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Early pregnancy sex steroids and maternal risk of epithelial ovarian cancer

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Abstract

Well-established associations between reproductive characteristics and epithelial ovarian cancer (EOC) support an involvement of sex steroid hormones in the etiology of EOC. Limited prior studies have evaluated circulating androgens and risk of EOC, and estrogens and progesterone have been investigated in only one prior study. Further, there is little data on potential heterogeneity in the association between circulating hormones and EOC by histologic subgroup. Therefore, we conducted a nested case-control study within the Finnish Maternity Cohort and the Northern Sweden Maternity Cohort to investigate the associations between circulating pre-diagnostic sex steroid concentrations with the histologic subtypes of EOC. We identified 1,052 EOC cases among cohort members diagnosed after recruitment (1975-2008) and before March 2011. Up to three controls were individually matched to each case (n=2,694). Testosterone, androstenedione, 17-hydroxyprogesterone (17-OHP), progesterone, estradiol, and sex hormone-binding globulin were measured in serum samples collected during the last pregnancy before EOC diagnosis. We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals [CI]. Associations between hormones and EOC differed by tumor histology and invasiveness. Sex steroid concentrations were not associated with invasive serous tumors, however, doubling of testosterone and 17-OHP concentration was associated with ~40% increased

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

risk of borderline serous tumors. A doubling of androgen concentrations was associated with a 50% risk increase for mucinous tumors. Risk of endometrioid tumors increased with higher estradiol concentrations (OR: 1.89 [1.20-2.98]). This large prospective study in pregnant women supports a role of sex steroid hormones in the etiology of EOC arising in the ovaries.

Keywords

prospective study; case-control study; pregnancy; sex steroids; ovarian neoplasms

Introduction

Worldwide, more than 200,000 women are diagnosed with epithelial ovarian cancer (EOC) each year. It is the seventh most common cancer in women and the leading cause of gynecologic cancer death among women with an overall 5-year survival rate of only about 40% in developed countries (Ferlay, et al. 2014). EOC can be subdivided into invasive and borderline disease, approximately 15% of EOC are borderline tumors with similar epidemiologic risk factors as invasive tumors, but occurring at a younger age, presenting at an earlier stage, and with a more favorable prognosis (Trope, et al. 2012).

Further, EOC includes different histological subtypes, with the most common being serous (75%), endometrioid (10%), clear cell (10%), and mucinous (3%) (Prat 2012). Growing evidence indicates that EOC subgroups represent clinically, morphologically, and molecularly distinct diseases (Prat 2012).

EOC may develop from inclusion cysts by metaplasia of ovarian surface epithelium or implantation of other epithelium (e.g. tubal tissue) (Auersperg, et al. 2001; Kurman and Shih Ie 2010). The pathogenic mechanisms involved in the development of ovarian cancer are poorly understood. The prevailing etiological hypotheses implicate long periods of ovulatory cycles (Fathalla 1971), retrograde menstrual flow (Cramer and Xu 1995), and endogenous, as well as exogenous, hormonal exposure (Risch 1998). Sex steroid hormones (androgens, progesterone, and estradiol) are likely to be involved in the etiology of EOC, as there are well-established associations between reproductive characteristics impacting sex steroid concentrations and EOC. Examples include the protective effect of pregnancy and use of oral contraceptives, and the increased risk associated with current use of hormone replacement therapy (Morch, et al. 2009; Tsilidis, et al. 2011).

To date, studies directly relating pre-diagnostic endogenous hormone concentrations to risk of EOC are confined to androgens, and results are inconclusive (Helzlsouer, et al. 1995; Lukanova, et al. 2003; Ose, et al. 2014; Rinaldi, et al. 2007; Tworoger, et al. 2008). Only one small study related progesterone and estradiol to EOC risk (Helzlsouer et al. 1995). This is most likely because concentrations of progesterone and estradiol show large intra-individual variation during the menstrual cycle among premenopausal women, making a measurement difficult, and concentrations in postmenopausal women are low (Rannevik, et al. 1995; Speroff and Marc 2005).

Given sparse data on the relationship between sex steroid hormones and EOC, and the established association between parity and EOC, we investigated early pregnancy sex steroid hormones and subsequent ovarian cancer risk in a case-control study nested in two prospective maternity cohorts. Further, we present the first data on early pregnancy hormones and EOC risk by histologic subtype and invasiveness. Androgens in early pregnancy are similar to preconception concentrations; therefore our study is characterizing premenopausal circulating androgen concentrations with risk of EOC. On the other hand, progesterone and estradiol are elevated in early pregnancy and their concentrations increase further during pregnancy, thus we are able to explore whether these hormones contribute to the protective effect conferred by pregnancy.

Material and Methods

Study population

A case-control study was nested within the Finnish Maternity Cohort (FMC) and the Northern Sweden Maternity Cohort (NSMC). These two bio-repositories store serum samples collected during the late weeks of the first, or early weeks of the second, trimester at −25°C and −20°C, respectively. The FMC was established in 1983 and includes close to two million specimens from almost 99% of pregnancies in the country (http://www.thl.fi/en/web/thlfi-en/research-and-expertwork/projects-andprogrammes/projects/2823, accessed May 2014). The NSMC was established in 1975 and contains almost 120,000 samples from pregnancies in the three northernmost counties of Sweden (Pukkala 2011).

Study subjects were selected among members from both cohorts with: 1) no history of twin or multiple pregnancies; 2) a blood sample obtained during the first trimester of a pregnancy leading to childbirth; and 3) no history of invasive cancer (except for non-melanoma skin cancer) and/or borderline ovarian cancer prior to blood donation.

Identification of Cases—Cases diagnosed with invasive or borderline EOC after blood donation were identified through linkages with the Finnish Cancer Registry (founded in 1952) and the Swedish Cancer Registry (founded in 1958). Reporting of newly diagnosed cases is mandatory in both nationwide cancer registries, leading to very high (>95%) completeness for solid tumors (Barlow, et al. 2009; Teppo, et al. 1994). We identified 1,105 incident EOC cases among FMC participants and 146 incident EOC cases among NSMC members; cases were diagnosed before December 2009 and March 2011, respectively. The serum sample from the last singleton pregnancy (or the most recent available for 68 cases) resulting in delivery of a neonate prior to diagnosis was selected for the study.

Selection of Controls—Selection of controls was done in two steps. First, up to 12 potentially eligible controls were selected for each case through linkages with the national population registries. Controls matching the case on study cohort, age at sampling (±6 months), date of sampling (±3 months), parity at sampling (1, 2, >2 children), and parity at diagnosis (1, 2, >2 children) were selected using incidence density sampling. In a second step, up to three controls were selected at random.

Cases with insufficient serum volume for laboratory measurements (FMC: n=157; NSMC: n=31) and cases for whom no eligible controls could be identified (FMC: n=5; NSMC: n=6) were excluded. Therefore, a total of 1,052 EOC cases (FMC: n=943; NSMC: n=109) and 2,694 controls (FMC: n=2,383; NSMC: n=311) were included in the study.

