SESSION 2

Onco-Genetics and Cancer Prevention – Defining Risk Groups

S2. Application of Genetics to the Prevention of Colorectal Cancer

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It is well established that, on average, a first-degree relative of an individual with colorectal cancer is at about a two-fold increased risk. This increased risk is greater the younger the age at diagnosis, and the younger the age of the at-risk relative. This seemingly modest risk could not occur without there being strong underlying risk factors that are correlated in relatives. If these "familial" risk factors are genetic (correlation between first-degree relatives = 0.5), individuals in the top 25% of genetic risk are at least 20 times more likely to develop colorectal cancer than those in the lower 25%. Consequently, 90% of colorectal cases are in people in the upper half of the wide distribution of genetic risk. Therefore, there is great potential to use genetics to prevent colorectal cancer, provided individuals who are at higher, if not highest, genetic risk can be identified. To date, two rare syndromes have been identified - familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) – that explain only a small fraction of the broad spectrum of genetic risk. Identification of "HNPCC families" was originally based on cancer family history, and recruitment clinic-based and usually through unaffected relatives. Microsatellite instability (MSI) and immunohistochemistry (IHC) testing of cases, combined with mutation testing in mismatch repair (MMR) genes, has changed this focus. Population-based series of early-onset cases have demonstrated the feasibility of a new regime. MMR gene carriers and their relatives can be much more efficiently identified by conducting IHC, but not MSI, testing of early-onset cases (even irrespective of family history), and mutation testing targeted to a specific MMR gene. That is, identification of genetically-susceptible individuals using the tumour phenotype of affecteds, rather than using family cancer history, could become the standard approach of cancer genetics and associated clinical services in the 21st century. Suggested protocols for such a service will be presented and discussed.