The Role of Genetics in Human Cancer

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Why does a cell undergo transformation and acquire a new characteristic of uncontrolled growth? One popular hypothesis, the somatic mutation theory, attributes the change to an alteration in the genetic apparatus of a cell, either at the gene or chromosome level. Viruses, which have been proposed as an important causative factor in some cancers, would also be somatic since the genome of a virus may interact or become integrated into the genome of the host cell. In either case, the genetic change is confined to the host. The genetic apparatus of a germinal cell may also undergo alteration or mutation. The mutation would not be confined to the host but could be transmitted, via the mutated germ cell, to the resultant offspring who would be predisposed to cancer.

Evidence for Germinal Mutations

Germinal mutations at the gene level are known to cause inherited susceptibility to a variety of neoplasms in experimental animals. However, in man, this concept apparently has not been fully accepted or appreciated. Cowdry has stated that inherited susceptibility to cancer in man is not so noticeable or frequent as in animals.1

Since the seventeenth century, many cases have been reported showing familial aggregations of cancer.2 However, because of problems in data collection and analysis as well as the lack of controls, these findings have generally been considered as curiosities or of little genetic value. In an attempt to avoid such criticisms, more recent studies have utilized a retrospective statistical approach, comparing the rate of cancer in the relatives of patients with a specified neoplasm with controls or with expected rates based on general population statistics. These numerous studies have not provided unequivocal evidence of inherited susceptibility to human cancer,3 regardless of the disparate source of patients or controls, type of cancer, type of data (i.e., morbidity and/or mortality statistics), type of investigative protocol or statistical analysis. Comparative studies of monozygotic and dizygotic twins, which theoretically can indicate the importance of a genetic basis, have also failed to provide definitive evidence of a genetic component in human cancer.
cancer. The general inconclusiveness of past studies may have helped nurture the impression that "... there is little factual information to support the concept that [hereditary] factors have an influence on neoplasms in man."4

The classic examples of inherited cancers are multiple exostoses, polyposis coli syndromes, retinoblastoma, von Recklinghausen's neurofibromatosis, and xeroderma pigmentosum. However, heritable cancers are now known to occur at virtually every major cancer site or organ category of man, including the common cancer sites or organs, 5-9 (Table 1.) The number of heritable cancers may widely vary for a specific site or organ. The question, therefore, is not whether cancer can be inherited, but how it is inherited, and how such cancers are clinically distinguishable from the noninheritable types. More importantly, how do cancer susceptibility genes act?

**A Two-Step Mutation Model for Childhood Cancer**

A hypothesis has been developed by Knudson to explain the occurrence of cancer in heritable and nonheritable forms. 10,11,12 This model is based on the assumption that cancer is caused by two mutational events and that cancer arises from a single cell. When the first mutation occurs in a germ cell, the mutation will be present in all cells of the resultant individual and will be hereditary. The gene carrier may develop none, one or multiple tumors; the number will follow a Poisson distribution. If the first mutation is somatic, it will be confined to a single cell and the cancer will be nonhereditary. The second mutation is always somatic in both the hereditary and nonhereditary types. Thus all tumors require two mutational events. In the hereditary form, the first event has already occurred and is present in all cells; therefore, only a single second event is necessary for tumor development. Hereditary tumors will occur at an

| Table 1. Heritable and Nonheritable Tumors, According to Site |
|------------------|------------------|
| Site             | Type             |
| Skin             | Basal cell carcinoma  |
|                  | Squamous carcinoma  |
|                  | Keratoacanthoma    |
|                  | Malignant melanoma  |
|                  | Glomus tumor       |
| Nervous system   | Acoustic neuroma   |
|                  | Neurofibroma       |
|                  | Nonchromaffin para-ganglioma (chemo-dectoma) |
|                  | Medulloblastoma    |
| Eye              | Melanoma          |
|                  | Retinoblastoma     |
| Bone & connective tissue | Paget's disease of bone |
|                  | Chondrosarcoma     |
|                  | Sarcoma (bone & soft tissue) |
| Reticuloendothelial system | Leukemia         |
|                  | Lymphoma          |
| Breast           | Carcinoma of breast |
| Endocrine system | Medullary carcinoma of thyroid |
|                  | Adenoma of parathyroid |
|                  | Pheochromocytoma   |
|                  | Islet cell carcinoma of pancreas |
|                  | Neuroblastoma      |
| Urological system| Renal cell carcinoma |
|                  | Wilms' tumor       |
|                  | Adenocarcinoma of prostate |
| Genital system   | Papillary cystoadeno-carcinoma of ovary |
|                  | Adenocarcinoma of endometrium |
|                  | Dysgerminoma       |
|                  | Gonadoblastoma     |
|                  | Teratoma           |
| Digestive system | Squamous carcinoma of esophagus |
|                  | Adenocarcinoma of stomach |
|                  | Adenocarcinoma of colon |
|                  | Carcinoid          |
|                  | Liver cell carcinoma |
|                  | Embryonal hepatoma (hepatoblastoma) |
earlier average age than nonhereditary tumors, and will likely be multiple. The nonhereditary type will be late and single in occurrence, since it requires two infrequent mutational events for tumor development in a single or derivative cell.