Morphology codes were provided by the Finnish and Swedish cancer registries and recoded according to the World Health Organization guidelines (Lee, et al. 2003) to histologic subgroups of EOC as serous (n=477, 45%), mucinous (n=356, 34%), endometrioid (n=102, 10%), clear cell (n=26, 3%), and NOS (n=66, 6%) tumors. Data on histology was not available for 25 cases (2%) and thus they were included only in overall analyses and analyses by tumor invasiveness, as were tumors diagnosed as NOS. Data on stage of EOC at diagnosis was not available for cases from the NSMC but was available for 87% of cases from the FMC. For cases from the FMC, stage I (n=482, 58%) was classified as localized, whereas stages II (n=6), III (n=306), and IV (n=30) were classified as advanced EOC (n=342, 42%).

Characteristics related to pregnancy (e.g. pregnancy length, smoking during pregnancy, maternal age at first birth, number of incomplete pregnancies) and to the newborn (e.g. gender, birth weight and length) were obtained through linkages from the country specific birth registries. For 2,200 members of the FMC (n=629 case-control sets, 60%) information on malignant cancers diagnosed among first-degree relatives was obtained through linkages with the Finnish Population and Cancer Registries.

The study was approved by the ethical committees of the National Institute for Health and Welfare, Finland; University of Umeå, Sweden; and German Cancer Research Center, Germany.

Laboratory analyses

All hormonal analyses were performed at the Clinical Chemistry Laboratory of Umeå University Hospital, Umeå, Sweden. Serum specimens of individually-matched case and control subjects were always included in the same laboratory batch. The technicians performing the assays were blinded to the case, control, or quality control status of the specimens. In addition to routine laboratory quality controls, two pools of serum from each of the cohorts were created at the beginning of the study and 3 aliquots, undistinguishable from the test samples, were inserted in each laboratory run.

Concentrations of androgens (testosterone and androstenedione), 17-hydroxyprogesterone (17-OHP), progesterone, and estradiol were quantified by high-performance liquid chromatography tandem mass spectrometry on an Applied Biosystems API4000 triple stage quadrupole mass spectrometer. Inter- and intra-run coefficients of variation (CV) based on the blinded pooled quality controls were <10% and <11% for samples from the FMC and <11% and <9% for samples from the NSMC for all sex steroids.

Sex hormone-binding globulin (SHBG) was quantified with solid-phase competitive chemiluminescence assays on Immulite 2000 Siemens analyzer. Inter- and intra-run CV based on the blinded pool quality controls were <10% in both cohorts.

Statistical analysis

All hormone values were $\log_2$-transformed to normalize their distributions and to allow for estimation of risk with a doubling of hormone concentration. Concentrations of progesterone, 17-OHP, estradiol, and SHBG varied linearly with gestational age (r=0.49, -0.26, 0.69, and 0.57, respectively; $p<0.0001$); thus analyses including these hormones were limited to women with information on gestational age (n=765 case-control sets, 73%) and gestational age was included as a covariate in the statistical models. Pearson partial correlation coefficients were used to assess correlations between individual hormone concentrations in control samples.

We used conditional logistic regression to assess differences between cases and controls and to calculate odds ratios (OR) and corresponding 95% confidence intervals [CI]. For each of the hormones, ORs were calculated for tertiles of hormone concentrations using the cohort-specific frequency distribution in controls. Likelihood ratio tests were used to assess linear trends across categories based on the median hormone values for the tertiles. In addition, ORs were calculated for a unit change of $\log_2$- transformed hormones.

The effect of potential confounders (maternal age at first birth, smoking during index pregnancy, family history of breast and/or ovarian cancers, child's sex, birth length and weight) was evaluated. Missing values were assigned to a ‘missing’ category for categorical covariates, whereas for continuous variables missing values were assigned the individual cohort (NSMC or FMC) median value for that variable. Analyses that excluded subjects with missing values for any of these covariates were similar to those with values imputed as described. Among the available covariates none changed point estimates by >10%. We repeated the analyses for each of the hormones mutually adjusting for the other hormones.

Stratified analyses were performed by histology, ages at sampling and diagnosis (histology-specific; below/above median), and time between blood donation and diagnosis (i.e., ‘lag-time’; below/above median). We also stratified by stage (localized vs. advanced disease), number of children by diagnosis date of the matched case (1 vs. >1) and age at diagnosis (age <51 years vs. ≥51 years). The cut-off for age at diagnosis was chosen as the average age at menopause is 51 years in Sweden and Finland (Thomas, et al. 2001). Tests of heterogeneity between the ORs in different subgroups were based on chi-square statistics, calculated as the deviations of logistic regression coefficients observed in each of the subgroups, relative to the overall regression coefficient (Whitehead and Whitehead 1991).

We conducted sensitivity analyses limited to women diagnosed at least 2 or 3 years after blood donation to assess whether study results were influenced by the presence of undiagnosed, but hormonally active tumors. Additionally, we performed analyses limited to women with a full-term pregnancy or, for androgen analyses, with information on gestational age at blood draw. Results adjusted for gestational age were comparable to those with hormone concentrations for each study subject computed as the difference (residual) between the assay value and the estimated cohort-specific mean value determined for the day of gestation when the sample was drawn using local linear regression (Cleveland and Loader 1996) (data not shown).

All statistical tests were two-sided with significance level 0.05. Statistical analyses were conducted using the Statistical Analyses System (SAS), version 9.2 software (SAS Institute, Inc., Cary, North Carolina). The figure was prepared using R software (package 'rmeta', function 'forestplot) version 2.15.2 (Team 2014).

Results

Key characteristics of the study subjects and their newborns by study cohort are presented in Table 1. The majority of the 1,052 cases (n=943, FMC; n=109, NSMC) were diagnosed with invasive EOC (n=642, 61%). Of these, 283 (44%) were serous, 150 (23%) mucinous, 102 (16%) endometrioid, and 26 (4%) clear cell. Among the borderline tumors (n=410, 39%), 194 (47%) were serous and 206 (50%) mucinous. The distribution by histological subtype and invasiveness was consistent between the two cohorts. Invasive tumors were predominantly diagnosed as advanced disease (69%), whereas almost all borderline tumors were diagnosed as localized disease (97%). Median age at EOC diagnosis was 43.9 years and on average 12.2 years elapsed between blood donation and diagnosis among all cases.

In the FMC, maternal and child characteristics were similar for both cases and controls except for median age at first birth (26.0 vs. 26.9; $p<0.0001$), smoking during pregnancy (22% vs. 14%; $p<0.0001$), and family history of breast and/or ovarian cancer (8% vs. 5%; $p=0.008$). In the NSMC, only smoking during pregnancy was different between cases and controls (38% vs. 28%; $p=0.06$).

Cases with mucinous tumors (borderline and invasive) had the shortest lag-time between blood collection and cancer diagnosis (10.2 years) and the youngest median age at diagnosis (40.1 and 40.9 years, respectively), whereas cases diagnosed with endometrioid or clear cell tumors had the longest lag-time (16.3 and 17 years, respectively) and were the oldest at diagnosis (48.1 years) (Table 2).

