Christoph Frank

Dr. sc. hum.

Population Landscape of Familial Cancer

Fach/Einrichtung: DKFZ (Deutsches Krebsforschungszentrum)

Doktorvater: Prof. Dr. Kari Hemminki

The aims of this study were to highlight the full scope of familial cancer by examining variable levels of familial risk and to estimate the population impact of familial cancer. Furthermore, alternative methodological approaches to familial risk estimation and potential sources of bias were assessed.

Follow-up data were obtained from the nationwide Swedish Family Cancer Database for more than 8 million individuals, among whom around 350,000 cancers were recorded. For family members of cancer patients relative risks for developing a concordant cancer were calculated in terms of incidence rate ratios (IRRs) derived from Poisson regression models. Different family histories were investigated, distinguishing between single and multiple affected first-degree relatives and between early and late age at diagnosis.

Considering the 25 most common forms of cancer, significantly increased familial risks were found for all cancers when a parent or a sibling was affected. IRRs were around 2.00 for most cancers and highest for cancers of the testis (3.90 and 6.94 if a parent or sibling was affected, respectively), small intestine (4.81 and 10.11) and thyroid gland (5.13 and 5.43). A considerable IRR of 9.60 was also calculated for Hodgkin lymphoma among siblings. For almost all cancers sibling risks were higher than the risks in offspring of affected parents, but differences significant at the 5% level were detected only for stomach, colorectal, lung, prostate and testicular cancers and Hodgkin lymphoma.

Familial risks were significantly different for the majority of cancer types among independent groups associated with diagnostic age. IRRs were highest for almost all cancers at ages below 60 years if the affected relatives were also diagnosed at younger ages, but by far the most familial

cases were diagnosed at older ages, still showing significantly increased risks. Moreover, the number of affected family members was associated with increased risk, e.g. the IRR for melanoma was 5.99 if a parent and a sibling were affected and the IRR for prostate cancer was 6.65 if three brothers were affected.

The results obtained from Poisson regression were confirmed by standardized incidence ratios and IRRs derived from negative binomial regression. Hence, Poisson regression remained the method of choice since it enabled testing for significant differences among IRRs and the data were only slightly overdispersed.

Family size was found to interact significantly with family history for breast and colorectal cancers and should therefore always be considered as a potential confounder in the design of family studies, provided sample size is sufficiently large. With regard to truncated data, no general conclusion about the effect of cohort selection which would be valid for all cancers could be drawn from the present results. However, the bias caused by truncated data was acceptable. Risk estimates obtained by the register-based and the time-based definitions of familial risk were almost the same. Both definitions showed assets and drawbacks, but the register-based approach favored the appropriate classification of multiplex families.

As a crude estimate of the environmental component of familial risk, risks for couples that had lived together for at least 10 years were calculated. Apart from lung and esophageal cancers, the findings suggested that familial cancer risk is overwhelmingly due to heritable effects rather than shared environmental exposures.

With regard to the proportion of all cancers that could be attributed to familial risk, the population attributable fraction (PAF) was estimated among independent groups considering concordant invasive and in situ cancer in first- and second-degree relatives. The finding of a total PAF of 5.96% suggested that familial cancer may have a greater population impact than obesity and overweight, despite the fact that familial PAFs are underestimated for sex-specific cancers.

Overall, the results of this study emphasize the value of a detailed family history as a readily available tool which merits greater attention in the first oncology contacts and established referral mechanisms for clinical counseling. As the magnitude of familial cancer risk varies for different family relationships, patients and their family members should be provided with individually tailored cancer screening recommendations and prevention strategies.