EPIDEMIOLOGY AND GENETICS OF FAMILIAL CANCER

Kari Hemminki and Asta Försti

German Cancer Research Center, Heidelberg, Germany.

For common cancers, such as breast, prostate, colorectal and lung cancers, familial risk for a person who has an affected family member is typically around 2.0; approximately 5 - 20% of cases are familial when two generations are considered. Known susceptibility genes are estimated to explain some 30% of the familial clustering of breast, prostate and colorectal cancers but much less of the familial clustering of lung cancer. The recently identified low-penetrance genes/loci explain a large proportion of cancer occurrence (population-attributable fraction) but they explain only a small proportion of the known familial risks for these cancers. This apparent paradox is explained by the high allele frequency of the loci and the low conferred risk. However, the true functional gene variants may be much rarer and their contribution to familial risk would be higher. For many relatively common cancers, such as prostate and bladder cancers and non-Hodgkin lymphoma, mainly low-penetrance genes are known, and they have negligible contribution to the familial risk. Thus, there are large gaps in knowledge on the genetic basis of familial cancer that the Molecular Genetic Epidemiology group is addressing on two fronts. It is using the world's largest family dataset, the Swedish Family-Cancer Database to assess familial cluster in all cancers. It is characterizing gene underlying susceptibility to cancer through genetic association studies, increasingly using genome-wide approaches.

The Swedish Family Cancer Database includes increasingly older generations whereby case numbers increase and it is possible to study familial risks in rare and histology-specific cancers. As one example, familial clustering of cancer of unknown primary site is offering interesting insights into metastatic phenotype. The Database is being used to analyze age-group-specific familial risks, which will be turned into user-friendly algorithms for clinical genetic counseling of cancer patients and their relatives. In due course, the aim is to develop software packages that would provide relative and absolute risk estimates for a given family structure, age of onset of the diagnosed cancers, presentation of related tumors and other relevant data. There are several ongoing genome-wide association studies, for example on myeloma, Hodgkin disease, childhood leukemia, for which new low-penetrance genes have been described. There is a future interest to associate the findings with clinical parameters, such as survival and response to therapy. Recent success in identifying a high-risk melanoma mutation in TERT promoter region is shown as an example of usefulness of pedigree-based gene identification efforts.