Cases with borderline tumors were younger at first birth, cases with borderline and invasive mucinous and invasive serous tumors were more likely to smoke, and cases with invasive serous tumors were more likely to have a family history of breast and/or ovarian cancer relative to their matched controls (Table 2).

Case subjects from both cohorts had significantly higher geometric means of testosterone (FMC: 0.87 vs. 0.79 ng/mL; $p<0.0001$ and NSMC: 0.83 ng/mL vs. 0.72 ng/mL; $p=0.004$) and androstenedione (FMC: 1.91 vs. 1.73 ng/mL; $p<0.0001$ and NSMC: 1.98 vs. 1.71; $p=0.007$) relative to control subjects. In the FMC also 17-OHP was higher in cases compared to controls (2.37 vs. 2.24 ng/mL; $p=0.006$).

Associations between early pregnancy hormones and EOC differed by tumor histology and, for the serous subtype, also by tumor invasiveness (Table 3; Figure 1). We did not observe an association between the evaluated hormones with risk of invasive serous or clear cell tumors in our study population. High progesterone and SHBG were not associated with risk of EOC overall or with the histological subgroups.

High testosterone was associated with significantly increased risk of borderline serous tumors (3rd vs. 1st tertile: 1.87 [1.18-2.96]; p_{trend}=0.008) and an almost 2-fold increased risk of invasive and borderline mucinous tumors (3rd vs. 1st tertile: 1.79 [1.10-2.90]; p_{trend}=0.02 and 1.97 [1.30-2.99]; p_{trend}=0.001, respectively). High androstenedione concentrations were associated with increased risk of invasive and borderline mucinous tumors (3rd vs. 1st tertile: 1.78 [1.09-2.92]; p_{trend}=0.01 and 2.00 [1.32-3.02]; p_{trend}=0.001, respectively). High concentrations of 17-OHP were associated with increased risk of borderline serous tumors (3rd vs. 1st tertile: 1.85 [1.14-2.99]; p_{trend}=0.02). A significantly increased risk was observed for high estradiol concentrations with endometrioid tumors (3rd vs. 1st tertile: 2.76 [1.04-7.33]; p_{trend}=0.03), as well as with borderline mucinous tumors (3rd vs. 1st tertile: 1.80 [1.00-3.22]; p_{trend}=0.04).

We next assessed the impact of mutually adjusting for the evaluated hormones (Supplementary Table 1). Including androgens or 17-OHP in models evaluating the association of a doubling of progesterone or estradiol concentrations (and vice versa) with risk of EOC did not change the direction or the significance of the observed associations. After adjustment for androstenedione, the effect of a doubling of testosterone concentrations on invasive and borderline mucinous tumors was strongly attenuated and no longer significant (0.77 [0.43-1.36]; p=0.36 and 1.12 [0.73-1.71]; p=0.60), whereas the association with endometrioid tumors was strengthened (3.45 [1.62-7.35]; p=0.001). A doubling of androstenedione was significantly associated with increased risk of invasive serous tumors (1.67 [1.09-2.55]; p=0.02) and decreased risk of endometrioid tumors (0.33 [0.15-0.73]; p=0.006), after adjusting for testosterone. After adjustment for androgens, a doubling of 17-OHP was no longer significantly associated with risk of borderline serous tumors (from 46 to 23% increased risk for 17-OHP).

There was no evidence of heterogeneity (p_{het}>0.05) by age at blood donation (histology-specific; below/above median) or years between blood donation and diagnosis (histology-specific; below/above median), number of children, or study cohort. Heterogeneity by age at diagnosis (<51 vs. ≥51 years, proxy for menopausal status at diagnosis; Table 4) was observed in endometrioid tumors for a doubling of estradiol concentrations (<51 years: 1.36 [0.84-2.22]; ≥51 years: 14.11 [2.14-93.00]; p_{het}=0.02), but as only 14 cases were diagnosed at or after age 51 years this result should be regarded with caution. Although heterogeneity was not observed for invasive or invasive mucinous tumors, associations with androgens in women diagnosed <51 years were stronger than in older women. Heterogeneity by tumor stage at diagnosis (Table 5) was observed in invasive serous tumors for a doubling of circulating testosterone (localized: 1.91 [1.02-3.57], advanced: 0.88 [0.68-1.14]; p_{het}=0.03) and SHBG concentrations (localized: 2.38 [1.00-5.65], advanced: 0.88 [0.61-1.27]; p_{het}=0.04), but not for any other hormones or EOC subtypes.

Limiting the analyses on androgens to women with information on gestational age at blood draw did not change risk estimates with the exception of a doubling of androstenedione which was significantly associated with increased risk of borderline serous tumors (1.50 [1.10-2.05]; p=0.01). Limiting the analysis to women with lag-time >2 or >3 years, or who provided a blood sample during a full-term pregnancy did not change risk estimates. Results did not materially change when only women with blood donation during the last pregnancy

before diagnosis or selection as a control were included. Analyses limited to members from the FMC yielded similar results and analyses restricted to the NSMC (n=109 cases) were in the same direction but non-significant due to lack of power.

Discussion

This is the first prospective case-control study examining sex steroid concentrations during pregnancy and subsequent risk of EOC. We observed heterogeneity in the associations between sex steroid hormones by EOC subtypes: higher androgen concentrations were associated with increased risk of borderline serous and mucinous tumors, whereas higher estradiol was positively associated with risk of endometrioid tumors. None of the studied hormones were associated with risk of invasive serous tumors or clear cell tumors. Progesterone and SHBG were not associated with risk of EOC, regardless of tumor histology and invasiveness.

There are substantial alterations in the secretion, metabolism, and concentrations of circulating hormones in maternal serum during gestation. First and early second trimester androgen concentrations are similar to those in non-pregnant women with maternal testosterone increasing gradually throughout pregnancy and androstenedione concentrations remaining relatively stable (O'Leary, et al. 1991; Taylor and Lebovic 2004). During the very first weeks of pregnancy the corpus luteum secretes progesterone, 17-OHP, and estradiol in increasing quantities. The major site of synthesis for progesterone and estradiol shifts to the placental trophoblasts as the corpus luteum declines (after the 5^{th} week of gestation), and concentrations of these hormones increase further, whereas the concentration of 17-OHP decreases (Taylor and Lebovic 2004).

Support for an involvement of androgens in the pathogenesis of EOC comes from in vitro studies demonstrating increased cell proliferation of normal ovarian surface epithelium cells after androgen administration (Edmondson, et al. 2002; Syed, et al. 2001) and epidemiologic studies showing a protective effect of oral contraceptive use (which reduces circulating androgen levels and ovarian androgen synthesis (Lukanova and Kaaks 2005)) (Wiegratz, et al. 1995). Women diagnosed with polycystic ovary syndrome, a hyper-androgenic disorder, might be at increased risk but available data are sparse and inconclusive (Bodmer, et al. 2011; Olsen, et al. 2008; Schildkraut, et al. 1996).

