Familial Susceptibility to Cancer

The Editor interviews:
David E. Anderson, Ph.D.
Professor of Biology,
The University of Texas
System Cancer Center
M.D. Anderson Hospital and
Tumor Institute
Houston, Texas.

Editor: *Does a family history of cancer increase an individual’s risk of developing that cancer?*

Dr. Anderson: A number of retrospective studies conducted primarily during the first half of the century provided evidence indicating that a family history of a certain neoplasm could increase the risk for this cancer in first-degree relatives.

Editor: *What specific sites were associated with these increased risks?*

Dr. Anderson: Relatives of patients with cancer of the stomach, breast, large intestine, uterus, lung, childhood brain tumors and sarcomas were found to have two- to fourfold increased risks compared with control relatives or the general population. Results of studies on prostatic cancer and leukemia were equivocal. However, a recent consanguinity study in Japan suggests that genetic factors play an important role in the etiology of leukemia occurring in siblings. Retrospective studies on esophageal or cervical carcinoma revealed no significant excesses in familial risk.

These increased risks only applied to the patient’s type of cancer and not to cancer in general.

Editor: *Could exposure to environmental carcinogens be responsible for these increased risks or familial aggregations of cancer?*

Dr. Anderson: Probably not, since spouses of patients or spouses and their matched controls did not exhibit an increased incidence of the neoplasm under investigation. Furthermore, when the environmental factor was dissociated from the familial factor, as in Tokuhata and Lilienfeld’s interesting study on lung cancer, a genetic component was still discernible.

Editor: *How does familial susceptibility to lung cancer interact with the known carcinogenic effects of smoking?*
Dr. Anderson: In the absence of smoking, the lung cancer mortality rate among first-degree relatives of lung cancer patients was four-times higher than among control relatives. Without a family history of lung cancer, the mortality rate among smokers was five-times higher than non-smokers. The combined effect of smoking and the familial factor resulted in a 14-fold excess in lung cancer mortality, compared with control relatives who did not smoke. Air pollution was ruled out as a possibility for the increased risk, because experimental and control groups were matched according to neighborhood. Both groups should thus have had similar exposures.

Editor: Results of the lung study suggest that cancer may have heterogeneous etiologies.

Dr. Anderson: This is correct, because cancer is a heterogeneous disease. In fact, the assumption that cancer of a particular site was a single, homogeneous disease entity was one of the deficiencies of the early retrospective studies and even of comparisons of monozygotic and dizygotic twins. It is well known that cancer of a given site can be classified into various histologic types, which may have different etiologic mechanisms.

Editor: Does this imply that the findings of the early retrospective studies were fallacious?

Dr. Anderson: Not necessarily fallacious, but they significantly underestimated the role of familial susceptibility. For example, previous retrospective studies on breast cancer revealed a twofold to threefold increased risk for the disease in first-degree relatives. Yet, when breast cancer was assumed to be heterogeneous and patients were classified into more homogeneous groupings, according to their age at diagnosis and type of family history, the risks for the relatives of some groups of patients increased to levels as high as ninefold or 47-fold greater than that experienced by women in the general population.

Editor: How then can the role of familial susceptibility to cancer be most effectively determined?

Dr. Anderson: The evaluation of single families or pedigrees is the most satisfactory and meaningful approach for demonstrating familial susceptibility to cancer. One important advantage is that it bypasses the problem of heterogeneity. Pedigree studies have been criticized on the ground that resulting data are biased, but this problem can be overcome when families are unselected and aggregation is detected only by continued study.

Editor: Have the pedigree studies conclusively proven that some cancers are inherited?
Dr. Anderson: Yes. This approach has identified a variety of neoplasms that show familial distributions that are consistent with Mendelian inheritance patterns. Even more significant, observation of single families has led me and other investigators to conclude that not only do certain cancers show a genetic basis, but that virtually all cancers in man occur in a heritable as well as a nonheritable form.

Editor: Do heritable tumors also exhibit a high degree of heterogeneity?

