Studies on the clinical genetics of cancer
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Summary and Future Perspectives

Summary

The revolutionary progress in molecular genetics of hereditary cancer is pushing the clinical genetics of cancer into an accelerated development. For a discussion of the issues involved, it is important to clarify the vocabulary. Therefore, in chapter 1 of this thesis a list of definitions is given for frequently used notions in the clinical genetics of cancer. From the review presented in chapter 2 it is clear that many types of cancer may be associated with a human cancer syndrome. To assess the possible presence of one of these syndromes in a cancer patient and his or her family, the family history generally plays a central role. Unfortunately, the contribution of the family history to the genetic diagnosis is limited by its inaccuracy. The study reported in chapter 3 has looked at factors influencing family history accuracy. Its results may help in the interpretation of (as yet) unverified family histories and, if there is no opportunity to verify them all, in deciding which parts of those histories need to be verified.

Recognizing from family histories the clues that point to human cancer syndromes is usually the basis for the cancer-related referral to a clinical genetics centre. However, recognizing these clues may not be easy and some physicians may be better aware of the characteristics of the human cancer syndromes than others. In order to improve the quality of care to families with hereditary cancer it is important to (regionally) distribute and update information on the human cancer syndromes, criteria for referral, options for DNA analysis and preventive measures (e.g., screening protocols).

Such actions need, however, to be monitored in order to see whether this transfer of knowledge is successful. In chapter 4 we presented an analysis of the referral from the hospitals and general practitioners in our region.
We observed striking differences within both of these groups and will use the results in a dialogue with all parties involved to identify the cause of these differences and to see whether there is any need to adjust our system of knowledge transfer. This transfer should not be a one-way process. The clinical genetic workload has for an important part shifted in recent years from the traditional topics of congenital anomalies and mental retardation to cancer. Therefore, although non-geneticians may need to learn more about genetic aspects of cancer, clinical geneticists need to learn more about cancer in order to be equal partners in the discussion on hereditary cancer topics.

One way to assist in the recognition of hereditary cancer and in making a clinical genetic differential diagnosis in cancer patients and families, is to present information on this subject in the format of interactive software, as has been done for clinical cytogenetics (the Human Cytogenetics Database by Schinzel), dysmorphology (the London Dysmorphology Database by Winter and Baraitser; POSSUM by Bankier) and some other groups of hereditary disorders. We programmed the Familial Cancer Database (FACD), reported in chapter 5, for this purpose. Only time will tell how much help our programme offers in clinical practice.

Two of the human cancer syndromes, multiple endocrine neoplasia type 2A (MEN2A) and hereditary non-polyposis colorectal cancer (HNPCC) were studied with respect to the disease spectrum and tumour risk. Results are reported in appendices I-IV. In the two MEN2A studies, patients with familial cutaneous lichen amyloidosis (CLA) and familial or isolated Hirschsprung disease (HSCR), respectively, were examined for mutations in the RET gene (which is associated with MEN2). The reason for this was that both disorders have also been reported to occur in MEN2A patients. We therefore questioned whether CLA and HSCR patients without a MEN2A family history could carry MEN2A-associated RET mutations and thus could have an increased cancer risk. Indeed, such mutations were observed in HSCR patients. Although tumour risks for these HSCR patients are as yet difficult to estimate, our study underlines the fact that some patients with disorders known to be associated with human cancer syndromes, may carry mutant genes associated with an increased cancer risk in the absence of a family history fitting those syndromes. Physicians diagnosing and treating patients with such disorders should be aware of this phenomenon in the interest of tumour prevention.

Disease spectrum and tumour risk in HNPCC were explored in the studies reported in appendices III and IV. The first study used an epidemiological approach to look at the association of cancer of the urinary tract with HNPCC in all HNPCC families.
included in the National HNPCC Registry maintained by the Netherlands Foundation for the Detection of Hereditary Tumours and presents risk figures for these tumours. Studies such as this one have the advantage of generating risk figures, but cannot learn us much of the nature of tumours which occur only rarely in a human cancer syndrome.

The second study demonstrates a totally different approach to study the disease spectrum. Using molecular techniques, a single case of malignant fibrous histiocytoma (very rarely occurring in HNPCC) diagnosed in an HNPCC patient was tested for molecular characteristics of HNPCC. The results suggested that this tumour had indeed developed as part of HNPCC in this patient. Both types of study, each with its own particular advantages and disadvantages, are needed to further delineate the disease spectrum of the human cancer syndromes.

**Future Perspectives**

Many questions relevant to the clinical genetics of cancer remain to be answered. Some of these may be more readily answered than others. For example, it is unlikely that we will be able in the near future to precisely predict the clinical implications of a mutant gene in individual cases. Inter- and intra-familial differences in phenotypical expression of one and the same mutant gene are the rule rather than the exception in human cancer syndromes and can be explained by the multi-step nature of cancer development and the fact that a wide range of external as well as internal risk and protective factors may interact in complex and therefore largely unpredictable ways.

The future will, however, undoubtedly see an expansion of diagnostic capabilities. In particular, we can expect DNA analysis to contribute increasingly to the genetic diagnosis in patients and families suspected of having a human cancer syndrome. Although increased mutation detection rates will generate a further increase in demand for genetic services with all the practical budgetary problems tied in with this increase, the possibility to detect all mutations associated with human cancer syndromes will also alleviate the burden of family history verification and the 'wrestling' with differential diagnosis.

Questions with regard to tumour prevention in individuals and families will probably take many more years to solve, which implies that more people will be diagnosed with an inherited strong cancer predisposition at a time when the value of preventive options will still be very unclear for many of the human cancer syndromes as reviewed in chapter 2. Only large collaborative studies can address questions with
respect to outcome of periodic screening, tumour incidence after prophylactic surgery and the short- and long-range effects and side-effects of chemoprevention. This implies that the (preventive) treatment and follow-up of patients should be protocolized in order to be able to compare and pool data. This is a strong argument in favour of centralising these medical activities. However, in practice, many of these activities are not performed in central settings.

Although genetic analysis is often centralised per region because of the very specialised expertise involved (and because of legislation, as in our country), depending on the choice of inclusion criteria, the load of patients for further medical management may be too large to cope with in a central clinic. Also, patients may prefer to remain in the care of specialists working outside such central clinics. If decentralised medical management would follow the mentioned protocols and its local registration could be carried out in a way that would allow for the pooling of data on regional and preferably national levels so that a study population could be defined large enough for meaningful statistical analysis, then that could be an adequate alternative. Nevertheless, certain medical procedures (e.g. prophylactic thyroidectomy in small children, presymptomatic DNA testing including its psychological support) should remain centralised for the present in order to guarantee expertise.

Looking at the future, it can hardly be expected that diagnostic and even presymptomatic DNA testing and genetic counselling will forever remain the exclusive domain of clinical genetics centres. Simply because of the sheer number of patients involved and the opening of international markets for commercial DNA testing, decentralisation of testing and counselling seems likely. The role of clinical genetics centres may shift towards one which mainly focuses on hereditary disorders which are particularly complex with regard to DNA testing, risk analysis and counselling seems likely. The role of clinical genetics centres may shift towards one which mainly focuses on hereditary disorders which are particularly complex with regard to DNA testing, risk analysis and counselling, as well as on disorders for which, because of their rare nature, commercial testing is unavailable.

With respect to the other disorders, an increasing role as a consultancy service, rather than as a service which performs all of the actual testing and counselling, may be expected. However, these changes should not be encouraged until comprehensive mutation analysis will be possible and the clinical and psychosocial implications of the results from such analyses are further clarified.