Drugs with potential chemopreventive properties in relation to epithelial ovarian cancer – a nationwide case-control study

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English summary

Ovarian cancer has a poor prognosis because the disease in the majority of patients is diagnosed at an advanced stage as a result of nonspecific symptoms and lack of efficient screening methods. Because of the poor prognosis of ovarian cancer and the challenge of early detection of the disease, identification of protective factors is important. It has been suggested that some commonly used drugs may have a protective effect against cancer, including ovarian cancer; however, the literature on chemopreventive measures for ovarian cancer is sparse and the results are inconclusive. Most previous studies have substantial methodological constraints, including limited study size and self-reporting of drug use, which introduces potential recall bias and misclassification.

This PhD thesis includes a nationwide case-control study to evaluate associations between use of drugs with potential chemopreventive properties and risk of epithelial ovarian cancer. The study is nested in the entire Danish female population using data from the following nationwide registries: the Danish Cancer Registry, the Danish Civil Registration System, the Danish Prescription Registry, the Danish National Patient Register, and registries in Statistics Denmark on fertility, education, and income. Information from the included registries is linked by use of the unique personal identification number assigned to all Danish citizens.

The cases were all women in Denmark with epithelial ovarian cancer diagnosed during 2000–2009 (Paper 1) and 2000–2011 (Papers 2 and 3), identified in the Cancer Registry. Age-matched female population controls were randomly selected from the Civil Registration System by risk-set sampling. We required that cases and controls have no history of cancer (except non-melanoma skin cancer) and that controls not previously have undergone bilateral oophorectomy or salpingo-oophorectomy. The total study population comprised 3741 epithelial ovarian cancer cases and 50,576 controls in Paper 1, and 4103 epithelial ovarian cancer cases and 58,706 controls in Papers 2 and 3. We used the Danish Prescription Registry to assess use (≥2 prescriptions on separate dates) of paracetamol, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, and statins. Conditional logistic
regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for epithelial ovarian cancer associated with use of the study drugs, with adjustment for potential confounding factors selected à priori. We performed detailed analyses according to duration, intensity, and continuity of study drug use, and the analyses were stratified according to specific histologic types of epithelial ovarian cancer. In all studies, non-use (<2 prescriptions) of the individual study drugs was defined as the reference group.

A striking result of the PhD thesis was a strong inverse association between prescription use of paracetamol and risk of epithelial ovarian cancer. The risk estimates decreased with increasing duration and intensity of paracetamol use, reaching a more than 50% reduction for the longest duration (>10 years) and the highest doses (OR, 0.45; 95% CI, 0.24–0.86). In contrast, we did not observe an inverse association between use of non-aspirin NSAIDs and risk of epithelial ovarian cancer. Moreover, this thesis provides further evidence that use of low-dose aspirin is associated with a reduced risk of epithelial ovarian cancer. In particular, long-term (≥5 years) continuous use of low-dose aspirin, defined as overlapping prescription coverage periods, was associated with a large reduction in risk (OR, 0.56; 95% CI, 0.32–0.97). Finally, we found no apparent association between statin use and epithelial ovarian cancer risk, although the analysis by histologic type suggested an inverse association with the risk of mucinous tumors.

The results of this PhD thesis add important knowledge to the area of chemoprevention in relation to epithelial ovarian cancer. As for any observational study, we cannot exclude potential confounding and exposure misclassification; however, methodological limitations appear unlikely to fully explain the observed reductions in epithelial ovarian cancer risk associated with paracetamol and low-dose aspirin use. Additional research, ideally from clinical trials, is needed before our observations may lead to recommendations for chemopreventive measures against ovarian cancer. In case consensus points to a true protective effect of paracetamol or low-dose aspirin, comprehensive risk-benefit evaluations will also have to be performed. We hope that our results will encourage researchers to look more deeply into the potential chemopreventive effects of the study drugs against epithelial ovarian cancer risk.