necessary for cancer development. In contrast, development of the sporadic form of retinoblastoma requires two somatic mutations. Thus, patients with the hereditary form of retinoblastoma are at greater risk to develop multiple primary lesions at an earlier age. It should also be mentioned that retinoblastoma occurs relatively frequently in patients with an interstitial deletion of chromosome 13, although such a deletion is not found with the usual dominant form.

In contrast to the familial cancer syndromes which are expressed only through the development of neoplasia, non-neoplastic features predominate early in the course of others, and cancer develops only as a later manifestation. Among the most well-described of these are the xeroderma pigmentosa (XDP) and ataxia telangiectasia. XDP is represented by a group of disorders characterized by sun-sensitive skin eruptions beginning in childhood and illustrates the interaction of genetic and environmental factors in the pathogenesis of cancer. The development of cancer appears to depend on genetic susceptibility, age of patient and exposure to solar irradiation. The fundamental defect involves excision repair of DNA damage induced by ultraviolet (UV) irradiation of skin cells and results from an abnormality in UV endonuclease. Ataxia telangiectasia is associated with impaired immune response, IgA immunoglobulin deficiency and an increased risk for the development of lymphoid neoplasms containing cells with a translocation of chromosome 14. Bloom’s syndrome and Fanconi’s pancytopenia are related conditions characterized by an increased risk for leukemia, an increased tendency to acquired chromosomal aberrations and increased in vitro mutagenesis.

Another group of conditions associated with increased cancer risk is the congenital or acquired immunodeficiencies. The age-specific incidence of cancer in young persons with sex-linked or autosomal recessive im-
mune deficiency has been estimated to be 1,000 times that of age-matched controls. The body normally eliminates aneuploid cells and their persistence may reflect a failure in immune surveillance. Lymphoreticular neoplasms are the cancers generally acknowledged to occur most commonly in the immune deficiency diseases, but others have been sporadically reported.

The precise role of viruses in animal and human cancer is difficult to define because of the multiplicity of factors that may be involved, even though viral infection may be considered to be the most important. Age, sex, diet, immune competence, physiologic state and genetic constitution have been identified as critical factors in the induction and/or progression of several of the virus-induced animal cancers. Moreover, cocarcinogenesis occurs in animals through interactions between different chemical carcinogens, chemicals and viruses or different viruses. Among the human cancers, Burkitt's lymphoma is generally acknowledged to be virus-related. Less conclusive evidence is available also implicating nasopharyngeal carcinoma, carcinoma of the uterine cervix, acute myelogenous leukemia and breast cancer.

Boveri first suggested in 1914 that the cellular changes leading to cancer might be related to abnormalities in cell division resulting in an unbalanced distribution of genetic material among daughter cells. It is now known that many carcinogens, including irradiation, chemicals and viruses, may cause chromosomal aberrations. Moreover, certain chromosomal aberrations may affect specific target tissues and predispose to cancer. The first documented cancer-associated chromosomal anomaly was the Philadelphia chromosome, an abnormal chromosome 22 which is found in approximately 85 percent of patients with chronic myeloid leukemia and is virtually diagnostic of the disease. Characteristic chromosome abnormalities have also been described in other tumors.

Furthermore, human cancers may demonstrate nonspecific chromosomal alterations, which remain markers for an individual tumor throughout its course, although additional changes may occur. Whether the alterations are etiologic in the pathogenesis of the malignancy or merely represent secondary changes is not clear. Recent reports implicate chromosomal aberrations involving chromosomes 7, 8, 9, 14, 17, 20, 31 and 22 in human cancer, suggesting that the genetic loci influencing malignant transformation might reside on these chromosomes. In addition to chromosome changes found in neoplastic cells, specific aneuploid states, notably Down syndrome, are associated with an increased risk of malignancy.

Congenital malformations may signal an increased risk for specific cancers in children. A study of 371 children with cancer demonstrated an incidence of congenital malformations of 40 percent as opposed to 13 percent in a control, cancer-free population. Wilms tumor is associated with genitourinary anomalies, aniridia, hemihypertrophy or the Wiedemann-Beckwith syndrome. Hemihypertrophy and the Wiedemann-Beckwith syndrome have been reported also in association with adenocortical carcinoma, carcinoma of the uterine cervix, acute myelogenous leukemia and breast cancer.

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Many of the familial cancer syndromes involve cancers of endocrine glands or target organs. The former include pituitary, adrenal cortex and medulla, en-
docrine, pancreas, ovaries, testes and thyroid; the latter include uterus and breast. An estimated 90,000 deaths yearly are associated with cancer of endocrine-related organs. Endocrine tumors, like other neoplasms, may be induced by chemical or physical carcinogenesis, influenced in some instances by hormonal factors. Whether hormones act in the same manner as other carcinogens or merely as permissive or promoting agents is not clear. Thus, although tumors of the endocrine glands or target organs may arise in the same manner as other neoplasms, they are distinguished by a specific hormone responsiveness.

