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GENETICS

Family connections

Cancer pathogenesis often involves a subtle interplay between both genetic and environmental factors. A recent study by Kari Stefansson and colleagues highlights the value of combining cancer incidence statistics with extensive genealogical data to tease out information about the relative contribution of these factors in different cancers and about the familial distribution of cancer.

Using data from the Icelandic Cancer Registry and deCODE Genetics' genealogical database of Icelanders — two large and comprehensive data sets — the authors showed that, in 22 of the 27 cancers studied, close relatives of cancer patients were more likely than the general population to develop the same cancer. Moreover, for 8 of these 22 cancers there was still a significantly increased risk of an individual developing the disease even if only distant relatives (third- to fifth-degree relatives) had cancer.

So which cancers showed this 'familial clustering'? The highest risks (over a threefold increased risk) for close relatives were for lymphoid leukaemia, Hodgkin's disease, and cancers of the thyroid, meninges, lip, testis and larynx. Except for thyroid cancer, these cancers were among the least prevalent sites in the study. This is probably because rarer tumours are more likely to be caused by a trait determined by the action of a single gene with high penetrance

(a Mendelian trait), whereas common cancers are genetically complex. Also, the very fact that they are widespread in the general population means that common cancers have a high baseline frequency, which limits the power of risk estimates for these cancers in subsets of data.

The authors also investigated how the presence of a particular cancer within a family influenced the chances of a relative developing cancer at a different site. They found significantly increased familial clustering between different cancer sites in both close and distant relatives. Stomach and prostate cancer were most commonly associated with other cancers, followed by colon, ovarian and cervical cancers. Although some of the connections between cancer sites could be explained by known high-risk genes in heritable syndromes, others could not. For example, familial clusters were shown between lung, oesophageal, cervical and stomach cancers. The authors propose that this 'excess familiarity' between cancer sites can be explained by gene–environment

interactions. That is, the same environmental factor(s) might interact with the same genetic factor(s) to generate different cancers (for example, smoking in lung and cervical cancer), or different environmental factor(s) might interact with the same genetic factor(s) to induce different cancers (for example, smoking in lung cancer and human papilloma virus in cervical cancer).

It is important to keep in mind that even for the highest-risk cancers, the absolute increased risk for relatives remains small. Nevertheless, genetic counsellors will certainly be interested in this study and the implication that, in some cases, cancer should be considered in a broader familial context. The results are also valuable in that they indicate associations between previously unrelated cancers, so highlighting avenues for further investigation.

Oliver Childs

References and links

ORIGINAL RESEARCH PAPER Amundadottir, L. T. *et al.* Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med.* **1**, e65 (2004)