Assessment of multifactor gene-environment interactions and ovarian cancer risk: Candidate genes, obesity, and hormone-related risk factors

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ABSTRACT

Background: Many epithelial ovarian cancer (EOC) risk factors relate to hormone exposure, and elevated estrogen levels are associated with obesity in post-menopausal women. Therefore, we hypothesized that gene-environment interactions related to hormone-related risk factors could differ between obese and non-obese women.

Methods: We considered interactions between 11,441 single nucleotide polymorphisms (SNPs) within 80 candidate genes related to hormone biosynthesis & metabolism and insulin-like growth factors with six hormone-related factors: oral contraceptive use; parity; endometriosis; tubal ligation; hormone replacement therapy; and estrogen use; and assessed whether these interactions differed between obese and non-obese women. Interactions were assessed using logistic regression models and data from 14 case-control studies (6,247 cases; 10,379 controls). Histotype specific analyses were also completed.

Results: SNPs in the following candidate genes showed notable interaction: *IGF1R* (rs41497346, estrogen plus progesterone hormone therapy, histology = all, $p = 4.9 \times 10^{-6}$) and *ESR1* (rs12661437, endometriosis, histology = all, $p = 1.5 \times 10^{-5}$). The most notable obesity - gene - hormone risk factor interaction was within *INSR* (rs113759408, parity, histology = endometrioid, $p = 8.8 \times 10^{-6}$).

Conclusions: We have demonstrated the feasibility of assessing multi-factor interactions in large genetic epidemiology studies. Follow-up studies are necessary to assess the robustness of our findings for *ESR1, CYP11A1, IGF1R, CYP11B1*, *INSR*, and *IGFBP2*. Future work is needed to develop powerful statistical methods able to detect these complex interactions.

Impact: Assessment of multifactor interaction is feasible, and, here, suggest that the relationship between genetic variants within candidate genes and hormone-related risk factors may vary EOC susceptibility.

Keywords: body mass index; obesity; hormone related factors; SNP; gene-environment interaction; ovarian cancer;

Category: Epidemiology

INTRODUCTION

Little research has been conducted to determine multifactor gene-environment interaction at the candidate gene or genome-wide level despite the emerging evidence to show that these types of complex relationships do exist (1-3). In addition to the lack of studies assessing complex interactions in cancer risk, only a limited number of studies have assessed gene-environment (GE) interactions by histological subtype, as genetic and environmental risk factors have been found to differ by the histology. Recently, consortia have been established to give the large sample size needed to detect SNPs with small effects, providing the ability to study GE interactions. In April 2005, the Ovarian Cancer Association Consortium (OCAC) was formed; the largest international consortium conducting genetic epidemiology studies for epithelial ovarian cancer (EOC) (4). This international effort comprises more than 40 different genetic epidemiological studies, with the focus on assessing single SNP associations with EOC.

To date, OCAC has identified 18 confirmed novel susceptibility loci that are associated with EOC risk (5-12). In addition to finding new risk loci, GWAS also confirm the biological distinction of the various EOC histologies. For example, risk alleles in 8q24 and 19p13 associate almost exclusively with serous EOC (8, 13), yet those in 2q31 and 17q12 are also associated with other subtypes (8, 14). However, it is hypothesized that the known risk loci are likely to represent only a fraction of the common risk alleles for EOC and that numerous undetected common variant loci still remain to be discovered (15).

In addition to genetic susceptibility loci, there are several confirmed EOC environmental risk factors. Similar to other hormone-related cancers in women, many of these risk factors related to hormone exposure, including: obesity (risk) (16-19); history of

endometriosis (risk) (20); estrogen use menopausal hormonal therapy (MHT) (risk) (21); estrogen plus progesterone MHT (risk) (21); oral contraceptive use (protective effect that increases with time of use) (22); parity (protective effect increases with number of live births) (23, 24); tubal ligation (protective) (25); and breast feeding (protective) (26, 27). Similar to genetic risk factors, environmental risk factors also differ by histology (28); for example, endometriosis is associated with risk of only clear cell, low-grade serous, and endometrioid EOC (20, 29). The vast majority of epidemiological studies of EOC risk have focused on marginal effects of genetic and environmental factors. A recent study by OCAC investigators assessed GE interactions across six known genetic risk loci (30). While this study looked at GE by histotype, this study did not investigate a three-way interaction involving obesity.

Obesity is associated with an increase in insulin levels, resulting in an increase in insulin-like growth factor 1 (*IGF1*) activity (31, 32). Increased levels of adiposity also lead to increased aromatase activity, and thus to an increase in estrogen levels (31, 33-35). After menopause, adipose tissue is the major source of estrogen in women. In breast cancer, evidence suggests that increased estrogen levels might underlie the association between BMI, breast cancer risk and MHT (31). It has been found that in post-menopausal women, the association between breast cancer and BMI is stronger in women who have never received MHT, compared with women who have used MHT (36). Similarly, a recent meta-analysis (2012) found that use of MHT attenuated the effect of BMI on EOC risk (17). A recent OCAC study found that high BMI was associated with increased risk of EOC in 15 case-control studies (16). In addition to finding an association between BMI and EOC risk, they found that this association was more pronounced in borderline serous, invasive

endometrioid, and invasive mucinous histotypes. However, they found that MHT did not attenuate the effect of BMI on EOC risk when the analyses were restricted to post-menopausal women. Additionally, they also found no association of BMI with risk of ovarian cancer in the most common serous histotype (16). Based on these data, we hypothesize that GE effects could differ between obese and non-obese women.

Based on the complex relationship between hormone exposure, obesity, growth factors / insulin levels, and genetic factors we hypothesize that GE effects could be histology dependent and differ between obese and non-obese women. This hypothesis is illustrated in **Supplemental Figure 1**. In this candidate gene study, we sought to detect both two-way and multifactor obesity-gene-environment interactions for EOC risk. Overall, we assessed 11,441 SNPs located within 80 candidate genes related to hormone biosynthesis and metabolism in addition to those in insulin-like growth factors. The case-control analyses were run separately for case groups that involve: (1) all EOC invasive cases; (2) high-grade serous (HGS) invasive cases; and (3) endometrioid (ENDO) invasive cases. Candidate gene analyses specific to the less common histotypes were excluded due to the difficulty of assessing three-way interactions.

MATERIALS AND METHODS

Study Participants

Supplemental Tables 1 and **2** summarize the characteristics of the 14 OCAC studies used to assess GE interactions (37-49). The 14 studies included in this analysis were part of the Collaborative Oncological Gene Environment Consortium (COGS) study in which approximately 200,000 SNPs were genotyped in breast, ovarian and prostate

cancers. Each OCAC study included in the analyses had to contribute at least 50 ovarian cancer cases and 50 controls, with controls further required to be sampled from the same population as the cases. Thus, 6,247 invasive cases and 10,379 controls of European descent were included in this analysis. GE interactions have been explored in these studies previously (28) and are described in further detail therein. Each study provided information on age at diagnosis or enrollment, BMI and other reproductive and lifestyle factors as well as information regarding tumor histology (serous, endometrioid, clear cell, mixed, other), tumor behavior (invasive or borderline), and tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated). All patients provided informed consent, including for passive and active follow-up, using protocols approved by the appropriate Institutional Review Board. **Table 1** describes the clinical features of EOC cases (6247 all EOC, 3019 HGS, 961 ENDO) and controls (N = 10379).

Environmental and Genetic Risk Factors

Young Adult BMI

To quantify obesity we used BMI calculated in early adulthood (18-29 years of age) as opposed to BMI at diagnosis as early adulthood BMI would better approximate subjects obesity levels integrated over a lifetime (18, 50), and thus exposure to estrogen derived from adipose tissue. Measurement of weight in early adulthood was conducted in 9 of the 14 studies used for the GE analyses (16); and therefore the three-way BMI-GE interaction analyses were limited to these 9 studies. Five studies reported weight at age 18 (DOV, HAW, HOP, POL, UCI), two studies reported weight ‘in your 20s’ (MAL, USC), and two studies reported weight at age 20 (AUS, GER). The calculated BMIs were

classified according World Health Organization (WHO) standards: (<18.5 ‘underweight’; 18.5–24.9 ‘normal weight’; 25–29.9 ‘overweight’; 30-34.9 ‘class I obesity’; 35-39.9 ‘class II obesity’; and ≥40 ‘class III obesity’) (51). From these WHO standards the subjects BMI were further categorized into two groups for GE analyses: (1) underweight or normal weight individuals with BMI less than 25 and (2) overweight or obese individuals BMI greater than 25.