However, results from the three largest prospective studies on androgens reported so far (Rinaldi et al. 2007; Tworoger et al. 2008) did not show an association with risk or reported an inverse association of androstenedione for invasive serous tumors (Ose et al. 2014). In the current study, we observed an increased risk with both studied androgens for borderline serous tumors and mucinous tumors. Our study differs from previous investigations on the association between androgens and EOC in two important ways. First, we are the first study with the statistical power to study risk associations by tumor invasiveness and histology. Most of the previous reports included mainly invasive serous tumors, with negligible numbers of borderline and mucinous tumors. In the current study, we were able to investigate associations with the rarer subtypes, which are usually observed at a younger age (Chen, et al. 2003). Second, blood measurements in our study were collected exclusively

from pregnant women (by definition premenopausal); androgen concentrations are higher in premenopausal versus postmenopausal women. In previous prospective studies only 20% (Ose et al. 2014) to 42% (Helzlsouer et al. 1995) of cases were premenopausal.

It has been proposed that EOC originates via two main pathways of carcinogenesis and can be divided in two subtypes (Type I and Type II tumors) (Kurman and Shih 2011; Lim and Oliva 2013). Type I tumors include low grade serous and endometrioid carcinoma, clear cell, mucinous, and malignant Brenner tumors that develop slowly and are often diagnosed at an early stage. These tumors are typically confined to one ovary and progress from benign, with increasing degrees of atypia, to non-invasive and then invasive tumors. Thus, borderline ovarian tumors might be precursors of Type I tumors.

Type II tumors include high grade serous and endometrioid carcinoma, undifferentiated, malignant mixed mesodermal, and transitional cell tumors that are highly aggressive and usually present at an advanced stage. It has been suggested that Type II tumors mainly originate from the epithelium outside the ovary and invade the ovary secondarily (Kurman and Shih 2011; Lim and Oliva 2013).

We observed significant positive associations between androgen concentrations and borderline/invasive mucinous, as well as borderline serous subtypes, suggesting that androgens may be involved in the development of the slowly growing tumors in the ovaries, whereas they do not appear to influence the risk of the most aggressive cancers, which are likely of extra-ovarian origin. This hypothesis is also supported by the observation in our study that risk increases for a doubling of testosterone concentrations in invasive serous tumors diagnosed as localized (proxy for Type I: 1.91 [1.02-3.57]), but not advanced disease (proxy for Type II: 0.88 [0.68-1.14]; p_{het}=0.03).

Experimental studies and a number of indirect observations suggest that elevated progesterone concentrations may be inversely associated with risk of EOC. Progesterone has been shown to have a potent apoptotic effect on the surface epithelium (Rodriguez, et al. 1998) and to induce cellular senescence of ovarian cancer cells through FOXO1 (Diep, et al. 2013). Epidemiologic studies consistently show an inverse association of full-term pregnancies, increasing parity, and use of oral contraceptives with EOC (Merritt, et al. 2013; Tsilidis et al. 2011). Due to its potent apoptotic effect and elevated production during pregnancy, progesterone is the most plausible candidate to mediate a ‘washout effect’, i.e. eliminate from the ovary cells that have undergone malignant transformation, a hypothesis suggested to explain the greater protective effect of pregnancies completed at an older age (Adami, et al. 1994). In addition, observational studies have reported that incomplete pregnancies confer less protection than a pregnancy conducted to term (Riman, et al. 2002; Whittemore, et al. 1992) or are not associated with risk (Risch, et al. 1994).

However, we observed no association between early pregnancy progesterone and EOC risk. One explanation for the lack of association could be that only the very high progesterone concentrations as observed during the third trimester are etiologically important, whereas the substantially lower hormone concentrations during the first trimester are not. Cell culture models show that growth inhibition and apoptosis occur only at very high concentrations (≥

10^{-6} M) (Edmondson et al. 2002). In addition, during multiple pregnancies progesterone concentrations are higher compared to singleton pregnancies and women with a history of multiple births are at reduced risk to develop non-mucinous EOC (Whiteman, et al. 2000).

Our finding of a positive association between estrogen concentrations with risk of endometrioid tumors is novel. During pregnancy estradiol is synthesized by aromatization of androgens mainly in the placenta, with androgens derived from the ovary, the maternal adrenal, and also de novo synthesis in placental syncytiotrophoblasts (Escobar, et al. 2011). Elevated estrogen concentrations are consistently associated with increased risk of endometrial cancer in postmenopausal women (Allen, et al. 2008; Lukanova, et al. 2004). Furthermore, endometrial cancer and EOC share similar risk factor profiles, as well as several common genes and pathways that are involved in their molecular pathogenesis (Merritt and Cramer 2010). It has also been reported that patients with endometriosis, which is associated with molecular aberrations that favor increased local production of estradiol (Worley, et al. 2013), are at increased risk of developing endometrioid EOC (Pearce, et al. 2012). Although clear cell tumors may originate in part from endometriosis, we did not find any association between estradiol and clear cell tumors. This finding might be due to the small number of cases in our study (n=26) but it is in line with the hypothesis that clear cell tumors may arise from endometriosis through mechanisms independent of hormonal signaling (Conklin and Gilks 2013).

Our study has a number of strengths. We present data from two unique maternity cohorts in Finland and Northern Sweden and have conducted the largest prospective study on pre-diagnostic sex steroids and EOC to date (1,052 vs. 565 cases in the largest prior study by Ose et al.) with detailed analyses by tumor histology. Because this study was conducted in a pregnant population, it was easier to measure progesterone as early pregnancy concentrations do not cycle as observed in non-pregnant premenopausal women. As the population was relatively young (median age at blood draw=31.5 years) we had sufficient statistical power to assess invasive and borderline tumors. Case and control subjects were tightly matched for age and date at sampling, as well as parity at the index pregnancy, thus controlling for several sources of potential confounding (e.g. hormone concentrations differing by parity).

A major study limitation is the lack of information on grade and the incomplete data on stage (available for 824 (78%) cases). However, analyses by stage for invasive serous tumors showed the expected heterogeneity. Another limitation is the lack of data on oral contraceptive (OC) use prior to pregnancy. However, former OC use is unlikely to influence hormone concentrations during pregnancy as steroid levels suppressed during OC use return to normal levels within one cycle after cessation (Mall-Haefeli, et al. 1983). Although study samples had been stored for a long time (median of 21 years) at relatively high temperatures (−25°C / −20°C), hormone levels were uncorrelated with time in storage, as has been reported previously (Holl, et al. 2008), and case and control samples were stored under the same conditions. Another limitation is that we carried out multiple statistical tests to analyze associations with histologic subtypes and thus some of our findings could be due to chance.

