ENGLISH SUMMARY

Ovarian cancer is the fifth most common cancer among women in Western countries and the most lethal gynecological cancer. The poor prognosis is mainly related to an advanced stage at diagnosis in the majority of patients. The etiology and pathogenesis of ovarian cancer are still relatively poorly understood; however, inflammation has been proposed as an underlying biological mechanism for the development of the disease. Therefore, pelvic inflammatory disease (PID) has been suggested as a risk factor for ovarian cancer. However, few studies have investigated this association and the results are inconclusive. In addition, it is increasingly acknowledged that ovarian cancer is a heterogeneous disease consisting of several histotypes with differences in risk factor profile, proposed origin and genetic mutations, but few previous studies have performed analyses according to histotype. Considering the poor prognosis and the difficulties with early detection of the disease, further research to identify risk factors for ovarian cancer is important in order to achieve a better understanding of this disease.

The aim of the present PhD thesis was to investigate the association between PID and risk of ovarian cancer and borderline ovarian tumors. The thesis is based on three studies: A pooled analysis of 13 case-control studies from the Ovarian Cancer Association Consortium (OCAC) (Paper 1) and two cohort studies using data from various nationwide Danish health registries (Paper 2 and 3).

In Paper 1, we pooled data from 13 case-control studies from OCAC to investigate the association between a history of PID and risk of ovarian cancer and borderline ovarian tumors. OCAC is an international collaboration of ovarian cancer studies established in 2005. Based on 9,162 women with ovarian cancer, 2,354 women with borderline ovarian tumors and 14,736 controls, we observed an increased risk of borderline ovarian tumors in women with a history of PID, and a more than two-fold increased risk of borderline tumors among women with two or more episodes of PID. Comparable results were noted for serous and mucinous histotypes. For ovarian cancer overall, no compelling evidence for an association with PID was seen; however, we found indications of an increased risk of

low-grade serous ovarian cancer among women with a history of PID, while no convincing associations were noted for high-grade serous, mucinous, endometrioid or clear cell ovarian cancer.

In Paper 2, we assessed the risk of ovarian cancer in women with PID in a cohort of all Danish women during 1978–2012, who were born in 1940–1970 (n = 1,318,929). We identified women with PID from the National Patient Registry. Women in the cohort were followed for up to 35 years for development of ovarian cancer through linkage to the Cancer Registry. PID was not associated with risk of ovarian cancer overall. However, we noted a modestly increased risk of serous ovarian cancer among women with PID, while no associations were noted for mucinous, endometrioid or clear cell ovarian cancer.

In Paper 3, we studied the risk of borderline ovarian tumors in women with PID, using the same cohort as in Paper 2. Borderline ovarian tumors were identified in the Danish Pathology Data Bank. We observed an increased risk of borderline ovarian tumors among women with PID. However, the association differed significantly between histotypes; women with PID had a nearly two-fold increased risk of serous borderline tumors, whereas no association was seen for mucinous borderline tumors.

In conclusion, our results point to an increased risk of borderline ovarian tumors in women with PID, with the strongest evidence seen for serous borderline tumors. Concerning ovarian cancer, our results do not support any association between PID and risk of mucinous, endometrioid or clear cell ovarian cancer. For serous ovarian cancer, our results were not entirely consistent, and further studies are needed before any firm conclusions on the association between PID and risk of serous ovarian cancer can be drawn.

The results from this thesis add further knowledge regarding the etiology of ovarian cancer and borderline ovarian tumors, and emphasize that ovarian cancer and borderline ovarian tumors represent a heterogeneous group of tumors, and future studies should investigate invasive and borderline ovarian tumors separately and according to histotype. However, the underlying mechanism for a differential association with PID across ovarian tumor types are unknown and warrants further study.