Hormone-Related Environmental Factors

The GE analyses included seven hormone-related environmental factors: oral contraceptive use, parity, breast feeding, tubal ligation status, endometriosis, estrogen MHT, and estrogen plus progesterone MHT. To facilitate testing for multifactor interactions each environmental factor was dichotomized to ensure reasonable sample sizes in the various groups. Oral contraceptive use (years) was divided into (< 1 year; >= 1 year), parity (0 full births; >= 1 full birth), breast feeding was separated into (ever/never), estrogen MHT and estrogen plus progesterone MHT were categorized as (never/ever), while endometriosis and tubal ligation were included in terms of yes/no status.

Genetic Markers

We searched the literature to determine a set of candidate genes related to steroid biosynthesis, estrogen signaling and insulin-like growth factors (IGFs), as we hypothesize that genetic variants within these candidate genes modify EOC risk and that these effects are modified by hormone-related risk factors and obesity (52-54), and identified a list of 80 candidate genes (**Supplemental Table 3**). Using the National Center for Biotechnology Information (NCBI) website, SNPs were selected within 20 Kb of the first or last exon, as

this was expected to sufficiently cover the promoter regions of most genes, as well as SNPs in LD with variation in the gene region (55). Due to power limitations for testing multifactor gene-environment interactions, SNPs were excluded from the analysis if the minor allele frequency (MAF) was less than 10%. This approach extracted 11,441 candidate gene SNPs. The candidate gene SNPs were imputed using the 1000 Genomes project (56), from an original set of > 200,000 genotyped SNPs from the COGS custom Illumina SNP array (57, 58). Details on the number of imputed SNPs for each candidate gene are included in (**Supplemental Table 3**).

Statistical Analysis

The study population was restricted to individuals of European descent based on LAMP analyses (59) with complete covariate information; and only invasive EOC cases were considered. For analyses involving the MHTs, either estrogen use or estrogen plus progesterone (EPP) use, the cases and controls were further restricted to post-menopausal women. For both the GE and BMI-GE (or GEE) analyses, the presence or absence of the environmental factors were coded as either 0 or 1. Separate analyses were conducted for case groups that included: (1) all invasive EOC cases, (2) HGS cases, and (3) ENDO cases. Analyses were adjusted for age of diagnosis (enrollment), study site and the first 5 principal component scores from a principal component analysis to adjust for population substructure. With the goal to determine gene-environmental effects and not general genetic association, assessment of significance was restricted to the higher level interaction effects (as opposed to "omnibus" tests for both genetic main and interaction effects(60)).

The following logistic regression model was used to assess gene-environment interaction for each SNP. For *i = 1,…,n* let

$$\text{logit } \mathrm{P}\left(\mathrm{D}_i = 1 \middle| \mathrm{G}_{ij}, \mathrm{E}_{ik}, \mathrm{Z}_i\right) = \beta_0 + \beta_{\mathrm{G}}\mathrm{G}_{ij} + \beta_{\mathrm{E}}\mathrm{E}_{ik} + \beta_{\mathrm{GE}}\mathrm{G}_{ij}\mathrm{E}_{ik} + \mathrm{Z}_i\beta_{\mathrm{Z}},$$

where D_i represents that disease status (case =1, control = 0) for subject *i* , G_{ij} represents the number of minor alleles observed for subject *i* for SNP *j*, E_{ik} represents the absence or presence of environmental factor *k* for subject *i*, and Z_i represents a vector of covariates for subject *i* to account for potential confounding, and each β_{GE} represents a corresponding interaction regression coefficient. For each SNP *j* and environmental factor *k* we tested the null hypothesis of no GE interaction versus an alternative hypothesis that a GE interaction is present (i.e., null hypothsis: $\beta_{\mathrm{GE}} = 0$ vs. alternative hypothesis: $\beta_{\mathrm{GE}} \neq 0$). The hypothesis was tested with the likelihood ratio test statistic $D = -2\ln\left(\frac{\text{likelihood for reduced (null))model}}{\text{likelihood for full (alternative)model}}\right) \sim \chi_1^2$.

Similarly, to test whether GE interactions could be modified by BMI we considered the following logistic regression model. For *i = 1,…n* let

$$\text{logit } P\left(D_i = 1 \middle| G_j, E1_i, E2_{ik}, Z_i\right) = \beta_0 + \beta_G G_j + \beta_{E1} E1_i + \beta_{E2} E2_i + \beta_{GE1} G_j E1_i + \beta_{GE2} G_j E2_i + \beta_{E1E2} E1_i E2_i + \beta_{GEE} G_j E1_i E2_i + Z_i\beta_Z,$$

where $\mathrm{E1_i}$ represents the BMI status (low/high) at young adulthood of subject *i*, $\mathrm{E2_i}$ represents the presence of absence of the second environmental factor for subject *i*, and Z_i represents a vector of covariates for subject *i* that account for potential confounding, and each β represents a corresponding regression coefficient. To test whether GE interactions differ between non-obese and obese individuals we test the null hypothesis of no GEE interaction versus an alternative hypothesis of GEE interaction is present (i.e., null

hypothesis $\beta_{GEE} = 0$ versus alternative hypothesis : $\beta_{GEE} \neq 0$). This hypothesis was tested using a likelihood ratio test statistic $D = -2\ln\left(\frac{\text{likelihood for reduced (null)model}}{\text{likelihood for full (alternative)model}}\right)$ $\sim\chi_1^2$.

RESULTS

Gene-Environment Interaction

In total, the GE analyses were run across 11,441 candidate gene SNPs, and included 91,528 GE combinations (11,441 SNPs x (7 Environmental Factors + BMI)), and these analyses were run across 3 separate case groups (All, HGS, ENDO). However, the imputed SNPs were in high linkage disequilibrium, and the analyses across case groups were also highly correlated. The SimpleM method was used to estimate the effective number of independent SNPs tested within each gene (61) (**Supplemental Table 3**); and in total the analyses were estimated to involve independent 2336 SNPs. Using the estimated effective number of independent tests, the Bonferroni corrections for the number of total candidate gene SNPs was 0.05/2,336 = 2.1 x 10^{-5}, while adjusting for the total number of independent GE combinations gives 0.05/(2,336 x 8) = 2.7 x 10^{-6} respectively. Several SNP-environment interactions were significant using the former threshold, however using the latter strict threshold, no significant GE was detected. SNPs with GE interaction $p < 10^{-4}$ are presented in **Table 2**.

Figure 1 provides an image map that highlights interaction tests of environmental factors and candidate genes with at least one SNP p-value less than pre-defined significance

thresholds: $p = 10^{-3}$, $p = 10^{-4}$, and $p = 10^{-5}$. Within this plot, the candidate genes are grouped alphabetically according to their involvement in the production of hormones hypothesized to influence EOC risk (62) (Androgen, Estrogen, Progesterone, Gonadotropins, Insulin-related). A full list of SNPs with minimum p-values ($p < 10^{-3}$) in candidate genes for the GE interaction analyses are presented in **Supplemental Table 4**.

