Institutionen för medicinsk epidemiologi och biostatistik

Genetic determinants of breast cancer risk

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ABSTRACT

The main purpose of this thesis was to identify genetic risk factors using both hypothesis-based and hypothesis-free approaches.

In an attempt to identify common disease susceptibility alleles for breast cancer, we started off with a hypothesis-free approach, and performed a combined analysis of three genome-wide association studies (GWAS), involving 2,702 women of European ancestry with invasive breast cancer and 5,726 controls.

As GWAS has been said to underperform for studying complex diseases such as breast cancer, we investigated to see if the variance explained by common variants could be increased by studying specific disease subtypes. Breast cancer may be characterized on the basis of whether estrogen receptors (ER) are expressed in the tumour cells. The two breast cancer tumour subtypes (ER-positive and ER-negative) are generally considered as biologically distinct diseases and have been associated with remarkably different gene expression profiles. ER status is important clinically, and is used both as a prognosticator and treatment predictor since it determines if a patient may benefit from anti-estrogen therapy. We thus performed an independent GWAS using a subset of ER-negative breast cancer cases and all of the controls from the initial genome-wide study, and, in addition, also evaluated whether the two cancer subtypes are fundamentally different on a germline level.

Besides hypothesis-free GWAS, we also conducted hypothesis-based analyses based on candidate pathways to identify common variants associated with breast cancer. Several studies have examined the effect of genetic variants in genes involved in the estrogen metabolic pathway on mammographic density, but the number of loci studied and the sample sizes evaluated have been small and pathways have not been evaluated comprehensively. We evaluated a total of 239 SNPs in 34 genes in the estrogen metabolic pathway in 1,731 Swedish women who participated in a breast cancer case-control study.

Slightly venturing outside the genetic scope of this thesis, we looked at a breast cancer risk factor - body size - that is associated with very different postmenopausal breast cancer risks at different time points in a woman's lifetime, namely, birth, childhood, and postmenopausal adult.

The significance of these studies will be apparent when, using the new genetic and epidemiological knowledge found, we are able to classify women according to high or low risk of breast cancer on the basis of genetic disposition or other breast cancer risk factors, so that appropriate interventions and disease management decisions may be made, to ultimately reduce incidence and mortality of breast cancer.

Keywords: Breast Neoplasms, Genetic Epidemiology, Genetic Susceptibility, Genetic Predisposition to Disease/genetics*, Case-Control Studies, Genetic Association Studies, Candidate Gene Analysis, Gene Discovery, Single Nucleotide Polymorphism, Risk Factors,, Estrogen Receptors, Mammography, Body Size

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