In summary, we provide evidence that associations of steroids and EOC risk vary by tumor histology and invasiveness as we observed 1) positive associations of androgens with borderline serous, invasive and borderline mucinous tumors; 2) positive associations of estradiol with endometrioid, and to a lesser extent with borderline tumors; and 3) no associations with invasive serous tumors. These results support a role of sex steroid hormones in the etiology of EOC arising in the ovaries, but do not support an association between sex steroids and invasive serous tumors, which are presumed to originate in the fallopian tubes and metastasize to the ovaries. Our findings provide additional evidence that EOC is a heterogeneous disease, and indicate further research on sex steroids and the rarer histologic subtypes (endometrioid, clear cell, and mucinous) is necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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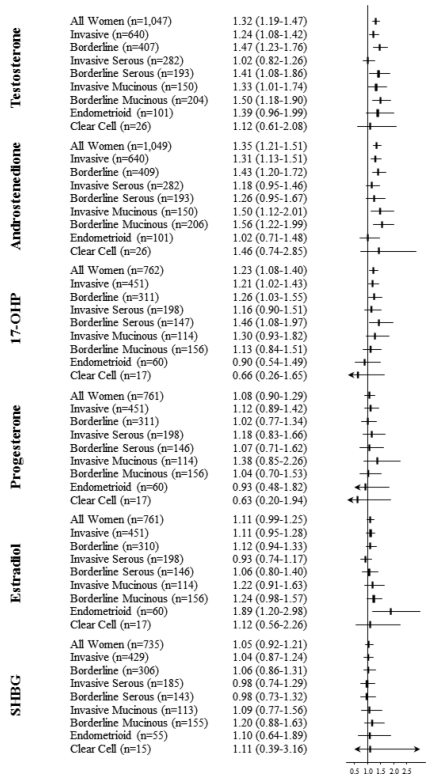

Figure 1.

Risk (OR (95% CI)) by tumor histology of epithelial ovarian cancer per unit change in $\log_2$ concentrations of circulating testosterone, androstenedione, 17-hydroxyprogesterone (17-OHP), progesterone, estradiol, and sex hormone-binding globulin (SHBG), adjusted for gestational age (except for androstenedione and testosterone). Number of case-control sets provided in brackets for each subgroup.

Table 1

Distribution of characteristics of EOC cases and their matched controls, median (min, max) or n (%) from the Finnish Maternity Cohort (1983-2009) and the Northern Sweden Maternity Cohort (1975-2011) [a]

	Finnish Maternity Cohort				Northern Sweden Maternity Cohort			
Characteristic	**% missing [b]**	**Cases (943)**	**Controls (2,383)**	**p**	**% missing [b]**	**Cases (109)**	**Controls (311)**	**p**
Age at blood donation (years)	-	31.8 (16.4-45.7)	31.7 (15.7-45.5)	-	-	29.0 (17.3-41.7)	28.8 (17.4-42.8)	-
Parity at index pregnancy	-			-	-			-
1 child		231 (24%)	597 (25%)			59 (54%)	170 (55%)	
2 children		386 (41%)	981 (41%)			27 (25%)	76 (24%)	
>2 children		326 (35%)	805 (34%)			23 (21%)	65 (21%)	
Gestational age (day)	25%	75 (39-142)	73 (39-142)	0.50	-	75 (38-148)	73 (38-148)	0.16
Age at first birth (years) [c]	-	26.0 (14.8-46.2)	26.9 (14.6-45.9)	<0.0001	15%	24.9 (16.1-40.8)	24.8 (16.8-40.0)	0.56
Pregnancy length [c]	25%			0.38	-			0.12
<37 weeks		35 (5%)	84 (5%)			1 (1%)	13 (4%)	
≥ 37 weeks		618 (95%)	1,768 (95%)			108 (99%)	298 (96%)	
Child weight (g) [c]	25%	3,620 (460-5,100)	3,610 (580-5,260)	0.50	-	3,460 (1,480-4,500)	3,500 (900-5,920)	0.78
Child length (cm) [c]	25%	51 (29-57)	50 (25-56)	0.95	-	50 (41-55)	50 (33-56)	0.42
Child gender	0.1%			0.46	-			0.18
Male		481 (51%)	1,255 (53%)			48 (44%)	160 (51%)	
Female		461 (49%)	1,126 (47%)			61 (56%)	151 (49%)	
Smoking during pregnancy [c]	27%	138 (22%)	245 (14%)	<0.0001	2%	41 (38%)	85 (28%)	0.06
Family history of breast and/or ovarian cancer	34%	51 (8%)	81 (5%)	0.008	100%	-	-	-
Age at diagnosis (years)	-	43.3 (19.0-66.0)			-	47.8 (20.2-68.0)		
Years between blood draw and diagnosis	-	11.5 (0.1-25.6)			-	19.5 (1.3-31.7)		
Cancer type	-				23%			
Borderline		367 (39%)				43 (39%)		
Serous		174 (47%)				20 (51%)		
Mucinous		189 (52%)				17 (44%)		
NOS		4 (1%)				2 (5%)		
Invasive		576 (61%)				66 (61%)		

Characteristic	Finnish Maternity Cohort				Northern Sweden Maternity Cohort			
	% missing [b]	Cases (943)	Controls (2,383)	p	% missing [b]	Cases (109)	Controls (311)	p
Serous		263 (46%)				20 (44%)		
Mucinous		143 (25%)				7 (16%)		
Endometrioid		92 (16%)				10 (22%)		
Clear Cell		23 (4%)				3 (7%)		
NOS		55 (9%)				5 (11%)		
Disease spread [d]	13%				100%	-		
Localized (stage I)		482 (58%)						
Advanced (stage II-IV)		342 (42%)						
Hormones [e,f]								
Testosterone (ng/mL)	0.5%	0.87 (0.84-0.90)	0.79 (0.78-0.81)	<0.0001	1%	0.83 (0.76-0.90)	0.72 (0.68-0.75)	0.004
Androstenedione (ng/mL)	0.5%	1.91 (1.85-1.97)	1.73 (1.71-1.77)	<0.0001	1%	1.98 (1.81-2.16)	1.71 (1.63-1.81)	0.007
17-OHP (ng/mL)	25%	2.37 (2.29-2.46)	2.24 (2.19-2.29)	0.006	1%	2.21 (2.02-2.42)	2.03 (1.93-2.14)	0.16
Progesterone (ng/mL)	25%	24.9 (24.3-25.5)	24.4 (24.1-24.8)	0.34	1%	21.4 (19.9-23.0)	21.4 (20.5-22.3)	0.97
Estradiol (ng/mL)	25%	1.97 (1.89-2.05)	1.89 (1.85-1.94)	0.09	1%	1.96 (1.75-2.19)	1.84 (1.72-1.96)	0.35
SHBG (nmol/L)	27%	211(205-218)	205 (201-209)	0.11	5%	122 (107-140)	131 (121-142)	0.33

17-OHP, 17-hydroxyprogesterone; SHBG, sex hormone-binding globulin

[a] conditional logistic regression models were used to compare differences between cases and controls.

[b] Percentage of missing values. - indicates no missing values.

[c] Data from the Finnish Birth Registry is available since 1987.