The most statistically significant GE-interaction was *IGF1R* (rs41497346, estrogen plus progesterone (EPP) MHT, histology = all, OR = .56, $p = 4.9 \times 10^{-6}$) (**Figures 2a, 2b**). The marginal odds ratio estimate of rs41497346 was .96 (p = .12). However, within non - EPP MHT users the presence of a minor allele increased risk for EOC (OR = 1.29); while within EPP MHT users rs41497346 provided a protective effect (OR = 0.72). The rs41497346 – EPP MHT interaction estimates were qualitatively similar across each histology included in our candidate gene analyses: HGS (OR = .55, $p = 1.7 \times 10^{-4}$), and ENDO (OR = .77, p = .38). The next most significant GE interaction result included *ESR1* (rs12661437, endometriosis, histology = all, OR = 1.71, $p = 1.5 \times 10^{-5}$) (**Figures 2c and 2d)**, where the minor allele decreased EOC risk in patients with no endometriosis and increased risk in patients with endometriosis. The marginal odds ratio estimate of rs12661437 was .95 (p = .17). However, within women with no endometriosis history, the presence of a rs12661437 minor allele decreased risk for EOC (OR = .92); while within women with a history of endometriosis, the rs12661437 minor allele provided increased risk (OR = 1.59). Subtype specific analyses for rs12661437 also found qualitatively similar effect sizes across all histologies (**Supplemental Table 4)**. Rs12661437 lies in an intron near the 5' end of *ESR1*.

When restricting the cases to HGS, the most notable interaction was for *CYP11A1* (rs9944175, endometriosis, histology = HGS, OR = .42, $p = 4.1 \times 10^{-5}$) (**Figures 2e and 2f)**. The marginal odds ratio estimate for HGS EOC risk of rs9944175 was 1.06 (p = .26). However, for women with no history of endometriosis, the estimated effect of one rs9944175 minor allele increased HGS EOC risk (OR = 1.1) but decreased HGS EOC risk in women with a history of endometriosis (OR = .47). This SNP showed no statistically significant interaction for the ENDO histology (OR = .69, p = .18). rs9944175 lies within 20Kb of the 3' end of *CYP11A1*.

Multifactor or BMI-Gene-Environment Interactions

For each gene, SNPs with notable BMI-GE interaction results ($p < 10^{-3}$) and their estimated interaction effects are presented (**Supplemental Table 5**). **Figure 3** provides an image map that highlights 3-way interaction tests of obesity, lifestyle and reproductive factors, and candidate genes with at least on SNP p-value less than: $p = 10^{-3}$, $p = 10^{-4}$, and $p = 10^{-5}$. This image map groups the candidate genes alphabetically and according to their involvement in the production of hormones hypothesized to influence EOC risk (62) (Androgen, Estrogen, Progesterone, Gonadotropins, Insulin-related). No statistically significant SNPs were detected after Bonferroni correction for the effective number of candidate gene SNPs ($p < 2.1 \times 10^{-5}$). A stricter threshold that adjusts for effective number of candidate gene SNPs by 7 environmental factors in the BMI-GE analyses was $p < 3.1 \times 10^{-6}$.

The most statistically significant SNP for the BMI-GE analyses lies in *INSR* (rs8102954, parity, histology = ENDO, BMI-GE OR = .074, $p = 8.83 \times 10^{-6}$) (**Figures 4a and 4b**). Within the low BMI women group the estimated SNP – Parity interaction of one

rs8102954 minor allele for the ENDO cases was negligible (OR $GE_{low\ BMI}$ = 1.4, p = .15); while within high BMI women the estimated GE effect is (OR $GE_{high\ BMI}$ = .10, p = .0021). The BMI – GE interaction effect was not significant for analyses with case groups that included all histology and high-grade serous cases. rs8102954 lies in a exonic region near the 3' end on INSR.

For case-controls analyses including all histologies, the most notable BMI-GE interaction was IGFBP2 (rs869564, parity, histology = All, BMI – GE OR = .096, p = 1.43 x 10^{-5}) (**Figures 4c and 4d**). For low BMI women the estimated SNP – parity interaction effect of one rs869564 minor allele was negligible (OR $GE_{low\ BMI}$, p = .48); however within high-BMI women the estimated GE interaction effect was (OR $GE_{high\ BMI}$ = .11, p = 4.14 x 10^{-5}). The three-way BMI-GE interaction effect was significant for the HGS cases (BMI – GE OR = .077, p = 1.23 x 10^{-3}), but not the analyses involving the ENDO cases (BMI – GE OR = p = .18). rs869564 resides in an exonic region on the 3' end of IGFBP2.

For HGS cases, the most statistically significant SNP for the BMI-GE analyses lies in *CYP11B1* (rs113759408, oral contraceptive use, histology = HGS, BMI-GE OR = .072, p = 2.2 x 10^{-5}) (**Figures 4e and 4f**). Within the low BMI women group the estimated SNP-OC use interaction effect of one rs113759408 minor allele for HGS cases was negligible (OR $GE_{low\ BMI}$= -.90, p = .41); while within high BMI women the estimated GE effect is large (OR $GE_{high\ BMI}$ = 4.52, p = .0028). The BMI-GE interaction effect was not statistically significant for the ENDO histology (BMI-GE OR= 2.11, p=.24). rs113759408 lies in an intronic region in the middle of *CYP11B1*.

DISCUSSION

In this paper, we investigated both gene-environment and multifactor obesity-gene environment interactions in epithelial ovarian cancer (EOC) risk. We used 14 case-control studies within the Collaborative Oncological Gene Environment Consortium (COGS) and Ovarian Cancer Association Consortium (OCAC) that provided more than 6,000 cases and 10,000 controls. Our main hypothesis was that some EOC risk due to SNPs could be explained by interactions with environmental factors. Similar to breast and endometrial cancers, many EOC risk factors relate to hormone exposure, and increased levels of estrogen has been associated with obesity in post-menopausal women. Therefore, we hypothesized that gene-environment interactions dealing with hormone-related risk factors could differ between obese and non-obese women. None of the tests of gene-environment interaction and multi-factor obesity-gene-environment interaction were significant at genome-wide level ($p = 5x10^{-8}$).

The most statistically significant gene-environment interaction result was *IGF1R* (rs41497346, estrogen plus progesterone MHT, Histology = All, OR = 0.56, $p = 4.9 \times 10^{-6}$). Rs41497346 lies in an intronic region near the 3' end of *IGF1R*, and is in the same linkage disequilibrium block as several SNPs hypothesized to have marginal risk in breast cancer (63). High expression levels of *IGF1R* were reported by Tang et al (64) in tumor tissue samples from 25 of 36 patients with epithelial ovarian cancer. Estrogen use is associated with increased *IGF1R* expression, while progesterone was associated with decreased *IGF1R* expression in breast cancer cells (65). Variation within the gene *ESR1* was also found to be involved in an interaction involving endometriosis in analyses of all histologies (rs12661437, intronic SNP near 5' end of gene, $p = 1.5 \times 10^{-5}$), where the minor allele decreased EOC risk in patients with no endometriosis and increased risk in patients

with endometriosis. Subtype specific analyses for rs12661437 also found qualitatively similar effect sizes across all histologies. Variation near *ESR1* (rs2295190) has been reported to be associated with EOC risk (66); however the SNPs are in low LD ($r^2 = 0.001$).

For the BMI-GE interaction analyses, the most statistically significant results were *INSR* (rs8102954, parity, histology = ENDO, BMI-GE OR = 0.074, $p = 8.83 \times 10^{-6}$) (**Figures 4a and 4b**) and *IGFBP2* (rs869564, parity, histology = All, BMI – GE OR = 0.096, $p = 1.43 \times 10^{-5}$) (**Figures 4c and 4d**). No genetic polymorphisms within *INSR* and *IGFBP2* have been associated previously with ovarian cancer risk. Nevertheless, considerable research exists on the role of insulin receptors and cancer as studies have shown that insulin receptors may be involved in the regulation of ovarian cancer cell growth(67) and that increased levels of insulin have been associated with breast and endometrium cancers for which these tumorigenic properties can be modified by insulin receptors (31). Similarly, the role of insulin-like growth factors (IGFs) have been extensive studied for their role in carcinogenesis(68). Specifically, *IGFBP2* has been linked ovarian cancer by promoting cancer cell invasion(69), while common variants in *IGF1*, *IGFBP1* and *IGFBP3* have been associated with ovarian (70) and endometrial cancers (71). *IGFBP2* has also been linked to other hormone-related cancers (72-74).

