

## GENES, ENVIRONMENT AND FAMILIAL CANCER

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I will cover two topics in this presentation: one on familial risk in lung cancer (LC) and the second on sharing of predisposition genes and familial risks between cancers.

Cigarette smoking is the main population-level cause of lung cancer (LC) in Europe with a life-time relative risk between 10 and 20, far higher than about 1.5 for second-hand exposure and around 2.0 in childhood exposure. Familial risk in LC may be largely attributed to shared smoking habits although a familial risk for LC (adenocarcinoma) has been reported also for non-smokers probably through heritable causes. We have recently analyzed familial risk in LC in two settings, between first-degree relatives and among half-siblings. For the latter we take advantage of the natural experiment of half-siblings in families of parental divorce. After divorce children normally remained with the mother in Sweden. Familial risk for LC was equal for full siblings and maternal half-siblings, significantly higher than for paternal half-siblings. The results suggest that smoking is a major contributor to familial risk of LC in this setting. Among first-degree relatives familial risks vary according to period, type of family relationships, sex and histology. The risks were highest between females, concordant histologies and in families with multiple affected LC patients.

More than 10 years ago whole-genome association studies (GWASs) provided evidence for sharing germline variants between several cancers (pleiotropy). These included hotspots, such as *TERT-CLPTMIL*, *TERC-MYNN3*, *MYC* and *HLA* genomic loci. Recently large-scale sequencing studies have expanded such conclusions demonstrating that many common cancers share predisposition genes. Using Swedish family data we have shown the risks for colorectal, lung, prostate and female breast cancers and rarer cancers increase in families where many patients have been diagnosed with discordant cancers. The results provide evidence of general susceptibility to cancer overriding the view that 'classical' cancer predisposition genes cause cancer in one or a few sites because many of the pleiotropic genes are the classical predisposition genes. In addition to the high-risk predisposition, the present data argue for an unspecific type of genetic predisposition to cancer which may encompass sets of various tumors.

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