This two-step mutation model has been applied to existing data on retinoblastoma,10 Wilms' tumor,11 neuroblastoma and pheochromocytoma.12 The hereditary forms of these tumors occurred earlier and manifested significantly increased frequencies of bilateral and/or multiple tumors compared with the nonhereditary forms. The incidence of a germin al mutation was estimated to range from 22 percent for all cases of neuroblastoma and simple pheochromocytoma to 39 percent for Wilms' tumor, and 40 percent for retinoblastoma. (Table 2.) In retinoblastoma, the data followed a Poisson distribution. The model predicted an average of three retinoblastomas per gene carrier (multiple tumor foci in one or both eyes), distributed so that five percent of gene carriers would develop no tumor, 35 percent would develop a unilateral tumor, and 60 percent would develop bilateral tumors.10 The observed frequency of gene carriers who developed no tumor was one to 10 percent, 25 to 40 percent for unilateral tumors, and 60 to 75 percent for bilateral tumors. There is obvious close agreement between predicted and observed frequencies. The germin al mutation rate was estimated at 5 x 10^{-6} per generation, and the rate of the second somatic event was similar. Other childhood cancers to which the model was applied have also indicated close agreement between observed and expected results.8,11,12 Knudson proposed that perhaps all childhood cancers will fit the two-mutation model,8 and furthermore that all bilateral and multiple cases of childhood cancers are probably the consequence of a germin al mutation.

**Table 2. Hereditary Rates of Childhood Cancers**

| Tumor             | Incidence | Hereditary Fraction | Avg. No. tumors per gene carrier |
|-------------------|-----------|---------------------|----------------------------------|
| Retinoblastoma    | 5 X 10^{-5} | 0.40               | 3                                |
| Wilms' Tumor      | 10 X 10^{-5} | 0.38               | 1                                |
| Neuroblastoma     | 7 X 10^{-5}  | 0.22               | 1.2                              |
| Pheochromocytoma  | 10 X 10^{-4} | 0.22               | 3                                |

*Modified from Knudson, et al.8

**Mutation Model and Adult Cancers**

The two-step model may also apply to adult cancers. Again, all identified heritable cancers are characterized by early onset and tumor multiplicity. The average age at diagnosis is several years or even decades earlier than the nonheritable or sporadic forms.5,6,8 For example, the average age at diagnosis for a hereditary form of basal cell carcinoma is 15 years while the average age at diagnosis for nonhereditary basal cell carcinoma is 50 years. As another example, medullary thyroid carcinoma is usually
first detected at 45 to 50 years of age; its heritable form, Sipple's syndrome, is usually first detected at about 30 years of age. Hereditary adenocarcinomatosis, a heritable form of colon cancer, is first detected at about age 40, again well below the usual detection age for colon cancer. A heritable form of breast cancer is also detected at an early age. (Fig. 1.) Moreover, the heritable forms of adult cancers, similar to childhood cancers and in agreement with the two-step model, exhibit a distinct tendency to develop at multiple sites of an organ or wherever a certain tissue type exists in the body.3,6,8 (Fig. 2.) The high frequency of multiple tumors in gene carriers is not related to the early age of onset of the primary, since subsequent tumors also occur at an earlier age than in the general population.

Because the adult forms of heritable cancers have characteristics similar to the childhood cancers, it is theorized that perhaps most patients with early onset and multiple cancers have the disease as a consequence of an inherited germinal mutation. Not all such patients give a positive family history of a cancer, because penetrance could be incomplete, or the gene carrier could die before manifesting cancer, or the patient could carry a new mutation.8 If the genetic defect is transmitted to offspring, their likelihood of ultimately developing a specific cancer could be as high as 50 percent.

The model may also apply to some of the common cancers. The risk of breast cancer developing in relatives of a patient is high when the patient has premenopausal and bilateral breast cancer and not when she has postmenopausal and unilateral cancer.9,13 This early and multiple disease, which tends to occur in direct descent through two or more gen-

![Fig 1: Age distribution of diagnosis of hereditary and nonhereditary forms of breast cancer](image-url)
erations, certainly seems to be inherited, much more so than the late and unilateral type. There are other heritable forms of breast cancer. One occurs in association with leukemia, sarcoma, brain tumors, and perhaps other neoplasms, and tends to follow a dominant inheritance pattern. Another heritable form involves breast cancer occurring in association with gastrointestinal and/or ovarian carcinoma; it is also dominantly inherited. Some inherited breast cancers may result from impaired estrone and estradiol hydroxylation by aryl hydroxylases. It has been estimated that 30 percent of all breast cancers are hereditary.