For the high-grade serous cases, the most statistically significant SNP for the BMI-GE analyses lies in *CYP11B1* (rs113759408, oral contraceptive use, Histology = HGS, BMI-GE estimate = 1.49, $p = 2.2 \times 10^{-5}$) (**Figures 4e and 4f**). Polymorphism rs113759408 lies in an intronic region in the middle of *CYP11B1* (between exons 3 and 4), the gene that encodes for steroid 11beta-hydroxylase. Mutations in this gene cause congenital adrenal hyperplasia (OMIM #202010). No research has been published showing a link between

EOC risk and variants within this gene. However, genetic variation in *CYP11B1* has been reported to be associated with breast cancer risk from a prediction model involving SNP rs4541 in exon 7 of *CYP11B1* (75) and the association with serum hormone levels in breast cancer patients (76) .

We chose to restrict our analyses to SNPs located within 80 candidate gene and 8 established ovarian cancer reproductive or lifestyle factors. An earlier study investigated 2-way interactions between 6 established SNP risk loci and 5 established environmental risk factors (30). Similar to our study results, their 2-way interaction analyses were not strong enough to rule out the role of chance. While these initial findings suggest that gene-environment interactions play a modest role in EOC risk, genome-wide studies are necessary to fully examine the potential interplay between SNPs and environmental factors.

For the obesity-gene-environment analyses, a strength of this study was the use of young adult BMI (low, high) as opposed to BMI at diagnosis, since young adult BMI may serve as an indicator of obesity integrated over a life-time and adipose-based estrogen exposure (18, 50). While a biological rationale exists for higher-order interactions, very little literature has focused on multi-factor interactions, perhaps due to the challenge of necessary power to detect these higher order interactions. Therefore, a limitation of the multi-factor gene-environment interaction analyses were modest sample sizes: especially for less well documented environmental factors and histology specific analyses (**Supplemental Tables 6 and 7**).

In conclusion, we have demonstrated the feasibility of assessing multi-factor interactions in large genetic epidemiology studies. Future work is needed to develop powerful statistical methods able to detect these complex interactions, as they may provide additional information regarding the genetic etiology of ovarian and other hormone – related cancers. Follow-up studies are necessary to assess the robustness of our notable findings in *ESR1*, *CYP11A1*, *IGF1R*, *CYP11B1*, *INSR*, and *IGFBP2*. To further follow-up our investigation of multi-factor gene-environment interactions, we will explore other potential modifiers of gene-environment risk, such as BRCA mutation status, and assess BMI-GE in other hormone-related cancers, such as breast, prostate and endometrial.

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Table 1: Clinical features in EOC cases & controls included in the GE and BMI-GE analyses. Sample sizes vary as not all studies collected data on each lifestyle and reproductive factor.

Characteristics	Controls: N (%)	Cases: N (%)	P
Age (years)			<.0001
Mean ± SD	57.5 ± 11.6	58.3 (11.0)	
Age (categorical)			<.0001
< 50 years	2604 (25.1)	1366 (21.9)	
50 to 55 years	1424 (13.7)	946 (15.1)	
55 to 60 years	1691 (16.3)	1071 (17.1)	
60 to 65 years	1629 (15.7)	1015 (16.2)	
> 65 years	3031 (29.2)	1849 (29.6)	
Young Adult BMI (kg/m^2)			<.0001
Underweight/Normal (< 25)	7607 (91.8)	4427 (89.7)	
Overweight/Obese (> 25)	679 (8.2)	508 (10.3)	
Parity			<.0001
(0 full births)	1415 (14.7)	1453 (25.1)	
(> 0 full births)	8234 (85.3)	4328 (74.9)	
Breast Feed			<.0001
No	2312 (30.3)	1641 (39.9)	
Yes	5320 (69.7)	2467 (60.1)	
Oral contraceptive use			<.0001
(<= 2 years)	4895 (47.4)	3487 (57.1)	
(> 2 years)	5428 (52.6)	2616 (42.9)	
Estrogen use			.44
No	3986 (78.9)	2250 (78.1)	
Yes	1068 (21.1)	631 (21.9)	
EPP MHT Use			<.0001
No	3420 (67.7)	2105 (73.3)	
Yes	1631 (32.3)	765 (26.7)	
Endometriosis			<.0001
No	8738 (93.9)	4802 (90.0)	
Yes	568 (6.1)	533 (10.0)	
Tubal Ligation			<.0001
No	6924 (77.8)	4692 (83.5)	
Yes	1976 (22.2)	926 (16.5)	
Tumor Grade			
Well-Differentiated		739 (12.1)	
Moderately Differentiated		1358 (22.2)	
Poorly Differentiated		2911 (47.6)	
Undifferentiated		459 (7.5)	
Other		647 (10.6)	
Histotypes			
Serous		3589 (57.4)	
Mucinous		403 (6.5)	
Endometrioid		961 (15.4)	
Clear Cell		468 (7.5)	
Others		827 (13.2)	

Table 2: Association with $p < 10^{-4}$ for GE and BMI-GE analyses. Results highlighted in green or red in **Figures 1** and **3**. More detailed summaries of these top hits are shown in **Supplemental Tables 4** and **5**.

Analysis	Histology	Environment	Gene	SNP	MAF	N cases	N controls	Interaction	P-value
GE	All	EPP MHT	IGF1R	rs41497346	0.28	2870	5051	-0.577	4.92×10^{-6}
GE	All	Endometriosis	ESR1	rs12661437	0.34	5335	9306	0.534	1.47×10^{-5}
GE	ENDO	Estrogen MHT	HSD17B2	rs2955162	0.23	405	5054	-1.12	3.44×10^{-5}
GE	HGS	Endometriosis	CYP11A1	rs9944175	0.24	2578	9306	-0.872	4.13×10^{-5}
GE	ENDO	Estrogen MHT	AKR1C3	rs61856140	0.10	405	5054	-1.47	5.30×10^{-5}
GE	ENDO	Endometriosis	CYP11B2	rs28526467	0.43	815	9306	-1.09	6.83×10^{-5}
GE	ENDO	OC Use	PRL	rs72836169	0.10	945	10323	-0.827	7.09×10^{-5}
BMI-GE	ENDO	Parity	INSR	rs8102954	0.37	778	8284	-2.56	8.35×10^{-6}
BMI-GE	All	Parity	IGFBP2	rs869564	0.11	4934	8284	-2.34	1.43×10^{-5}
BMI-GE	HGS	OC Use	CYP11B1	rs113759408	0.17	2296	8250	1.49	2.18×10^{-5}

Figure Legends:

Figure 1: Image map of top p-values for GE interactions results for 80 candidate gene SNPs and 7 hormone related environmental factors as well as BMI.

Figure 2: Locus zoom plots and estimated GE interaction effects of top results for *IGF1R*-Combination use (a,b), ESR1-Endometriosis (c,d), and *CYP11A1*-Endometriosis (e,f). The vertical black lines represent 95% confidence intervals for estimated odds ratios.

Figure 3. Image map of smallest p-values for multi-factor BMI-GE interactions results for Candidate Gene SNPs and 7 non-obesity related environmental factors.

Figure 4. Locus zoom plots and estimated BMI-GE interaction effects of top results for *INSR*-Parity-BMI (Histology ENDO) (a,b), *IGFBP2-Parity-BMI (Histology All)* (c,d), and *CYP11B1*-OC Use-BMI (Histology HGS) (e,f). The vertical black lines represent 95% confidence intervals for estimated odds ratios.