[d] Percentage of missing values among cases.

[e] Geometric means and 10^{th}-90^{th} percentile of hormone concentrations (adjusted for study cohort and, except for androgens, gestational age).

[f] Conversion from ng/mL to nmol/L (SI-units): Testosterone × 3.467, Androstenedione × 3.49, 17-OHP × 3.025, Progesterone × 3.18, and Estradiol × 3.671

Table 2

Distribution of characteristics of EOC cases by invasiveness and tumor histology, median (min, max) or n (%) from the Finnish Maternity Cohort (1983-2009) and the Northern Sweden Maternity Cohort (1975-2011)

	Serous			Mucinous				
	Invasive (642 cases)	**Invasive (283 cases)**	**Borderline (194 cases)**	**Invasive (150 cases)**	**Borderline (206 cases)**	**Endometrioid (102 cases)**	**Clear cell (26 cases)**	**Controls (2,694)**
Tumor characteristics								
Age at diagnosis (years)	45.4 (20.2-68.0)	45.9 (25.9-68.0)	42.5 (23.9-62.9)	40.9 (25.4-57.8)	40.1 (19.0-66.0)	48.1 (27.2-60.8)	48.1 (32.8-60.2)	-
Lag time (years)	13.1 (0.2-30.8)	13.5 (0.2-30.7)	11.4 (0-28.7)	10.2 (0.2-27.6)	10.2 (0.2-28.7)	16.3 (0.6-29.7)	17.0 (0.4-30.8)	-
Spread [b]								-
Localized	150 (31%)	38 (16%)	158 (96%)	78 (71%)	171 (98%)	18 (22%)	6 (43%)	
Advanced	332 (69%)	196 (84%)	6 (4%)	32 (29%)	3 (2%)	63 (78%)	8 (57%)	
Unknown	160 (25%)	49 (17%)	30 (15%)	40 (27%)	32 (16%)	21 (21%)	12 (46%)	
Covariates								
Age at first birth (years) [c]	26.9 (14.8-46.2)	26.9 (14.8-41.6)	25.8 (16.1-39.5) [a]	27.2 (15.8-46.2)	23.9 (15.5-42.5) [a]	26.5 (16.9-38.4)	28.6 (20.4-41.1)	26.7 (14.6-45.9)
Smoking during pregnancy [d]	94 (21%) [a]	35 (18%) [a]	22 (16%)	35 (31%) [a]	62 (40%) [a]	6 (10%)	2 (12%)	330 (16%)
Family history of breast/ ovarian cancer [e]	34 (9%) [a]	21 (12%) [a]	7 (6%)	3 (3%)	10 (8%)	5 (8%)	2 (22%)	81 (5%)
Hormones [f]								
Testosterone (ng/mL)	0.83 (0.79-0.87) [a]	0.76 (0.71-0.82)	0.79 (0.73-0.86) [a]	0.88 (0.78-1.00) [a]	0.88 (0.81-0.97) [a]	0.93 (0.82-1.04)	0.86 (0.67-1.10)	0.76 (0.74-0.78)
Androstenedione (ng/mL)	1.91 (1.83-2:00) [a]	1.77 (1.65-1.91)	1.80 (1.66-1.95)	2.15 (1.90-2.42) [a]	2.05 (1.88-2.23) [a]	2.00 (1.78-2.24)	2.11 (1.64-2.72)	1.73 (1.69-1.78)
17-OHP (ng/mL)	2.29 (2.18-2.40) [a]	2.28 (2.12-2.47)	2.22 (2.04-2.41) [a]	2.30 (2.04-2.60)	2.31 (2.11-2.52)	2.12 (1.88-2.39)	2.08 (1.62-2.68)	2.14 (2.08-2.19)
Progesterone (ng/mL)	23.4 (23.2-24.8)	24.9 (23.5-26.3)	22.2 (20.8-23.6)	24.0 (22.1-26.0)	22.5 (21.1-23.9)	23.7 (21.6-25.9)	22.5 (18.3-27.7)	22.8 (22.4-23.3)
Estradiol (ng/mL)	2.03 (1.92-2.14)	1.87 (1.71-2.04)	1.84 (1.68-2.01)	2.25 (1.97-2.58)	2.01 (1.81-2.24)	2.52 (2.17-2.93) [a]	1.79 (1.34-2.39)	1.88 (1.82-1.94)
SHBG (nmol/L)	169 (161-177)	171 (159-184)	153 (140-167)	145 (130-163)	168 (154-184)	173 (152-197)	167 (133-209)	163 (158-167)

17-OHP, 17-hydroxyprogesterone; SHBG, sex hormone-binding globulin

[a] Indicates that cases and controls are significantly different ($p<0.05$) in the respective subgroup.

[b] Tumor spread not available for cases from the Northern Sweden Maternity Cohort. Percentages for localized and advanced tumors are based on tumors with data, whereas percentages on unknown spread are based on histology subgroups.

[c] Data on age at first birth is missing for 15% of subjects from the NSMC.

[d] Data on smoking during pregnancy is missing for 27% of subjects from the FMC and for 2% of subjects from the NSMC.

[e] Data on family history of breast and/or ovarian cancer is available for 629 cases and 1,571 controls from the Finnish Maternity Cohort.

[f] Geometric means and 10^{th}-90^{th} percentile of hormone concentrations (adjusted for study cohort and, except for androgens, gestational age).

Table 3

ORs (95%-CI) by tumor invasiveness and histology across tertiles of circulating hormone concentrations from the Finnish Maternity Cohort (1983-2009) and the Northern Sweden Maternity Cohort (1975-2011) [a]

