CHAPTER 5 - INHERITED CANCER SYNDROMES

A small but significant fraction of human cancer cases are caused directly and specifically by inherited genetic factors. In some instances, the types of tumors found in these inherited cancer syndromes are rare or unusual; in others they are indistinguishable from the more common sporadic forms of non inherited tumors. The main features that differentiate most inherited cancers from sporadic cases are earlier age of onset, and a strong family history (usually two or three cases in first degree relatives) of the same tumor type and pattern. In a family where two brothers both develop colon cancer below the age of 40, and one of their uncles died of the same disease at age 45, there is a strong likelihood for the existence of an inherited cancer syndrome in the family. On the other hand, a person whose mother dies of breast cancer at age 73, and whose father dies of prostate cancer at age 82, is probably not a member of a cancer syndrome family, since at these ages the frequencies of these cancer types are common enough that two or more could occur in the same family simply by chance.

The situation vis a vis inherited cancer syndromes is complicated by the fact that these diseases vary widely in their degree of penetrance, their modes of genetic transmission, and their accompanying symptomology. Some genetic diseases that are not primarily cancer susceptibility syndromes, may be associated with increased cancer incidence as a relatively minor aspect of the disease. The variation in penetrance for the different cancer syndromes means that some families may have only a somewhat higher level of cancer than that seen in the average population, and this slightly higher incidence may be due to one or more inherited low penetrance genes. Although clearly genetics plays a role in the individual susceptibility to cancer in members of these families, that role is not sufficient to include such cases under the heading of cancer syndromes. In contrast, the syndromes to be discussed in this chapter are more clear cut, and represent a much more serious problem for the affected families, since the members of these families have a high risk of succumbing to some form of cancer at a relatively early age. While fortunately the incidence of these syndromes in the Western population is rare, taken together they may account for 5% of cancer deaths, and a much higher proportion of cancer at early ages.

CHILDHOOD CANCERS

Cancer is generally a disease of old age, and rarely strikes people below the age of 50. There are however important exceptions, such as brain tumors, leukemias and lymphomas, which show peaks of occurrence in childhood and young adulthood. The etiology of childhood cancers presents a challenge to researchers. As discussed previously, it is difficult to reconcile the idea of a 20 year latent period after exposure to an environmental carcinogen with the occurrence of leukemia in an infant or young child. Genetic factors have therefore been carefully investigated for many of the childhood cancers, and for some, such as retinoblastoma and Wilms tumor, specific inherited genetic defects have been discovered. It is important in this
context to stress an important mechanistic difference between inherited cancer cases and sporadic cancers at any age. In inherited cancers, by definition the gene mutation or other defect is found in the germline. This means that the affected subject is born with the genetic defect in every cell in the body. It also means that the same defect can be further passed on to the subject’s children. The type of cancer, the age of onset, and the prognosis, all depend on the specific syndrome, and sometimes on other factors such as environmental influences. In contrast to this situation, sporadic cancer cases may result from the very same mutation in the same gene, however this mutation is not inherited, but acquired after birth in one or a few somatic cells of the body. Such genetic defects are not therefore further transmitted to offspring.

Many cases of early childhood cancer probably result from the latter type of genetic damage, although in many other cases there may be a combination of an inherited susceptibility factor, combined with a somatic mutation. The pattern of the 2 hit tumor suppressor gene mutation, such as that described above for retinoblastoma, is an example of an inherited gene defect that produces an extremely high susceptibility to cancer in early childhood.

GENETICS OF INHERITED CANCERS

The most important advances in understanding of inherited cancer have been the identification of the precise genetic defects responsible for many of these diseases. This knowledge has also contributed to our understanding of the mechanisms of sporadic carcinogenesis. From a clinical point of view, it has allowed many families to resolve uncertainties about their situation with respect to a specific possible cancer syndrome in the family by means of simple genetic tests.

It isn’t possible to cover all the inherited cancer syndromes in detail in this chapter. Table 5-1 gives a list of some examples of known inherited cancer susceptibility syndromes. In some cases the frequencies in the population, and the genes responsible for their etiology are also presented. The Table is divided into 2 sections. The first presents information on inherited syndromes that produce common cancer types. The second part lists diseases that include cancer susceptibility as one of many symptoms of an inherited disease. Examples of both types of inherited cancer susceptibility syndromes will be further discussed in more detail below. These include syndromes responsible for two forms of common cancer types, namely colon and breast cancer, and some examples of rarer cancer types caused by cancer syndromes that have been intensively investigated, and about which a great deal of molecular mechanistic information has been obtained.