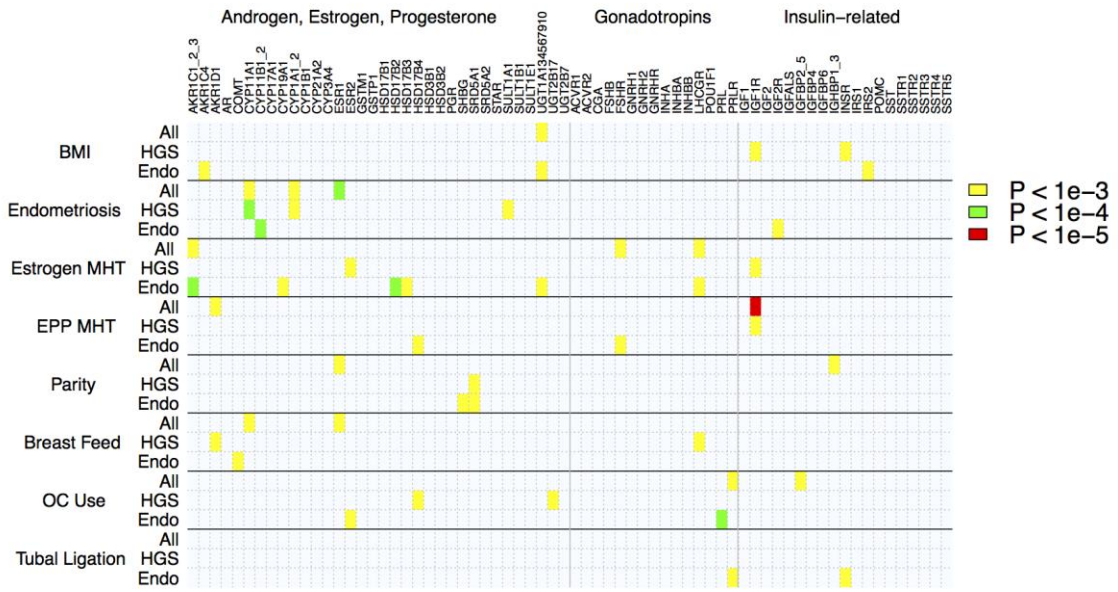
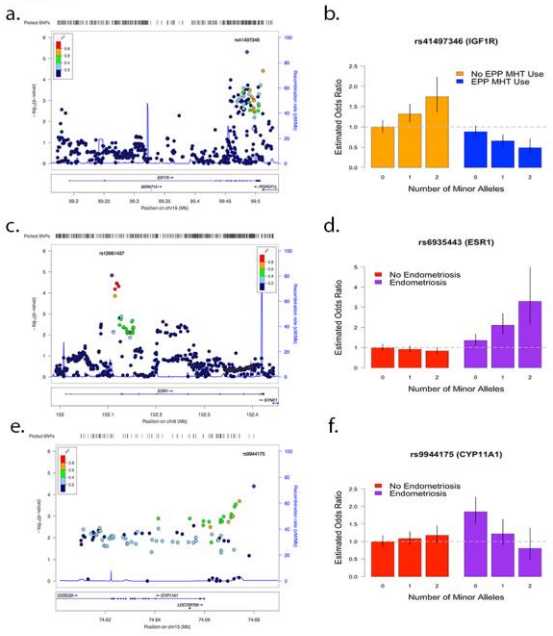

Androgen, Estrogen, Progesterone
Gonadotropins
Insulin−related
BMI
Endometriosis
Estrogen MHT
EPP MHT
Parity
Breast Feed
OC Use
Tubal Ligation
All
HGS
Endo
P < 1e−3
P < 1e−4
P < 1e−5

Figure 2


a.
b.
rs41497346 (IGF1R)
No EPP MHT Use
EPP MHT Use
Estimated Odds Ratio
Number of Minor Alleles
c.
d.
rs6935443 (ESR1)
No Endometriosis
Endometriosis
Estimated Odds Ratio
Number of Minor Alleles
e.
f.
rs9944175 (CYP11A1)
No Endometriosis
Endometriosis
Estimated Odds Ratio
Number of Minor Alleles

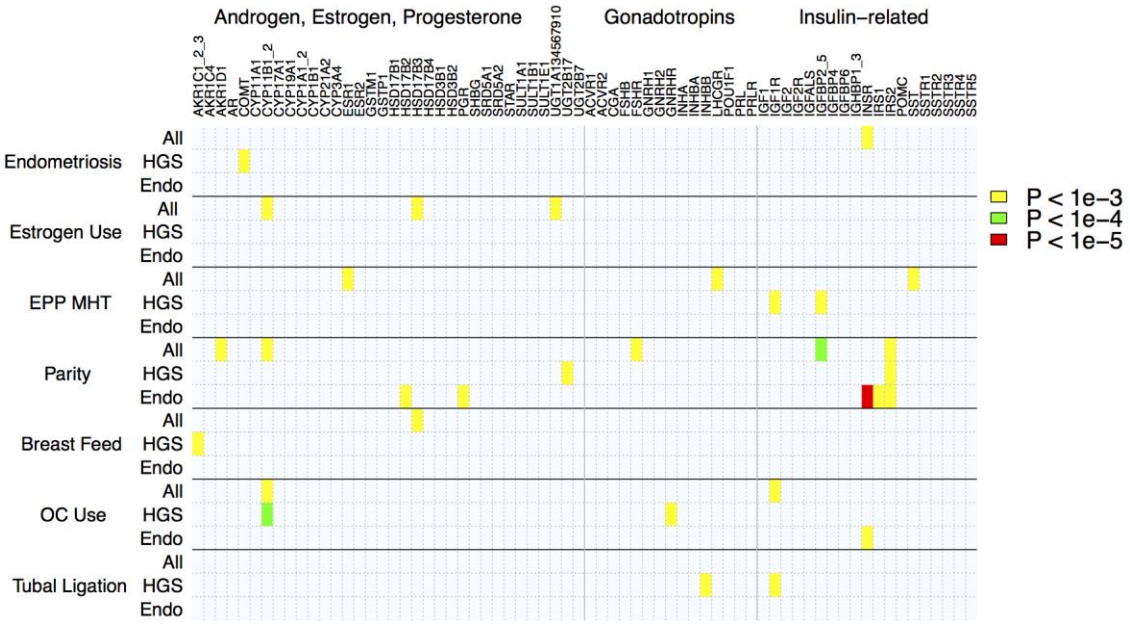
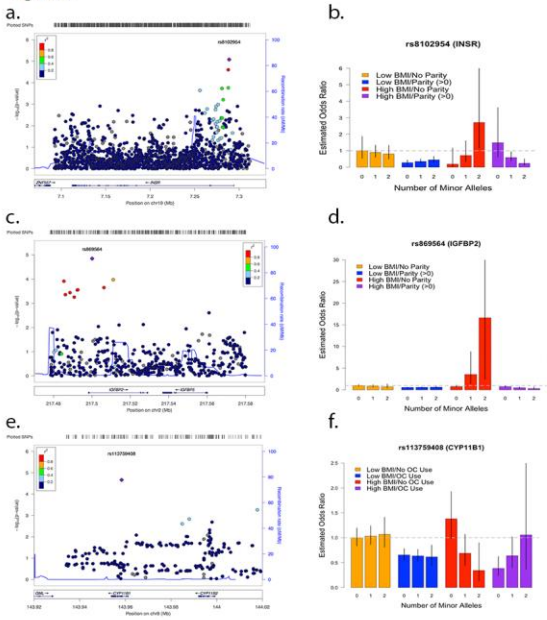
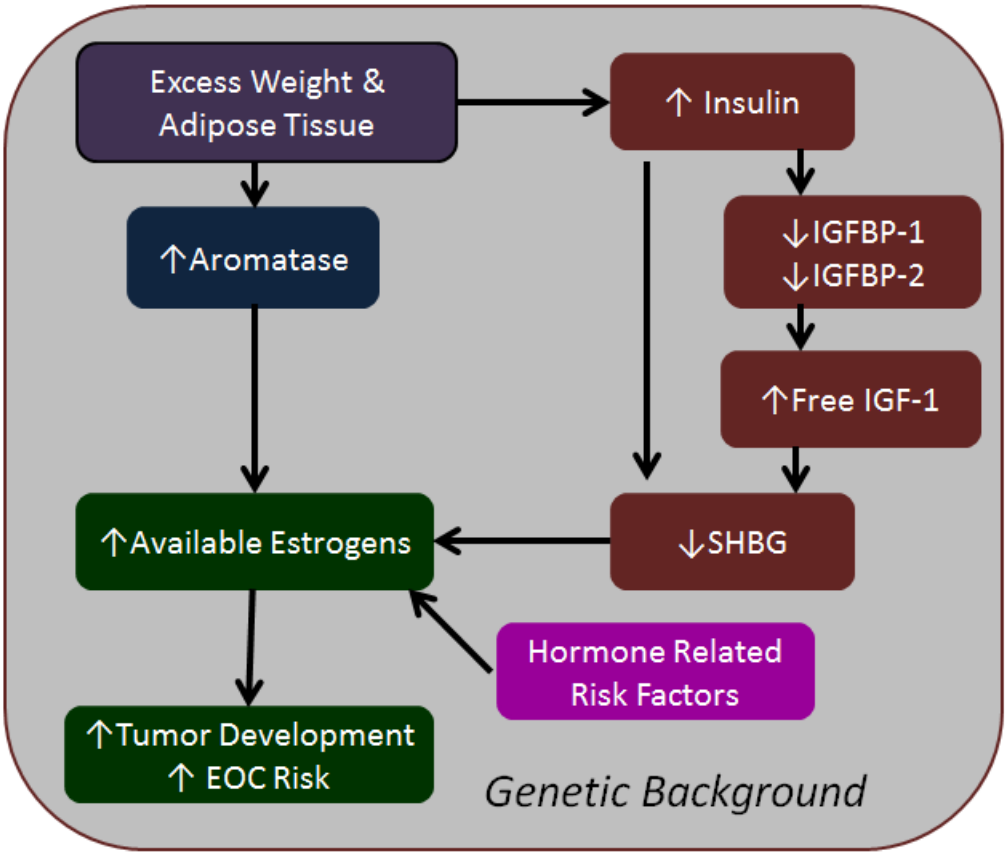

