Title: Genetic and epidemiological aspects of epithelial ovarian cancer

Danish title: Genetiske og epidemiologiske aspekter af epitelial ovariecancer

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ABSTRACT

Genetic and Epidemiologic Aspects of Epithelial Ovarian Cancer

This Ph.D. thesis originating from the Danish Cancer Society uncovers different aspects of familial disposition to epithelial ovarian cancer. First we examined the reliability of self-reported cancer diagnoses in first-degree female relatives by ovarian cancer cases and controls. We found that family cancer history is not always accurately reported by ovarian cancer patients and controls differing by cancer type. Type of relative, age at interview and length of education influenced the sensitivity and the specificity. The results indicate that studies of associations with family cancer history should validate self-reported family cancer diagnoses as carefully as possible.

Subsequently, we examined the risk of epithelial ovarian cancer in relation to the validated family history of cancer among first-degree relatives and found a significantly increased risk of ovarian cancer for women with a family history of ovarian cancer in first-degree relatives. The increased risk of ovarian cancer associated with a family history of ovarian cancer was most pronounced for early-onset ovarian cancer ($\leq$50 years) and for nonmucinous tumours.

The Nordic countries have the highest incidences of ovarian cancer in the world. We conducted a review of the recent literature on genetic susceptibility to ovarian cancer, and the clinical implications in relation to the BRCA1 and BRCA2 genes with focus on the Nordic countries. There are reports of BRCA1 and BRCA2 analysis in ovarian and breast cancer

cases from some Nordic countries, but the data from the Danish population are limited. Therefore, we evaluated the prevalence of BRCA1/2 mutations in a population based series of 445 ovarian cancer cases from Denmark using DNA sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis. Deleterious BRCA1 mutations were identified in 22 cases (4.9%) and BRCA2 mutations in 4 cases (0.9%). Five different mutations were identified in more than one individual and accounted for nearly 50 % of all mutations, suggesting they may be founder mutations in the Danish population. First-degree relatives of mutation carriers had increased relative risks of both breast cancer < 60 years and ovarian cancer compared to non-carriers. The average age at diagnosis of ovarian cancer was significantly younger in BRCA1/2 carriers compared to non-carriers. Ovarian cancers in mutation carriers were also diagnosed at a significantly later stage and tumours were more poorly differentiated compared to non-carriers.

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