Dr. Anderson: They do. For instance, breast cancer may include at least five hereditary types, and the colon may involve as many as 14 hereditary types, all resulting in adenocarcinomas. Some heritable tumors develop secondarily to certain hereditary conditions, such as adenocarcinoma of the colon arising in association with familial polyposis coli or Gardner’s syndrome. Lymphomas may develop in association with various inherited immunodeficiency diseases. Then, too, there are some heritable cancers that develop independently of any pre-existing state or premalignant lesion.

Editor: How can heritable tumors be identified?

Dr. Anderson: Pedigree studies have suggested two primary characteristics specific to heritable tumors. One of these characteristics is early age at onset or diagnosis. A heritable tumor usually occurs several years or even decades earlier than the same neoplasm in the general population. For instance, 50 years is the average age of onset for patients with basal cell carcinoma, while a dominantly inherited form, as in the nevoid basal cell carcinoma syndrome, develops at an average age of 20 years. (Figure.) Medullary thyroid carcinoma is generally first detected in patients 45 to 50 years old, but a heritable form, Sipple’s syndrome, is first diagnosed at about 30 years of age. The heritable forms of colonic adenocarcinoma occurring independently of polyps first occur in patients 40 to 45 years of age, well below the average age in the general population. Early ages at onset or diagnosis also characterize the heritable forms of malignant melanoma and breast cancer.

Editor: What other characteristics do heritable tumors exhibit?

Dr. Anderson: The other of the two primary characteristics is the tendency of heritable tumors to develop at multiple sites in the same organ or bilaterally in paired organs. The frequency of multiple primary tumors in patients with a family history of cancer is probably larger than current estimates, because we have little information on the incidence of multiple tumor foci or multicentric tumors in a single organ.

Another characteristic of familial neoplasms, primarily those
with a strong genetic effect, is their limited range of phenotypic expression. Affected family members usually develop either: (1) the same type of neoplasm in a single site or tissue system, such as the hereditary forms of non-chromaffin paraganglioma and malignant melanoma; (2) a single histologic type of cancer in various sites or organs, as in hereditary multiple cancers of the colon and uterus; or (3) different types of tumors in one organ system, for example, Sipple’s syndrome or multiple endocrine adenomatosis.

Editor: *Can early age at diagnosis be considered the consequence of early detection in a cancer conscious family?*

Dr. Anderson: Yes, in part. However, even second primary heritable tumors
Dr.

Editor: 

Is it possible that the frequency of multiple heritable tumors might be attributed to a longer period of risk?

Dr. Anderson: 

This is apparently not the case, since second or third primary heritable tumors occur at an earlier average age than do the nonheritable types of the same tumor. I might add that tumor onset in inbred strains of mice with high frequencies of a certain neoplasm is earlier than that in resistant strains. Also, the susceptible strains have high frequencies of multiple tumors, comparable to the human situation.

Editor: 

Can these characteristics—early age at onset, multiplicity of tumors and limited phenotypic expression—serve to distinguish between heritable tumors and those cancers arising from environmental exposure to a carcinogen?

Dr. Anderson: 

Although these characteristics may apply to some tumors resulting from environmental exposure to carcinogens, such as mesothelioma among asbestos workers and leukemia following radiation or benzene exposure, such occurrences can usually be identified either by the uniqueness of the tumor type or by adequate medical and occupational histories. Generally, however, a genetic basis results in similar ages at diagnosis, whereas common exposure to an environmental carcinogen results in similar times of onset, as is sometimes seen in Hodgkin’s disease. Highly variable ages of onset of diverse tumor-types among even distant relatives suggests a heterogeneous etiology.

Editor: 

Through what mechanism do heritable tumors develop?