Androgen, Estrogen, Progesterone
Gonadotropins
Insulin−related
AKR1C1_2_3
AKR1C4
AKR1D1
AR
COMT
CYP11A1
CYP11B1_2
CYP17A1
CYP19A1
CYP1A1_2
CYP1B1
CYP27A2
CYP3A4
ESR1
ESR2
GSTM1
GSTT1
HSD17B1
HSD17B2
HSD17B3
HSD17B4
HSD3B1
HSD3B2
PGR
SHBG
SRD5A1
SRD5A2
STAR
SULT1A1
SULT1B1
SULT1E1
UGT1A13456791O
UGT2B17
UGT2B7
ACVR1
ACVR2
CGA
FSHB
FSHR
GNRH1
GNRH2
GNRHR
INHA
INHBA
INHBB
LHCGR
POU1F1
PRL
PRLR
IGF1
IGF1R
IGF2
IGF2R
IGFALS
IGFBP2_5
IGFBP4
IGFBP6
IGFBP1_3
INSR
IRS1
IRS2
POMC
SSTR1
SSTR2
SSTR3
SSTR4
SSTR5
Endometriosis
Estrogen Use
EPP MHT
Parity
Breast Feed
OC Use
Tubal Ligation
All
HGS
Endo
P < 1e−3
P < 1e−4
P < 1e−5

Figure 4


a.
b.
rs8102954 (INSR)
Low BMI/No Parity
Low BMI/Parity (>0)
High BMI/No Parity
High BMI/Parity (>0)
Estimated Odds Ratio
Number of Minor Alleles
c.
d.
rs869564 (IGFBP2)
Low BMI/No Parity
Low BMI/Parity (>0)
High BMI/No Parity
High BMI/Parity (>0)
Estimated Odds Ratio
Number of Minor Alleles
e.
f.
rs113759408 (CYP11B1)
Low BMI/No OC Use
Low BMI/OC Use
High BMI/No OC Use
High BMI/OC Use
Estimated Odds Ratio
Number of Minor Alleles

Supplemental Figure 1: Potential Hormonal Mechanism to motivate investigation of multi-factor obesity-hormone related risk factors – SNP interactions.



Supplementary Table 1. Study Sites Information

Study Name	OCAC Acronym	Country	Years	Oral	Parity	Endom	Tubal	Estroge	Combi	Breast	Young	Young Adult BMI Reporting
Australian Ovarian Cancer Study	AUS	Australia	2002-2006	Y	Y	Y	Y			Y	Y	Weight at age 20
Diseases of the Ovary and their Evaluation	DOV	USA	2002-2005	Y	Y	Y	Y	Y	Y	Y	Y	Weight at age 18
Germany Ovarian Cancer Study	GER	Germany	1993-1995	Y	Y	Y	Y	Y	Y	Y	Y	Weight at age 20
Hawaii Ovarian Cancer Study	HAW	USA	1992-2008	Y	Y	Y	Y	Y	Y	Y	Y	Weigh at age 18
Hormones and Ovarian Cancer Prediction	HOP	USA	2003-2009	Y	Y	Y	Y	Y	Y	Y	Y	Weight at age 18
Danish Malignant Ovarian Tumor Study	MAL	Denmark	1994-1999	Y	Y	Y	Y			Y	Y	Weight in your 20s
Mayo Clinic Ovarian Cancer Case Control Study	MAY	USA	2000-2007	Y	Y	Y	Y	Y	Y		Y	Not reported
North Carolina Ovarian Cancer Study	NCO	USA	1999-2008	Y	Y	Y	Y			Y	Y	Not reported
Nijmegen Polygene Study & Nijmegen Biomedical Study	NTH	Netherlands	2008	Y	Y	Y	Y	Y	Y	Y	Y	Not reported
Ovarian Case-Control Study in Poland	POL	Poland	2000-2003	Y	Y	Y	Y	Y	Y	Y	Y	Weight at age 18
Family Registry for Ovarian Cancer and Genetic Epidemiology	STA	USA	1997-2001		Y		Y			Y		Not reported
UC Irvine Ovarian Cancer Study	UCI	USA	1993-2005	Y	Y	Y	Y		Y	Y	Y	Weight at age 18
UK Ovarian Cancer Population Study	UKO	UK		Y	Y	Y	Y	Y	Y	Y		Not reported
Los Angeles County Case-Control Studies of Ovarian Cancer	USC	USA	1993-2005	Y	Y	Y	Y	Y	Y	Y	Y	Weight in your 20s

Supplementary Table 2: Sample Sizes by Study Site.

Site	Controls	All Cases	High-Grade Serous Cases	Endometrioid Cases
AUS	822	529	288	71
DOV	1461	891	429	143
GER	413	191	82	21
HAW	145	57	34	11
HOP	1435	564	272	83
MAL	822	440	183	54
MAY	800	535	355	93
NCO	808	675	334	109
NTH	322	255	65	65
POL	664	235	96	36
STA	313	246	133	30
UCI	367	280	152	52
UKO	945	672	266	108
USC	1062	677	330	85
Totals	**10379**	**6247**	**3019**	**961**

Sample sizes correspond to white, non-hispanic women, with non-missing data for ag

Supplementary Table 3. Candidate Gene Summary

Gene	Chromosome	Number of COGS SNPs	Effect Number of Independent Tests
GSTM1	1	94	40
HSD3B2	1	71	18
HSD3B1	1	159	21
POMC	2	72	19
SRD5A2	2	117	28
CYP1B1	2	119	25
LHCGR	2	268	52
FSHR	2	642	70
INHBB	2	64	26
ACVR2	2	107	22
ACVR1	2	97	28
IGFBP2_5*	2	102	53
INHA	2	61	15
IRS1	2	21	17
UGT1A1_3_4_5_6_7_9_10*	2	355	66
POU1F1	3	73	21
SST	3	82	26
GNRHR	4	99	14
UGT2B17	4	192	34
UGT2B7	4	288	10
SULT1B1	4	122	22
SULT1E1	4	82	19
SRD5A1	5	168	38
PRLR	5	304	53
HSD17B4	5	167	37
PRL	6	98	26
CYP21A2	6	31	20
CGA	6	100	14
ESR1	6	772	152
IGF2R	6	258	78
SHBG	7	147	23
INHBA	7	45	14
IGHBP1_3*	7	128	30
CYP3A4	7	20	10
AKR1D1	7	155	28
GNRH1	8	46	9
STAR	8	17	16
CYP11B1_2*	8	212	26
HSD17B3	9	260	34
AKR1C1_2_3*	10	735	112
AKR1C4	10	207	32
CYP17A1	10	80	22
IGF2	11	159	51
FSHB	11	81	14
GSTP1	11	81	13
PGR	11	346	32
IGFBP6	12	76	26
IGF1	12	82	27
IRS2	13	186	31
SSTR1	14	76	21
ESR2	14	152	37
CYP19A1	15	271	58
CYP11A1	15	98	14
CYP1A1_2*	15	48	24
IGF1R	15	475	128
SSTR5	16	127	43
IGFALS	16	230	18
SULT1A1	16	120	41
HSD17B2	16	111	33
IGFBP4	17	47	22
HSD17B1	17	53	13
SSTR2	17	102	26
INSR	19	599	106
GNRH2	20	113	35
SSTR4	20	86	23
COMT	22	221	44
SSTR3	22	210	27
AR	23	54	9
Totals		**11441**	**2336**

