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# Genetics and Cancer*

**W. K. Cavenee, B. Ponder and E. Solomon**

## INTRODUCTION

THE CURRENT issues of *Cancer Surveys* [1, 2] bring up to date our present knowledge on cancer and genetics.

The first issue of *Cancer Surveys* [3] was devoted to inherited susceptibility to cancer. In the years since then progress—and interest in the subject—has been enormous. It is interesting to reread the 1982 issue and see the major developments of the next few years already foreshadowed and particularly to note the title of the last paper in that volume, by Ray White: "DNA polymorphisms: New approaches to the genetics of cancer". The bar to progress in 1982 was that apart from a few candidates such as HLA, there were no real clues as to what the genes involved in cancer susceptibility might be; and the only way to make an empirical search for them by genetic linkage was frustrated by lack of linkage markers. Since then the use of DNA polymorphisms has allowed the rapid development of the human genome map; and it is no accident that the genetic loci for six of the inherited cancer syndromes were mapped for linkage in a single year (1987–1988) as the map reached a critical level of definition.

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## CANCER GENES

Exciting as these developments are they are only the very beginning. As several of the chapters in this volume show, moving from a genetic linkage for a cancer gene to the gene itself can be a slow and difficult business. Even when the gene itself has been identified—as in retinoblastoma, Wilms' tumour and neurofibromatosis type 1 (NF-1)—elucidation of the function of the normal gene and an explanation of the disease phenotype in terms of altered gene function remains a challenge. In NF-1, for example, it will be necessary to explain how the inherited inactivation of one copy of a gene which normally is apparently widely expressed and which probably is active as part of the *ras*-GTP signalling pathway can result in a huge range of possible phenotypic abnormalities in specific tissues, which range from a failure of development of a segment of one tibia (pseudoarthrosis) through melanocytic abnormalities (cafe au lait spots) to benign tumours of the optic nerve. The tools exist to provide a description of these genes at the level of the molecular biology of an individual cell: but how clearly this will point the way to an explanation in terms of the biology of a tissue or the whole organism is yet to be seen.

The predisposing genes that so far have been mapped are those for the so-called "inherited cancer syndromes" where the familial pattern of the disease is so clear-cut as to make genetic linkage easy. Numerically more important are the common cancers which tend to occur in familial clusters, such as breast, ovarian and colorectal cancers. An achievement of the past few years has been to set up large population-based studies of these cancers and to develop the statistical methods to analyse them.

In this way, the probable role of inherited predisposition has been more clearly defined (as discussed by Peto and Easton; King; Bishop and Thomas, this volume). This done, the same techniques of genetic linkage with DNA polymorphisms have been applied to search for the putative genes; and the first probable success (in families with young-onset breast cancer) is described by King in her chapter. An immediate problem with this group of cancers (apart from finding the gene itself and elucidating its function) will be to determine what proportion of cancers are due to predisposition at a given locus. Different loci may be involved in different families; furthermore because classical methods of genetic linkage need large families with several affected members, there may be a bias towards detecting only rare genes of "strong" effect (that is, most people who inherit the gene develop the cancer). In principle, a significant proportion of inherited predisposition in populations could also be due to commoner genes of "weaker" effect, which will seldom result in striking family pedigress. Until the genes themselves are cloned and mutations can be sought directly this question may be difficult to resolve.

## "CANCER FAMILIES"

The recognition of "cancer families" allows the identification of a group of family members at hight risk; and with genetic markers, identification is becoming easier and more precise. What can be done for these people? In many of the inherited cancer syndromes described in this volume, risks are clear, screening is effective, and surgical treatment is available. For the more numerous individuals with a family history of common cancers, though, especially women with a family history of breast or ovarian cancer, risks are less clear, screening is of unproven effectiveness, and prophylactic surgery may be unacceptable. As more and more women and their doctors become aware of the possible significance of family history, it is already a major challenge to develop and evaluate better methods of screening, and ultimately to use understanding of the mechanisms of predisposition to devise new methods for prevention or treatment.

## GENETIC ANALYSIS

Exciting as these advances in our understanding of cancer predisiposition are, they are only one element in the developing molecular genetic analysis of disease. The identification of genetic defects that occur primarily in low or high stage disease offers an opportunity for a new set of laboratory-based estimates of the progress of the malignant process. This approach is outlined in this volume by James *et al.* for astrocytic tumours and more dramatically by the successes in management of childhood neuroblastoma accomplished by Brodeur and his colleagues. Clearly, the development of rapid methods of obtaining this information that are suitable for the surgical pathologist is a field likely to blossom in the next years. Yet another application for genetic analysis of tumour tissues is in differential diagnosis. Tumours of different types respond differently to therapeutic approaches. Emerging information suggests that in many cases the success of treatment is limited by our ability to identify variants among tumour types and match them to the appropriate therapy. Genetically based diagnosis may significantly enhance the efficacy of the weapons we already have in hand. Thus genetic analysis of human cancer is showing itself not only to be capable of unlocking some of the secrets of the disease be also to have high predictive and diagnostic value, applications that were only a hope just a few years ago.

## PREDISPOSING GENES

In the longer term, the best prospects for prevention of cancer deaths from an understanding of inherited predisposition will probably come not from "cancer families" but from investigation of common predisposing genes with less striking effects. If a predisposing gene causes cancer in only a minority of individuals who inherit it family clusters will be rare; but (as discussed by Peto and Easton, this volume), such a gene can have the effect of concentrating most of the incidence of a specific cancer in a minority of the population. This predisposed minority would be an obvious target for screening or prevention. The limiting factor is that our knowledge of likely predisposing genes to test is at present so poor. The major progress of the past few years has come from the human gene map, which has enabled us to exploit genetic linkage in families to search for genes empirically, without knowledge of their function. Although statistical methods are being developed for genetic linkage in "families" which consist of only a pair of affected relatives, an empirical search in such material is likely to be difficult and tedious. Progress may more easily come from the exploration of genetic variation in candidate genes, for example those involved in carcinogen metabolism, discussed by Wolf (this volume). If this is successful, we can look forward to an expanding genetic epidemiology of the common cancers, which will help us to identify both the critical carcinogens and the individuals who are most susceptible.

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