Andreas Brandt
Dr. sc. hum.

Analysis of the relationship between age and the risk of familial cancer

Geboren am 13.2.1981 in Saarbrücken
Diplom der Fachrichtung Mathematik am 2.11.2006 an der Universität Bonn

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Dr. Kari Hemminki

Population based estimates of the differences in the age of onset between familial and sporadic cancers are important for the etiological understanding of familial cancer and clinical practice. In particular, these estimates may be helpful for the definition and revision of the recommended age to start surveillance in individuals at increased risk. The Swedish Family-Cancer Database covers the complete country of Sweden. It includes more than 11.8 million individuals and their cancers from 1958 to 2006. Information on cancers and familial relationships are based on reliable registered sources. Utilizing the Database, differences in the onset age of familial and sporadic cancers were estimated by calculating the age to reach a given cumulative risk for individuals with and without a family history and, alternatively, by calculating the age at which individuals at familial risk reached the same cumulative risk as individuals lacking a family history at a given age. Cumulative risks were estimated with a stratified Cox model based on Breslow's estimator. The thesis is organized around five major points:

1. 'Being at familial risk' may have different connotations in studies on familial risk of cancer. The 'register-based definition' of a family history considers individuals with an affected relative at familial risk independently of the family member's diagnostic time. Alternatively, individuals are classified to be at familial risk only after the diagnosis date of their relative, the 'time-based definition', which is also germane to clinical counseling

situations. In this thesis, familial risks of breast and prostate cancer were calculated according to the two definitions. The results provide evidence that the risks according to the two definitions are equal. The register-based approach will offer a methodological advantage in the analysis of rare events such as multiplex familial cases of breast and prostate cancers or early onset cases.

2. Specific studies on the age of onset of familial cancer compared to sporadic cancer are less common than studies on familial risks and these are almost lacking for rare cancers. In this thesis, it is shown that for most common types of cancer, individuals with affected parents or siblings are diagnosed at earlier ages than individuals without a family history. The difference in age of onset depends on the number of affected relatives, while the affected proband, parent or sibling, caused no large difference. The present data offer scientific bases for the improvement of clinical counseling and screening activities and for the implementation of counseling for familial cancers currently lacking established management options.

3. Familial breast cancer is known to be of early onset. The number of familial breast cancers in the Swedish Family-Cancer Database permitted the analysis of diagnostic age and the age of death in familial breast cancer according to the relative's diagnostic age. The diagnostic age of breast cancer decreased with decreasing relative's diagnostic age, while the type of proband (mother or sister) seemed to play a minor role. The trend for mortality was essentially similar to the incidence data. The present data should encourage further analysis in order to derive evidence-based recommendations for the starting age of screening in women with a family history of breast cancer.

4. Clinical criteria based on family history have been developed to identify women at high risk of breast cancer. In this thesis, relative and cumulative risks according to seven of such criteria were estimated. The risks associated with the different clinical criteria were diverse. The results offer scientific bases for clinical counseling and screening activities targeted at high risk patients; these should commence around 10 years earlier than for women at average risk. However, women who fulfilled the high risk criteria were rare. Therefore, the number of additional cases attributable to family history was larger among women with one affected first degree relative outside the high risk groups, although the familial excess risk was smaller.

5. The aim of the fifth part of the thesis was the estimation of the age of onset and the age to die in familial prostate cancer. It was found that men with a father or a brother affected are diagnosed at earlier ages than men without family history. The differences in age of diagnosis were larger for men with multiple affected relatives, and the diagnosis age was lower for brothers than for sons of prostate cancer patients. The differences also depended on the diagnostic age of the relative. Furthermore, the cumulative risk of prostate cancer specific mortality was related to the number and type of affected relatives but there was no clear evidence for a dependency on the diagnostic age of the relative. These results should encourage further trials to assess the risks and benefits of screening for prostate cancer in men at increased risk.