***** Underscores (_) represent that the results correspond to multiple genes whose SNPs overlap in the analyses.

Supplementary Table 4. Candidate Gene GE Analyses top hits (p-value < 10^{-3})

Gene	SNP	Chromosome	Build 37 Position	MAF	Histology (Most Significant)	Environment	GE Est (all)	OR GE (all)	OR no (all)	OR yes (all)	GE LRT p-value (all)	GE Est (HGS)	OR GE (HGS)	OR no (HGS)	OR yes (HGS)	GE LRT p-value (HGS)	GE Est (Endo)	OR GE (Endo)	OR no (Endo)	OR yes (Endo)	GE LRT p-value (Endo)
AKR1C1_2_3	rs61856140	10	5111785	0.15	All	Estrogen Use	-0.49	0.61	1.11	0.68	3.79E-04	-0.37	0.69	1.02	0.71	2.99E-02	-1.47	0.23	1.36	0.32	5.30E-05
AKR1D1	rs75681380	7	137741527	0.28	All	EPP MHT Use	0.36	1.43	0.92	1.29	4.35E-04	0.30	1.35	0.90	1.20	1.62E-02	0.33	1.39	0.99	1.30	1.73E-01
CYP11A1	rs9944175	15	74679948	0.13	All	Breast Fed	0.31	1.37	0.85	1.17	7.69E-04	0.29	1.34	0.88	1.19	1.29E-02	0.27	1.32	0.73	0.99	2.09E-01
CYP11A1	rs9944175	15	74679948	0.13	All	Endometriosis	-0.50	0.61	1.09	0.69	7.86E-04	-0.87	0.42	1.12	0.47	4.13E-05	-0.37	0.69	0.96	0.79	1.78E-01
CYP1A1_2	rs183556665	15	74999266	0.11	All	Endometriosis	-0.60	0.55	1.02	0.58	7.98E-04	-0.72	0.49	1.04	0.51	2.75E-03	-0.88	0.41	1.01	0.47	1.10E-02
ESR1	rs1293950	6	151992921	0.26	All	Breast Fed	-0.24	0.79	1.22	0.96	3.38E-04	-0.14	0.87	1.13	0.98	9.48E-02	-0.35	0.70	1.47	1.04	1.63E-02
ESR1	rs12661437	6	152107936	0.20	All	Endometriosis	0.53	1.71	0.92	1.59	1.47E-05	0.54	1.72	0.94	1.66	1.04E-03	0.45	1.58	0.91	1.43	3.91E-02
ESR1	rs3020327	6	152301645	0.11	All	Parity	-0.35	0.70	1.26	0.88	7.36E-04	-0.36	0.70	1.22	0.85	9.75E-03	-0.47	0.62	1.29	0.80	1.49E-02
FSHR	rs7591064	2	49177601	0.18	All	Estrogen Use	-0.35	0.71	1.11	0.81	7.70E-04	-0.28	0.75	1.09	0.84	2.68E-02	-0.25	0.78	1.11	0.88	3.19E-01
IGF1R	rs41497346	15	99485931	0.14	All	EPP MHT Use	-0.58	0.56	1.29	0.72	4.92E-06	-0.59	0.55	1.23	0.68	1.76E-04	-0.26	0.77	1.06	0.82	3.80E-01
IGFBP2_5	rs4674105	2	217499149	0.31	All	OC Use	0.23	1.25	0.95	1.19	6.63E-04	0.22	1.25	0.96	1.22	8.68E-03	0.39	1.47	0.88	1.31	6.88E-03
IGHBP1_3	rs34416860	7	45910276	0.18	All	Parity	0.30	1.35	0.81	1.09	1.40E-04	0.23	1.25	0.87	1.09	3.20E-02	0.37	1.44	0.80	1.13	1.51E-02
LHCGR	rs4953625	2	48977778	0.30	All	Estrogen Use	0.35	1.42	0.89	1.30	7.15E-04	0.33	1.39	0.87	1.25	9.95E-03	0.62	1.85	0.95	1.83	1.79E-02
PRLR	rs10941235	5	35185580	0.29	All	OC Use	-0.18	0.84	1.05	0.87	6.69E-04	-0.12	0.89	1.01	0.90	8.80E-02	-0.12	0.89	1.00	0.89	2.95E-01
UGT1A134567910	rs17868323	2	234590970	0.42	All	BMI	-0.37	0.69	1.02	0.71	1.35E-04	-0.31	0.74	1.00	0.74	2.55E-02	-0.44	0.64	1.00	0.66	1.99E-02
AKR1C1_2_3	rs61856140	10	5111785	0.15	Endometrioid	Estrogen Use	-0.49	0.61	1.11	0.68	3.79E-04	-0.37	0.69	1.02	0.71	2.99E-02	-1.47	0.23	1.36	0.32	5.30E-05
AKR1C4	rs10795254	10	5236360	0.15	Endometrioid	BMI	-0.18	0.84	0.94	0.76	2.12E-01	0.00	1.00	0.93	0.90	9.91E-01	-1.16	0.31	1.01	0.31	8.45E-04
COMT	rs740603	22	19945177	0.48	Endometrioid	Breast Fed	-0.03	0.97	1.04	1.01	6.63E-01	-0.15	0.86	1.12	0.96	4.66E-02	0.47	1.60	0.85	1.36	3.10E-04
CYP11B1_2	rs28526467	8	143996964	0.49	Endometrioid	Endometriosis	-0.22	0.80	1.01	0.83	1.47E-01	0.12	1.12	0.98	1.13	5.61E-01	-1.09	0.34	1.13	0.35	6.83E-05
CYP19A1	rs72729214	15	51643333	0.23	Endometrioid	Estrogen Use	0.15	1.16	0.94	1.12	1.58E-01	-0.04	0.96	1.02	0.99	7.39E-01	0.80	2.23	0.82	1.90	9.80E-04
ESR2	rs17766755	14	64715773	0.34	Endometrioid	OC Use	-0.05	0.95	1.03	0.97	2.71E-01	0.02	1.02	1.02	1.04	7.43E-01	-0.38	0.68	1.10	0.75	4.79E-04
FSHR	rs6708637	2	49241849	0.39	Endometrioid	EPP MHT Use	-0.17	0.85	1.08	0.92	5.07E-02	-0.08	0.92	1.11	1.04	4.30E-01	-0.66	0.52	1.18	0.61	8.64E-04
HSD17B2	rs2955162	16	82128777	0.26	Endometrioid	Estrogen Use	-0.23	0.80	0.98	0.80	2.50E-02	-0.11	0.90	0.94	0.85	3.87E-01	-1.12	0.32	1.09	0.34	3.44E-05
HSD17B3	rs6479221	9	99045539	0.17	Endometrioid	Estrogen Use	0.07	1.08	1.08	1.17	5.65E-01	0.00	1.00	1.11	1.09	9.94E-01	1.28	3.61	0.87	2.86	5.57E-04
HSD17B4	rs11956614	5	118882502	0.17	Endometrioid	EPP MHT Use	-0.21	0.81	1.14	0.93	4.70E-02	-0.17	0.85	1.19	1.02	2.02E-01	-1.03	0.36	1.32	0.48	2.22E-04
IGF2R	rs1867348	6	160456163	0.10	Endometrioid	Endometriosis	-0.22	0.81	0.97	0.72	2.07E-01	0.00	1.00	0.96	0.88	9.98E-01	-1.48	0.23	0.93	0.19	7.09E-04
INSR	rs12463045	19	7295964	0.22	Endometrioid	Tubal Ligation	0.25	1.28	0.94	1.21	3.67E-02	0.10	1.10	0.94	1.05	5.12E-01	1.14	3.14	0.80	2.51	6.08E-04
IRS2	rs12584564	13	110391742	0.42	Endometrioid	BMI	-0.15	0.86	1.06	0.90	1.42E-01	-0.19	0.83	1.06	0.84	1.99E-01	-0.80	0.45	1.10	0.47	3.14E-04
LHCGR	rs12987764	2	48961338	0.21	Endometrioid	Estrogen Use	0.30	1.35	0.90	1.22	7.25E-03	0.26	1.29	0.83	1.08	6.83E-02	0.97	2.63	0.91	2.43	1.10E-04
PRL	rs72836169	6	22269312	0.11	Endometrioid	OC Use	-0.16	0.85	1.07	0.91	9.01E-02	-0.12	0.89	1.13	1.01	3.36E-01	-0.83	0.44	1.42	0.61	7.09E-05
PRLR	rs13159459	5	35182738	0.11	Endometrioid	Tubal Ligation	-0.03	0.97	0.98	0.95	7.58E-01	0.06	1.07	0.94	1.02	6.36E-01	-1.35	0.26	0.98	0.25	3.93E-04
SHBG	rs62453193	7	7538557	0.22	Endometrioid	Parity	0.03	1.03	0.95	1.00	7.12E-01	-0.10	0.90	1.12	0.99	3.85E-01	0.61	1.85	0.61	1.16	5.19E-04
SRD5A1	rs8192125	5	6633447	0.22	Endometrioid	Parity	-0.08	0.93	1.11	1.04	3.30E-01	0.00	1.00	1.03	1.04	9.79E-01	-0.50	0.61	1.41	0.88	6.53E-04
UGT1A134567910	rs1587493	2	234689751	0.18	Endometrioid	BMI	-0.26	0.77	0.98	0.78	3.15E-02	-0.16	0.85	0.92	0.82	3.53E-01	-0.75	0.47	1.08	0.53	9.03E-04
UGT1A134567910	rs7581102	2	234694727	0.29	Endometrioid	Estrogen Use	0.01	1.01	1.04	1.06	8.84E-01	-0.15	0.86	1.10	0.95	1.79E-01	0.80	2.22	0.90	1.85	2.04E-04
AKR1D1	rs6954846	7	137750696	0.22	High Grade Serous	Breast Fed	-0.20	0.82	1.18	0.98	1.10E-02	-0.34	0.71	1.25	0.90	6.51E-04	-0.19	0.83	1.38	1.14	3.10E-01
CYP11A1	rs9944175	15	74679948	0.13	High Grade Serous	Endometriosis	-0.50	0.61	1.09	0.69	7.86E-04	-0.87	0.42	1.12	0.47	4.13E-05	-0.37	0.69	0.96	0.79	1.78E-01
CYP1A1_2	rs2960192	15	75049943	0.39	High Grade Serous	Endometriosis	0.21	1.24	0.97	1.23	2.45E-02	0.45	1.57	0.97	1.60	4.34E-04	-0.02	0.98	1.00	1.04	9.23E-01
ESR2	rs6573551	14	64738106	0.11	High Grade Serous	Estrogen Use	-0.43	0.65	1.05	0.66	3.63E-03	-0.73	0.48	1.20	0.56	1.03E-04	0.14	1.15	0.76	0.83	7.05E-01
HSD17B4	rs3797372	5	118870452	0.34	High Grade Serous	OC Use	0.10	1.11	0.92	1.02	3.69E-02	0.22	1.24	0.85	1.07	9.23E-04	-0.02	0.98	0.96	0.94	8.48E-01
IGF1R	rs12898261	15	99308666	0.32	High Grade Serous	BMI	-0.19	0.83	0.98	0.81	5.82E-02	-0.46	0.63	0.99	0.63	8.30E-04	0.10	1.11	0.88	1.02	6.12E-01
IGF1R	rs28612945	15	99458902	0.18	High Grade Serous	EPP MHT Use	0.43	1.54	0.85	1.34	1.04E-04	0.51	1.67	0.83	1.38	1.60E-04	0.20	1.22	0.97	1.27	4.36E-01
IGF1R	rs7168671	15	99454962	0.18	High Grade Serous	Estrogen Use	0.23	1.26	0.99	1.23	2.76E-02	0.44	1.55	0.95	1.46	5.55E-04	0.02	1.02	1.02	1.04	9.45E-01
INSR	rs11880482	19	7131685	0.27	High Grade Serous	BMI	0.26	1.29	0.95	1.20	1.68E-02	0.51	1.67	0.91	1.49	4.37E-04	0.20	1.22	1.02	1.23	3.54E-01
LHCGR	rs36068361	2	48999621	0.16	High Grade Serous	Breast Fed	-0.25	0.78	1.25	0.98	8.58E-03	-0.45	0.64	1.44	0.93	2.70E-04	-0.15	0.86	1.18	1.03	4.74E-01
SRD5A1	rs274657	5	6680115	0.12	High Grade Serous	Parity	-0.22	0.80	1.18	0.96	2.92E-02	-0.44	0.64	1.39	0.91	8.40E-04	-0.03	0.97	0.96	0.97	8.79E-01
SULT1A1	rs11074905	16	28614472	0.44	High Grade Serous	Endometriosis	0.20	1.22	0.99	1.21	1.46E-01	0.67	1.95	0.98	1.89	3.62E-04	-0.30	0.74	0.92	0.70	2.39E-01
UGT2B17	rs34664906	4	69433714	0.37	High Grade Serous	OC Use	-0.14	0.87	1.06	0.92	6.00E-02	-0.34	0.71	1.19	0.84	5.25E-04	0.22	1.25	0.83	1.04	1.84E-01