From the evidence presently available, it appears that (1) childhood and adult cancers occur in heritable and non-heritable forms at virtually all sites; (2) the heritable forms, particularly in cases of breast cancer and colon cancer, may be more frequent than is generally suspected; (3) the heritable forms have an early average age at onset and tend to be bilateral or multiple; and (4) the heritable forms that have been studied so far fit the two-step mutation model. Thus all early and multiple-occurring tumors, whether in children or adults, may be the consequence of an inherited germinal mutation.

Nature of Genetic Susceptibility

How these germinal mutations or cancer susceptibility genes act in the development of cancer is unknown, except for one heritable condition, xeroderma pigmentosum. This recessively inherited condition causes extreme sensitivity to sunlight and predisposes the individual to the development of multiple cutaneous neoplasms early in life. Once

| Non-Hereditary | Hereditary |
|----------------|------------|
| Neuroblastoma | Medullary Thyroid Ca |
| Retinoblastoma | Compound Pheochromoctomona |
| Adenocarcinomatosis | Simple Pheochromocytoma |
| Chemodectoma | Breast Cancer |
| Melanoma | Nevoid Basal Cell Ca |
| Wilm’s Tumor | 97% |
|                  | 87% |
|                  | 57% |
|                  | 97% |

Fig. 2. The percent frequency of multiple primaries in hereditary and nonhereditary forms of neoplasms.
again the characteristics of early onset and multiplicity should be noted. This disorder results from a deficient enzyme that is required to repair DNA damaged by ultraviolet light. Patients with heritable disorders, such as ataxia telangiectasia, Bloom’s syndrome, and Fanconi’s aplastic anemia, exhibit increased frequencies of leukemias, implicating chromosomal imbalance and instability. In breast cancer, a specific enzyme inefficiency or deficiency, i.e., an impaired estrone and estradiol hydroxylatation to estriol by aryl hydroxylases, has been proposed. Beyond these general types of associations, the nature of the genetic defect in the various heritable cancers still remains an unresolved question.

Practical Aspects

Since the majority of heritable cancers are dominantly inherited, early detection and genetic counseling is important. Patients with such tumors should be made aware that approximately half of their children will be susceptible to the same tumor. These patients are also apt to develop multiple primaries in the same or other organs and should be periodically examined. In Sipple’s syndrome, for example, medullary thyroid carcinoma is almost always bilateral, and the utility of partial thyroidectomy is questioned.

Gene carriers with Sipple’s syndrome can now be identified before the thyroid tumors become clinically evident by a radioimmunoe assay for serum calcitonin. Thyroid tumors, some of which were microscopic foci, were detected in 13 patients who had abnormally high calcitonin levels after calcium gluconate infusion. Seven of the 13 had no prior clinical abnormality of the neck to suggest a thyroid tumor, and the remainder had palpable tumors apparent to the examining physician but not to the patients themselves. This assay procedure demonstrates the real possibility of detecting tumors in gene carriers while the tumors are still in a very early stage of development.

A detection program for individuals with family histories of common neoplasms is feasible. A small scale detection program is presently under way at this institution involving women at high genetic risk for breast cancer. These women are examined clinically as well as by xeroradiography and thermography. To date, out of 75 women, two were found to have carcinoma. The average age of the entire examined group was 40 years. In a much larger survey being conducted at this institution by the Department of Radiology, four proven cases of cancers have been detected in 630 nonhospitalized women by thermography and xeroradiography, a crude detection rate of 0.6 percent.

In another program, individuals at high risk for colon cancer because of their family histories are being evaluated by a physical examination, proctoscopy and air contrast barium enema studies. Women in this group also receive gynecologic and breast examinations including xerographic and thermographic surveys. Asymptomatic adenocarcinoma of the colon was newly detected in four of 89 individuals. The average age of all examined individuals was 36 years. The colon cancer detection rate was 4.5 percent, especially significant considering the relatively young age of the examined individuals. It is reasonable to assume that periodic examination of individuals at high risk of a heritable tumor will result in the detection of tumors at an earlier and more easily treated stage than is presently possible when detection is based on signs and symptoms.
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Training the Physician for Tomorrow

The idea that the health of the American people will benefit from an all-inclusive streamlining and acceleration of the educational production line is an example of grasshopper thinking: an erratic and often frantic hopping in response to the stimulus of the moment, and with little thought where subsequent hops might take you. So when doctors are in short supply, you jump to the immediately obvious solution. You just make more of them. And the doctor you put out is a chromeplated if somewhat cheaper version of the doctor who served so well in the good old days. How will the doctor so trained cope with the changing scene of advancing technology and social change. . . . These are the realities of tomorrow, and in their kind of world the graduate of an abbreviated and “more practical” medical education system may indeed be just another health worker, possibly one with a civil service rating above a well-trained medical assistant. He may indeed be all too apt to perform with his hands what the computer’s “brain” tells him to do. He may, like a well-trained pup, heel well as an obedient functionary of the state, but he will be a poor healer. —"Training the Sufficient Physician for Tomorrow," an editorial in The New England Journal of Medicine 284: 390, 1971.