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CIRCULATING INFLAMMATORY FACTORS, ANDROGENS AND RISK OF EPITHELIAL OVARIAN CANCER

STUDIES WITHIN THE EPIC COHORT AND THE OVARIAN CANCER COHORT CONSORTIUM

Fach: Epidemiologie

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EOC has historically been regarded as single disease originating from the surface epithelium of the ovary. However, compelling data shows that EOC is comprised of five distinct diseases based on the main histological subtypes (e.g., low-grade and high-grade serous, mucinous, endometrioid and clear cell tumors), with a substantial proportion originating outside of the ovary (e.g., in the fallopian tube and endometrium). Molecular and genetic evidence points to two different pathways of EOC development, i.e., type I and type II. Type I tumors (e.g., low-grade serous, low-grade endometrioid, mucinous and malignant Brenner tumors) are thought to develop in a step-wise manner from borderline tumors or endometriosis within or directly on the surface of the ovary. In contrast, type II tumors (e.g., high-grade serous, high-grade endometrioid tumors) are aggressive neoplasms that typically present at an advanced stage and are further characterized by genetic instability and a very high frequency of TP53 mutations. Prior experimental and epidemiologic data suggest etiologic differences by histologic subtype, while differences by the developmental pathways have been minimally explored. To date, the etiology of EOC remains poorly understood.

Prior studies provide strong evidence for an association between inflammatory (e.g., endometriosis, tubal ligation) and hormone-related risk factors (e.g., parity, oral contraceptive use) and EOC. However, the limited epidemiologic data on circulating inflammatory markers, androgens, and growth factors and EOC risk is inconclusive. Only one prior study, in pregnant women, has investigated these factors and EOC risk by histologic subtype; there are no prior data by the developmental pathways (i.e., type I and type II).

Prior investigations of EOC as a composite outcome may have obscured differences in risk between subtypes. Given accumulating experimental data, and the need for large epidemiologic investigations, this thesis addressed the following hypotheses:

1. Elevated hormone blood levels of inflammatory markers [C-reactive protein (CRP), Interleukin 6 (IL-6)], endogenous androgens [e.g., testosterone, androstenedione], and Insulin-like growth factor (IGF)-I are associated with increased risk of EOC.
2. The pathways investigated in hypothesis 1 are differentially associated with EOC subtypes (e.g., histological subtypes, grade and stage, dualistic pathway), reflecting distinct etiologies.

These hypotheses were investigated in nested case-control studies within (1) the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and (2) the Ovarian Cancer Cohort Consortium (OC3). Inflammatory markers (CRP; IL-6) were investigated in the EPIC cohort [cases n= 754, controls n=1,497], while androgens, sex hormone binding globulin (SHBG) and IGF-I were investigated in both the EPIC cohort [cases n= 565, controls n= 1,099] and the OC3 [cases n= 1,027, controls n= 2,845]. The study in the OC3 was the first worldwide biomarker pooling project in the Ovarian Cancer Cohort Consortium (OC3), allowing detailed investigation of rarer histological subtypes (e.g., mucinous and clear cell tumors). These investigations are the largest and most comprehensive studies to date.

Inflammation and adiposity – A combined effect in ovarian carcinogenesis?

High circulating CRP (>10 vs. <1 mg/L) was associated with increased risk of overall EOC, while IL-6 was not associated with overall risk. In analyses by tumor characteristics, there was no heterogeneity across EOC subtypes. Significant heterogeneity was observed in analyses stratified by anthropometric indices. Higher CRP and IL-6 concentrations were associated with increased risk of EOC in women with central adiposity at blood donation; the increased risk was most pronounced for serous and type II tumors. In line with prior research, the current study provides additional evidence for an association between relatively high concentrations of CRP and overall EOC risk. Furthermore, these results suggest that adiposity-related systemic low-grade inflammation plays a role in ovarian carcinogenesis. It is plausible that inflammation is more strongly associated with EOC risk in the context of the altered hormonal milieu of obesity. Further prospective studies are needed to confirm these observations. A pooled study on CRP and IL-6 is planned in the OC3; the results of the present study will contribute substantially to this investigation.

Endogenous androgens and IGF-I and ovarian carcinogenesis

Androgens were not associated with overall EOC risk (all histological subtypes combined) in EPIC and the OC3. Higher concentrations of androgens were associated with increased risk of mucinous and endometrioid EOC, and type I tumors, but not serous or clear cell EOC, or type II tumors.

Experimental models show that androgens have proliferative and anti-apoptotic effects. Androgens are the predominant hormone in Müllerian inclusion cysts, thought to be the precursor lesion of a proportion of type I tumors (e.g., low-grade serous carcinomas); this is in line with the observed positive association between androgens and risk of type I tumors in this study. Further,

androgens are an intermediate on the estrogen-synthesis pathway. Beyond this, women with an ovarian failure termed hyperandrogenism (excess secretion of androgens), and consequent anovulation are characterized by progesterone deficiency, that is associated with increased risk of EOC. Therefore, androgens may have a direct impact on ovarian carcinogenesis, or act via their function as precursors to estrogens or the progesterone deficiency. *In vitro* data demonstrate the carcinogenic effects of estrogens, and a prior epidemiologic study observed increased risk of endometrioid ovarian cancer with higher estrogen concentrations in early pregnancy. Further estrogens have been consistently associated with increased risk of endometrial cancer, and based on the shared tissue of origin; similar associations appear to be plausible for endometrioid tumors of the ovary.

Pathways through which IGF-I may impact risk of EOC have been identified in experimental models. In spite of the well-described biologic pathway, no association between IGF-I and overall EOC risk or by histological subtype or by type I and type II was observed.

Taken together, this is the first investigation demonstrating that obesity-related inflammation, and androgens may have differential effects on risk of EOC by histological subtypes and developmental pathways. Inflammation-related exposures were associated with serous and type II tumors, and hormone-related exposures were related to mucinous, endometrioid and type I tumors. However, no risk associations were observed for IGF-I and EOC risk overall, or by EOC subtype. In addition to providing novel findings on important biologic pathways (e.g., inflammation, hormonal-related mechanisms and IGF-I) in ovarian carcinogenesis, these findings support emerging data on the heterogeneity of EOC and underscore the importance of examining etiologic differences for EOC by subtype.