It is generally accepted that the cellular changes resulting in malignant behavior facilitate the unrestricted proliferation of certain cells in an environment that otherwise imposes effective control over the growth of normal cells. In endocrine tissues, this is usually accompanied by a change in target cell responsiveness to hormonal influences. Since such influences are mediated through membrane or cytoplasmic receptors, an alteration in responsiveness might reflect a change in functional receptor activity, an increase in which has been postulated to imply a transition in cellular properties to an earlier developmental stage.

Neoplastic tissues with properties characteristic of fetal cells, containing demonstrable fetal antigens and enzymes, have been reported. The concept of neoplastic de-differentiation is also applicable to the ectopic hormone syndromes and the phenomenon of tumor stimulation by "inappropriate" hormones. All cells of an organism possess the same genetic information, much of which is repressed as differentiation progresses. It has been hypothesized, however, that depression may occur during carcinogenesis and result in the elaboration of polypeptide hormones, which are recognized only if they possess biologic activity. That biologically inactive polypeptides may be produced by certain neoplasms is exemplified by the carcinoembryonic antigen of colonic carcinoma.

In contrast, tumor responsiveness to inappropriate hormone stimulus may represent receptor de-differentiation. A corticosterone-producing rat adrenal carcinoma has been reported, which responded to catecholamines and thyroid stimulating hormone. The tumor also possessed receptors for luteinizing hormone and follicle stimulating hormone. In humans, Hinshaw and Ney reported three human pheochromocytomas which responded to glucagon.

Among the familial neoplasms, isolated site-specific tumors of the adrenal cortex, uterus and ovary occur uncommonly. The majority of familial cancers involving those organs are associated with other tumors. Carcinoma of the adrenal cortex has been reported in siblings and in association with hemihypertrophy; however, it also occurs in association with specific patterns of other tumors. Carcinoma of the adrenal cortex has been reported in siblings and in association with hemihypertrophy; however, it also occurs in association with specific patterns of other tumors. An estimated 13 percent of endometrial malignancy is inherited in an autosomal dominant pattern, and the majority is associated with other tumors. Site-specific familial tumors of the ovary have also been recorded, but they occur most commonly in association with other neoplasms.

In contrast to ovarian neoplasms, familial tumors of normal testes occur rarely and most are of germ cell origin. Familial testicular tumors occur uncommonly in the absence of abnormal sex differentiation and include all cell types. The occurrence of more than one cell type in the same pedigree or in the same mass implicates a common germ cell origin for the tumor and an inherited predisposition not specific for cell
Patients with a 45,XO karyotype and at least one cell line containing a Y chromosome may have gonadal dysgenesis and phenotypes ranging from males with cryptorchidism or penile hypospadias to females indistinguishable from the 45,XO Turner syndrome. Although gonadal dysgenesis is usually associated with an abnormal chromosome constitution it is found occasionally in patients with normal 46,XX or 46,XY complements. If it is associated with a chromosome constitution lacking a Y chromosome, gonadal malignancy rarely occurs. Gonadoblastoma, however, occurs with a high incidence in intersexual individuals, most commonly females with gonadal dysgenesis and a 46,XY or 45,XO/46,XY karyotype. The incidence of gonadoblastoma or dysgerminoma has been estimated to be 10 to 20 percent in 45,XO/46,XY mosaicism and 30 to 40 percent in patients with XY gonadal dysgenesis. Complete testicular feminization may occur as an X-linked recessive or male-limited dominant condition, even in sex chromosome mosaics. Individuals with complete testicular feminization, an X-linked recessive or male-limited autosomal dominant trait, undergo normal pubertal feminization and breast development but have normal, usually intra-abdominal testes, female external genitalia and no Mullerian derivatives. These abnormalities are caused by a target organ insensitivity to androgens resulting from an androgen receptor defect. Complete testicular feminization is associated with an increased risk of gonadal tumors which has been estimated to be as high as 20 percent. The incidence of testicular neoplasia is not increased in incomplete testicular feminization.

The hormone receptor concept in human cancer has been extensively studied with respect to breast cancer. Estrogen has been clearly shown to influence the growth of some breast tumors, although it cannot sustain tumor growth in the absence of the pituitary. The concentration of estrogen by target tissues has been attributed to the presence of high-affinity estrogen-binding cytoplasmic proteins. Normal, resting mammary tissue contains low or undetectable levels of estrogen receptors, while some breast cancers contain levels comparable to those found in lactating mammary gland and respond to estrogen with the enzyme changes seen during lactation. Increased hormone responsiveness is thought to reflect a change in the quantity of specific hormone receptors. Other neoplastic tissues also have been reported to show changes in hormone receptors. Jensen has suggested that the estrogen receptor assay in human breast cancer might be of clinical value in predicting response to endocrine therapy.