	Cases / Controls	Tertiles			p_{trend}	p_{het} [b]
		T1	T2	T3		
Testosterone						
All women	1,047 / 2,673	ref.	1.27 (1.06-1.53)	1.56 (1.30-1.87)	<0.0001	
Invasive	640 / 1,609	ref.	1.18 (0.93-1.49)	1.37 (1.08-1.72)	0.008	0.08
Borderline	407 / 1,064	ref.	1.45 (1.07-1.96)	1.94 (1.43-2.63)	<0.0001	
Invasive serous	282 / 713	ref.	1.11 (0.78-1.57)	0.99 (0.70-1.41)	0.97	0.03
Borderline serous	193 / 499	ref.	1.62 (1.06-2.48)	1.87 (1.18-2.96)	0.008	
Invasive mucinous	150 / 388	ref.	1.21 (0.74-1.98)	1.79 (1.10-2.90)	0.02	0.76
Borderline mucinous	204 / 537	ref.	1.36 (0.88-2.10)	1.97 (1.30-2.99)	0.001	
Endometrioid	101 / 235	ref.	1.41 (0.74-2.68)	1.83 (0.97-3.45)	0.06	
Clear cell	26 / 65	ref.	0.52 (0.16-1.66)	0.62 (0.21-1.84)	0.36	
Androstenedione						
All women	1,049 / 2,677	ref.	1.03 (0.85-1.24)	1.50 (1.24-1.80)	<0.0001	
Invasive	640 / 1,609	ref.	0.91 (0.71-1.16)	1.36 (1.08-1.72)	0.004	0.21
Borderline	409 / 1,068	ref.	1.25 (0.91-1.70)	1.74 (1.29-2.35)	0.0003	
Invasive serous	282 / 714	ref.	0.98 (0.69-1.41)	1.25 (0.88-1.77)	0.19	0.72
Borderline serous	193 / 499	ref.	1.37 (0.87-2.16)	1.38 (0.88-2.18)	0.18	
Invasive mucinous	150 / 387	ref.	0.98 (0.58-1.64)	1.78 (1.09-2.92)	0.01	0.73
Borderline mucinous	206 / 541	ref.	1.14 (0.74-1.77)	2.00 (1.32-3.02)	0.001	
Endometrioid	101 / 235	ref.	0.71 (0.37-1.38)	0.98 (0.54-1.79)	0.85	
Clear cell	26 / 65	ref.	0.90 (0.27-3.06)	1.00 (0.33-3.07)	0.99	
17-OHP						
All women	762 / 2,138	ref.	1.05 (0.85-1.30)	1.26 (1.01-1.56)	0.04	
Invasive	451 / 1,251	ref.	0.90 (0.68-1.18)	1.10 (0.83-1.46)	0.48	0.14
Borderline	311 / 887	ref.	1.35 (0.96-1.88)	1.53 (1.09-2.15)	0.02	
Invasive serous	198 / 555	ref.	0.96 (0.63-1.44)	1.09 (0.72-1.67)	0.69	0.11
Borderline serous	147 / 418	ref.	1.56 (0.96-2.55)	1.85 (1.14-2.99)	0.02	
Invasive mucinous	114 / 321	ref.	0.68 (0.38-1.21)	1.11 (0.65-1.91)	0.56	0.71
Borderline mucinous	156 / 445	ref.	1.25 (0.78-2.00)	1.28 (0.78-2.08)	0.35	
Endometrioid	60 / 159	ref.	1.12 (0.53-2.37)	0.84 (0.38-1.85)	0.69	
Clear cell	17 / 46	ref.	0.61 (0.15-2.52)	0.52 (0.10-2.76)	0.42	
Progesterone						
All women	761 / 2,136	ref.	0.88 (0.71-1.08)	0.96 (0.76-1.21)	0.67	
Invasive	451 / 1,252	ref.	0.90 (0.68-1.19)	0.99 (0.73-1.35)	0.95	0.71
Borderline	310 / 884	ref.	0.85 (0.62-1.18)	0.91 (0.63-1.31)	0.56	
Invasive serous	198 / 555	ref.	0.98 (0.64-1.48)	1.03 (0.65-1.63)	0.93	0.96
Borderline serous	146 / 415	ref.	0.86 (0.53-1.41)	1.05 (0.61-1.82)	0.92	
Invasive mucinous	114 / 322	ref.	1.04 (0.59-1.85)	1.11 (0.60-2.06)	0.73	0.47

	Cases / Controls	Tertiles			p_{trend}	p_{het} [b]
		T1	T2	T3		
Borderline mucinous	156 / 445	ref.	0.75 (0.48-1.18)	0.83 (0.50-1.37)	0.42	
Endometrioid	60 / 159	ref.	0.61 (0.28-1.32)	0.81 (0.34-1.95)	0.59	
Clear cell	17 / 46	ref.	0.24 (0.04-1.53)	0.47 (0.10-2.23)	0.43	
Estradiol						
All women	761 / 2,136	ref.	1.01 (0.81-1.26)	1.24 (0.94-1.62)	0.11	
Invasive	451 / 1,252	ref.	1.00 (0.75-1.33)	1.26 (0.88-1.79)	0.20	0.88
Borderline	310 / 884	ref.	1.03 (0.73-1.46)	1.20 (0.79-1.84)	0.36	
Invasive serous	198 / 555	ref.	0.79 (0.51-1.21)	0.98 (0.57-1.69)	0.89	0.78
Borderline serous	146 / 415	ref.	0.82 (0.50-1.35)	0.87 (0.46-1.64)	0.64	
Invasive mucinous	114 / 322	ref.	1.06 (0.59-1.89)	1.54 (0.77-3.07)	0.21	0.74
Borderline mucinous	156 / 445	ref.	1.42 (0.85-2.35)	1.80 (1.00-3.22)	0.04	
Endometrioid	60 / 159	ref.	1.41 (0.59-3.41)	2.76 (1.04-7.33)	0.03	
Clear cell	17 / 46	ref.	1.93 (0.46-8.08)	1.58 (0.26-9.64)	0.53	
SHBG						
All women	735 / 2,088	ref.	1.01 (0.81-1.26)	1.14 (0.89-1.46)	0.40	
Invasive	429 / 1,209	ref.	1.00 (0.75-1.34)	1.11 (0.80-1.53)	0.64	0.79
Borderline	306 / 879	ref.	1.03 (0.73-1.45)	1.19 (0.80-1.77)	0.45	
Invasive serous	185 / 528	ref.	1.25 (0.81-1.92)	1.02 (0.63-1.67)	0.83	0.90
Borderline serous	143 / 413	ref.	0.94 (0.58-1.54)	1.08 (0.59-1.96)	0.85	
Invasive mucinous	113 / 319	ref.	0.73 (0.40-1.31)	1.37 (0.72-2.62)	0.56	0.99
Borderline mucinous	155 / 443	ref.	1.20 (0.73-1.98)	1.38 (0.79-2.43)	0.27	
Endometrioid	55 / 150	ref.	0.88 (0.37-2.10)	1.29 (0.51-3.26)	0.63	
Clear cell	15 / 43	ref.	0.91 (0.20-4.24)	1.25 (0.24-6.53)	0.86	

17-OHP, 17-hydroxyprogesterone; CI, confidence interval; OR, odds ratio; SHBG, sex hormone-binding globulin.