Dr. Anderson: 

Knudson developed a model to explain the occurrence of heritable and nonheritable cancers, based on the assumption that cancer arises from a single cell and is caused by two mutational events. The first event may be prezygotic or postzygotic, but the second event is always postzygotic. When the first mutation is prezygotic and occurs in a germinal cell, the mutation may be transmitted via the zygote and will be present in every cell of the recipient, and will be hereditary. The gene carrier may develop zero, one, two or more tumors in accordance with a Poisson distribution. When the first mutation is postzygotic and occurs in a somatic cell, the mutant will be confined to a single cell and all subsequent daughter cells, and will not be hereditary. Since one mutation has occurred in the heritable type and is present in all cells, only a single second event is necessary for tumor development. Consequently, the heritable tumor will be early and frequently occur earlier than usually encountered in the general population. Also, relatives tend to resemble one another in their age at diagnosis to a greater degree than unrelated individuals. Early age of onset among relatives thus appears to be a biologic characteristic of neoplasms involving a heritable component.
multiple. The nonheritable type, however, requires two infrequent mutational events in a single cell and will thus be late and single in occurrence.

Editor:  
*Has this two-step model been tested?*

Dr. Anderson:  
The model has been applied to retinoblastoma, Wilms’ tumor, neuroblastoma and pheochromocytoma with excellent agreement between the observed and expected numbers of gene carriers with zero, one, two or more tumors. As predicted with the model, the gene carriers were found to have an early age at onset and a high incidence of multiple tumors, compared with patients with the nonheritable forms of the same tumors. Furthermore, the fraction of surviving patients with a heritable tumor shows a linear decline with time, implying that a single event was occurring at a constant rate in a declining population of embryonal cells, therefore agreeing with a single-hit hypothesis. The nonhereditary cancers, however, showed a more curvilinear decline with time, implying a two-hit curve. It has been proposed that perhaps all bilateral or multiple cases of childhood cancers are the consequence of a germinal mutation.

Editor:  
*Do heritable cancers in adults also follow the model?*

Dr. Anderson:  
The two-step model may also apply to adult cancers, which are similar to childhood cancers in that they occur in heritable and nonheritable forms. The heritable adult forms also have significantly earlier ages at diagnosis than the same neoplasm in the general population, and they exhibit a distinct tendency to develop at multiple sites, features that are expected with the two-step model. However, the model has not been applied to tumors that arise secondarily to an inherited disease. Whether the two-step or a more complex model can be applied in these cases must still be investigated.

Editor:  
*How do gene mutations act?*

Dr. Anderson:  
Unfortunately, in familial neoplasms where the genetic influence on tumor development is direct, little or no evidence is available on the mechanisms of gene action. In neoplasms that arise secondarily to an inherited condition, such as immune deficiency diseases that predispose patients to reticuloendothelial cancers, the effect seems to be related to the production of a defective or immature cell. This cell has an immune or surveillance function that is impaired, and/or an enhanced likelihood of undergoing malignant transformation following exposure to some environmental stimulus.

Editor:  
*Can familial susceptibility to certain cancers be anticipated even in the absence of any definitive information on the underlying mechanism?*
**Dr. Anderson:** High-risk individuals can be identified through pedigree analysis that pinpoints those patients in a direct line of descent for susceptibility genes to heritable tumors. For example, we know that premenopausal relatives of patients with premenopausal and/or bilateral breast cancer whose mothers were also affected have a higher risk of developing this cancer than relatives of patients with postmenopausal and/or unilateral disease whose mothers were unaffected. However, studies are still required to more precisely determine the empiric risks of certain tumor constellations in relatives.

**Editor:** *Can you suggest other areas for future study?*

**Dr. Anderson:** We would like to be able to identify genetic and chromosome markers that will provide a handle for identifying high-risk family members.

**Editor:** *And for the present?*

**Dr. Anderson:** Periodic examination of individuals at high risk for heritable tumors is essential and will result in the detection of these cancers at earlier and more curable stages. In addition, members of families with a history of heritable cancer should be counseled on the possible genetic transmission of cancer susceptibility genes and the risks of subsequent cancer, because these risks can be as high as 50 percent.

**Editor:** *Thank you, Dr. Anderson.*