SESSION 2

S2. Genetic Susceptibility and Predicting Cancer Risk in Individuals

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The human genome sequence is the starting point for the compilation of detailed information about the range of genetic differences between individuals. Whereas current approaches to the genetics of disease are mostly based on the Mendelian inheritance of single, strong, but uncommon predisposing genes, knowledge of the range of genetic variation across many loci in the population will allow a 'polygenic' approach, in which risks will be estimated from the combined effect of this variation. The promise of a polygenic approach to common diseases has generated much excitement. Some have claimed that the greater understanding of genetic risk factors and their interactions with the environment will allow diseases to be predicted and to be prevented at both individual and population levels, by directing interventions at individuals shown to be at high risk. Others are less sure: in particular, they question whether molecular testing for common genetic variants can have sufficient predictive power to be of practical use either for the individual or for defining risk groups in the population at large.

We have therefore examined the potential for prediction of risk based on common genetic variation, and compared this with the predictions that could be made using established risk factors. To do this, we needed to address three questions: (1) What is the likely distribution of genetically-determined risk in the population? (2) What is the distribution of risk described by established risk factors? (3) What are the implications of these risk distributions for the effective targeting of interventions to individuals, and within the population? We have used breast cancer as a model to explore these questions.

To investigate the genetic models that best account for the familial aggregation of breast cancer not due to the high-penetrance BRCA genes, we have analysed the occurrence of breast cancer in the relatives of patients in the Anglian Breast Cancer Study, a population-based series of 1,484 cases, all of whom were screened for mutations in *BRCA1/2*. The model best describing these data was a polygenic model, in which susceptibility to breast cancer is conferred by a large number of alleles. The risk associated with any individual allele is small; but the effects are multiplicative so that a woman with several susceptibility alleles is at high risk. The model also fits well the pattern of breast cancer in a series of multiple case families not due to *BRCA* mutations. It is likely to be an appropriate model for many common cancers and other diseases.

The data are compatible with a log-normal distribution of genetic risk in the population, which is sufficiently wide to provide useful discrimination of high- and low-risk groups. Assuming all the susceptibility genes could be identified, the half of the population at highest risk would account for 88% of all cases. In contrast, if currently identified risk factors for breast cancer were used to stratify the population, the half of the population at highest risk would account for only 62% of all cases. These results suggest that in the future the construction and use of genetic risk profiles may provide significant improvements in the efficacy of population-based programmes of intervention for cancers and other diseases.