[a] adjusted for gestational age (except for testosterone and androstenedione)

[b] heterogeneity is tested between invasive and borderline tumors

Table 4

ORs (95%-CI) for doubling of circulating hormone concentrations by age at diagnosis from the Finnish Maternity Cohort (1983-2009) and the Northern Sweden Maternity Cohort (1975-2011) [a]

	Age at diagnosis < 51 years		Age at diagnosis ≥ 51 years		
	Ca / Co	OR (95%-CI)	Ca / Co	OR (95%-CI)	p_{het}
Invasive tumors					
Testosterone	475 / 1,228	1.32 (1.12 - 1.55)	165 / 381	1.05 (0.81 - 1.36)	0.15
Androstenedione	475 / 1,227	1.40 (1.18 - 1.65)	165 / 382	1.10 (0.84 - 1.43)	0.13
17-OHP	357 / 1,004	1.26 (1.04 - 1.53)	94 / 247	0.98 (0.66 - 1.45)	0.26
Progesterone	357 / 1,005	1.14 (0.88 - 1.48)	94 / 247	1.04 (0.62 - 1.75)	0.76
Estradiol	357 / 1,005	1.07 (0.91 - 1.27)	94 / 247	1.23 (0.88 - 1.72)	0.47
SHBG	350 / 993	1.04 (0.85 - 1.27)	79 / 216	1.07 (0.73 - 1.58)	0.88
Invasive serous					
Testosterone	195 / 506	1.01 (0.78 - 1.31)	87 / 207	1.04 (0.72 - 1.53)	0.88
Androstenedione	195 / 506	1.23 (0.94 - 1.61)	87 / 208	1.10 (0.77 - 1.57)	0.63
17-OHP	145 / 413	1.27 (0.93 - 1.73)	53 / 142	0.91 (0.55 - 1.51)	0.27
Progesterone	145 / 413	1.25 (0.82 - 1.88)	53 / 142	1.01 (0.53 - 1.92)	0.59
Estradiol	145 / 413	0.91 (0.69 - 1.21)	53 / 142	0.95 (0.64 - 1.42)	0.86
SHBG	142 / 407	0.98 (0.71 - 1.35)	43 / 121	0.98 (0.53 - 1.78)	0.98
Invasive mucinous					
Testosterone	128 / 339	1.46 (1.07 - 1.99)	22 / 49	0.94 (0.52 - 1.68)	0.19
Androstenedione	128 / 338	1.64 (1.18 - 2.28)	22 / 49	1.05 (0.55 - 2.02)	0.23
17-OHP	103 / 291	1.29 (0.90 - 1.84)	11 / 30	1.33 (0.49 - 3.64)	0.95
Progesterone	103 / 292	1.38 (0.82 - 2.31)	11 / 30	1.19 (0.24 - 5.78)	0.86
Estradiol	103 / 292	1.18 (0.87 - 1.59)	11 / 30	2.07 (0.47 - 9.16)	0.46
SHBG	102 / 290	1.10 (0.72 - 1.67)	11 / 29	1.11 (0.56 - 2.21)	0.97
Endometrioid					
Testosterone	67 / 159	1.47 (0.95 - 2.27)	34 / 76	1.20 (0.62 - 2.32)	0.61
Androstenedione	67 / 159	1.06 (0.69 - 1.64)	34 / 76	0.92 (0.45 - 1.90)	0.74
17-OHP	41 / 111	0.87 (0.49 - 1.56)	19 / 48	1.00 (0.36 - 2.76)	0.82
Progesterone	41 / 111	0.86 (0.39 - 1.88)	19 / 48	1.17 (0.30 - 4.52)	0.69
Estradiol	41 / 111	1.36 (0.84 - 2.22)	19 / 48	14.11 (2.14 - 93.00)	0.02
SHBG	39 / 108	0.92 (0.49 - 1.73)	16 / 42	1.84 (0.61 - 5.56)	0.28

17-OHP, 17-hydroxyprogesterone; Ca, number of cases; CI, confidence interval; Co, number of controls; OR, odds ratio; p_{het}, test for heterogeneity; SHBG, sex hormone-binding globulin

[a] adjusted for gestational age (except for testosterone and androstenedione)

Table 5

ORs (95%-CI) for doubling of circulating hormone concentrations in invasive tumors by tumor stage from the Finnish Maternity Cohort (1983-2009) [a]

	Local (stage I)		Advanced (stages II-IV)		
	Ca / Co	OR (95%-CI)	Ca / Co	OR (95%-CI)	p_{het}
Invasive					
Testosterone	150/377	1.44 (1.10 - 1.90)	331/804	1.11 (0.91 - 1.34)	0.12
Androstenedione	150/377	1.44 (1.09 - 1.90)	331/805	1.17 (0.96 - 1.43)	0.24
17-OHP	104/292	1.15 (0.82 - 1.61)	213/580	1.24 (0.95 - 1.61)	0.74
Progesterone	104/292	1.18 (0.70 - 1.98)	213/580	1.27 (0.90 - 1.81)	0.81
Estradiol	104/292	1.19 (0.87 - 1.61)	213/580	1.09 (0.87 - 1.36)	0.66
SHBG	100/284	1.37 (0.90 - 2.08)	199/563	1.06 (0.79 - 1.42)	0.32
Invasive Serous					
Testosterone	38 / 96	1.91 (1.02 - 3.57)	196 / 481	0.88 (0.68 - 1.14)	0.03
Androstenedione	38 / 96	1.60 (0.91 - 2.80)	196 / 482	1.09 (0.84 - 1.40)	0.22
17-OHP	23 / 67	1.37 (0.75 - 2.51)	131 / 360	1.28 (0.90 - 1.81)	0.84
Progesterone	23 / 67	1.44 (0.60 - 3.41)	131 / 360	1.33 (0.84 - 2.09)	0.88
Estradiol	23 / 67	1.41 (0.75 - 2.67)	131 / 360	0.89 (0.67 - 1.18)	0.20
SHBG	23 / 67	2.38 (1.00 - 5.65)	120 / 341	0.88 (0.61 - 1.27)	0.04
Invasive Mucinous					
Testosterone	78 / 198	1.31 (0.90 - 1.90)	32 / 83	1.46 (0.78 - 2.71)	0.77
Androstenedione	78 / 198	1.45 (0.98 - 2.13)	32 / 83	1.79 (0.91 - 3.53)	0.59
17-OHP	57 / 161	1.15 (0.72 - 1.84)	22 / 63	1.93 (0.92 - 4.04)	0.24
Progesterone	57 / 161	1.73 (0.79 - 3.81)	22 / 63	2.96 (0.93 - 9.43)	0.45
Estradiol	57 / 161	1.23 (0.82 - 1.86)	22 / 63	1.42 (0.65 - 3.09)	0.75
SHBG	56 / 160	1.40 (0.77 - 2.55)	22 / 63	1.41 (0.51 - 3.89)	0.98
Endometrioid					
Testosterone	18 / 45	1.12 (0.49 - 2.56)	62 / 139	1.53 (0.97 - 2.42)	0.52
Androstenedione	18 / 45	1.05 (0.45 - 2.46)	62 / 139	1.05 (0.66 - 1.65)	0.99
17-OHP	13 / 35	0.87 (0.32 - 2.34)	33 / 85	0.75 (0.38 - 1.48)	0.82
Progesterone	13 / 35	0.43 (0.07 - 2.72)	33 / 85	0.86 (0.37 - 2.04)	0.51
Estradiol	13 / 35	0.71 (0.27 - 1.86)	33 / 85	2.15 (1.06 - 4.36)	0.07
SHBG	11 / 30	0.65 (0.20 - 2.07)	31 / 85	1.39 (0.67 - 2.85)	0.28

17-OHP, 17-hydroxyprogesterone; Ca, number of cases; CI, confidence interval; Co, number of controls; OR, odds ratio; p_{het}, test for heterogeneity; SHBG, sex hormone-binding globulin

[a] adjusted for gestational age (except for testosterone and androstenedione)