Breast cancer is the leading cause of death from cancer in women and accounts for 22 percent of all neoplasms in American women. Genetic, environmental, sociobiologic and physiologic factors appear to influence the risk of breast cancer, but no known single factor or combination of factors fully explains the etiology of the disease. Evidence suggestive of the importance of genetic factors in breast cancer susceptibility included the following: family history, especially of bilateral; marked differences in incidence among different racial groups; and concordance of breast cancer in monozygotic twins and of laterality in close relatives. An estimated 13 percent of cases are familial. Family studies consistently show a two-to-fourfold greater risk for carcinoma of the breast in first degree relatives of probands as compared with controls. Among the families studied by
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Lynch et al, 55.8 percent demonstrated predominantly site-specific breast cancer, while 44.2 percent showed several patterns of tumor association. Lynch et al identified the following familial associations: site-specific breast carcinoma; breast carcinoma with carcinoma of the gastrointestinal tract; breast carcinoma with carcinoma of the ovary and endometrium; breast carcinoma with a complex of sarcoma, leukemia and brain tumors; breast carcinoma in association with Cowdens disease. A miscellaneous category was also defined, lacking a specific pattern of tumors, but including breast cancer in association with an excess of various other tumors.52,53

Anderson has classified breast cancers according to age at onset, laterality, family history and associated neoplasms.3 The incidence of breast cancer among relatives of patients with premenopausal disease was 6.7 percent as compared to 2.3 percent in controls. Among relatives of propositi with bilateral tumors, the incidence increased to 13 percent. Among relatives of premenopausal patients with bilateral disease, the incidence increased further to 17 percent. The observation of a significantly greater risk among relatives of patients with early and bilateral disease is similar to the pattern seen in other familial cancers which are characterized by early onset and tumor multiplicity. It is not known whether a single gene or multiple genes are involved in the predisposition to breast cancer.4,56,72

Another example of an association between a chromosomal aberration and a specific cancer is that of breast carcinoma with Klinefelter syndrome. Males with at least one Y chromosome and two or more X chromosomes have the Klinefelter syndrome. Approximately 20 percent of individuals with this condition have gynecomastia and a higher percentage have palpable parenchymal breast tissue.11 Gonadal tumors rarely occur in these patients regardless of chromosomal complement, but the incidence of breast carcinoma in Klinefelter males is 20 times that of normal males and about one-fifth that of normal females.26,78,86

The multiple endocrine neoplasias, which are characterized by some combination of medullary thyroid carcinoma, pheochromocytoma, parathyroid disease, pituitary adenomas, pancreatic islet cell adenomas and mucosal neuromas, are among the most extensively studied familial endocrine cancer syndromes.5,59,46,77 The mechanisms underlying their development, however, have not been defined.9 Pearse has postulated that the majority of tumors in each syndrome arise from a specific cell series termed "APUD" (Amine Precursor Uptake and Decarboxylation), which defines a group of peptide hormone secreting cells possessing the biochemical capacity to take up biogenic amine precursors and convert them to amine neurotransmitters through decarboxylation.56,69,96 Pearse et al theorize that most peripheral endocrine cells with APUD characteristics originate embryologically from the neural crest.69,70

New evidence, however, suggests that the tissues involved are not only of neural crest origin but originate from specialized neural ectoderm, including the neural ridges, the neural crest and the neural tube.24,70 Pearse has suggested that the differences in the clinical manifestations between multiple endocrine neoplasias might be attributed to the events occurring in the embryonic neural crest at the time of their development.56,69,70 Lynch et al speculate on the existence of a series of dominant genes, each determining specific events in the embryologic differentiation of the neural crest which, by mutation, could give rise to the entire range of neuroectoderm-related disease.56

Some familial cancers, including the multiple endocrine neoplasia (MEN) syndromes, may be characterized by a variety of cutaneous lesions.9,56 Approximately 50 genetic disorders demonstrate
an association between cutaneous abnormalities and cutaneous or internal malignancy. Lynch et al suggest that a unifying etiologic concept might explain certain clinical findings in these conditions based on their common origin in the neural crest and relating to a specific developmental stage of gene action, such as neural crest differentiation. For example, Von Recklinghausen's neurofibromatosis, Von Hippel-Lindau disease and tuberous sclerosis share an increased risk for the development of pheochromocytoma with the MEN syndromes, although they are not primarily considered to be hereditary endocrine tumor disorders.

Although the MEN syndromes may develop as a consequence of a defect in a single cell system or embryologic structure, the precise nature of the abnormality remains undefined. The two mutation model proposed by Knudson, postulating the origin or retinoblastoma and the pheochromocytoma of MEN-II through two mutations has been suggested. Alternatively, an interaction between immunologic, viral and genetic factors has also been suggested and is supported by the results of a study in relatives of patients with familial medullary thyroid carcinoma who were found to have cell-mediated immunity to thyroid carcinoma antigens. Comparable results have been found in families of patients with neuroblastoma and in household contacts of patients with sarcoma or carcinoma of the breast.

References


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