Methods for Studying Heritability of Cancer Diagnosis Using Twins

Sören Möller[1], **Thomas Scheike**[2], **Klaus Holst**[2], **Jennifer R. Harris**[3], **Hans-Olov Adami**[4], **Kamila Czene**[4], **Lorelei A. Mucci**[5], **Kaare Christensen**[1], **Axel Skytthe**[1], **Jaakko Kaprio**[6], and **Jacob B. Hjelmborg**[1]

[1] Epidemiology, Biostatistics and Biodemography, Institute of Public Health, University of Southern Denmark, Denmark

[2] Department of Biostatistics, University of Copenhagen, Denmark

[3] Division of Epidemiology, The Norwegian Institute of Public Health, Oslo, Norway

[4] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[5] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[6] Department of Public Health & Institute for Molecular Medicine, University of Helsinki, Finland

Different kinds of cancer are known to be quite heritable, although the extent to which variation in risk by age is explained by genetic factors remains uncertain.
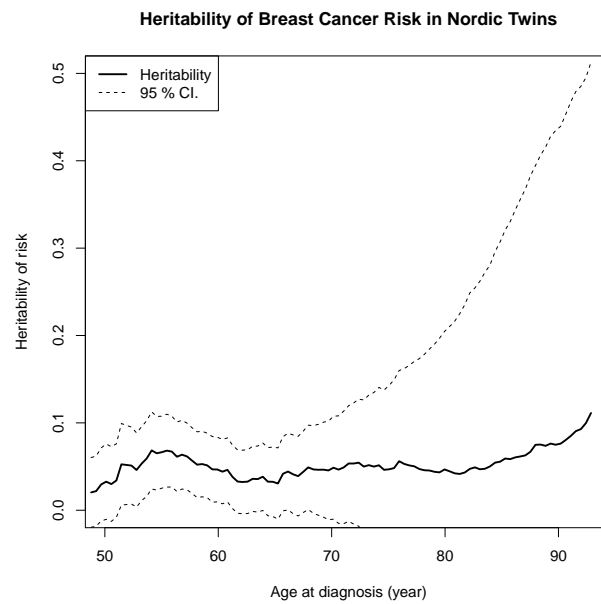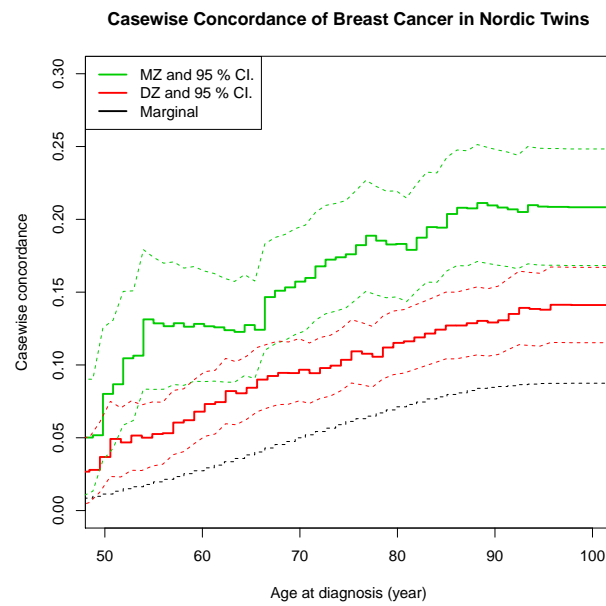
To address this question with respect to breast cancer, we study 20,561 monozygotic and 30,289 dizygotic same sex female twin pairs from the Nordic Twin Study of Cancer cohort the largest in the world. We incorporate time-to-event analyses to estimate the concordance risk and heritability accounting for right-censoring due to individuals still alive or lost to follow-up and competing risks of death, essential sources of biases that have not been accounted for before.

We estimate the cumulative incidence using the non-parametric Aalen-Johansen estimator and taking account for left-censoring due to variable initiation of cancer registration. We determine the casewise concordance in MZ and DZ twins and its dependency on the age at diagnosis, weighting the sample by use of the additive Aalen model and the Kaplan-Meier method to handle censoring. Moreover, we estimate the cumulative heritability using a time-varying biometric ACE-model both on the liability and on the risk scale.

We compare these analysis with conventional models applied to this dataset, which do not take into account the censoring or competing risks, to investigate the impact of ignoring these factors in the model.

Furthermore, we discuss possible strategies to estimate the point-wise time-varying heritability from the cumulative heritability.

We present results on heritability of risk and case-wise concordance as well as on the heritability of liability of breast cancer, both with respect to time-at-risk and age at diagnosis. We take into account possible differences between countries and check assumptions on homogeneity with respect to zygocity and similar incidence to the general population.

Casewise Concordance of Breast Cancer in Nordic Twins

Heritability of Breast Cancer Risk in Nordic Twins