Supplementary Table 5. Candidate Gene BMI-GE Analyses top hits (p-value < 10^{-3})

Gene	SNP	Chromosome	Build 37 Position	MAF	Histology (Most Significant)	Environment	GEE Est (all)	OR GEE (all)	OR low bmi/no (all)	OR low bmi/yes (all)	OR high bmi/no (all)	OR high bmi/yes (all)	GEE LRT p-value (all)	GEE Est (HGS)	OR GEE (HGS)	OR low bmi/no (HGS)	OR low bmi/yes (HGS)	OR high bmi/no (HGS)	OR high bmi/yes (HGS)	GEE LRT p-value (HGS)	GEE Est (Endo)	OR GEE (Endo)	OR low bmi/no (Endo)	OR low bmi/yes (Endo)	OR high bmi/no (Endo)	OR high bmi/yes (Endo)	GEE LRT p-value (Endo)
AKR1D1	rs12671202	7	137822376	0.13	All	Parity	1.32	3.73	1.24	1.00	0.55	1.58	3.25E-04	1.16	3.20	1.34	1.07	0.60	1.49	3.17E-02	1.65	5.21	1.53	0.96	0.67	1.49	8.79E-03
CYP11B1_2	rs6391	8	143956965	0.43	All	Estrogen Use	-2.55	0.08	1.09	0.95	0.92	0.03	2.72E-04	-2.46	0.09	1.11	0.88	0.82	0.00	1.36E-02	-1.83	0.16	1.11	1.46	0.46	0.00	1.54E-01
CYP11B1_2	rs80062072	8	143994398	0.32	All	OC Use	-1.17	0.31	1.14	1.08	2.01	0.57	6.28E-04	-1.07	0.34	1.14	1.11	1.53	0.54	2.59E-02	-0.46	0.63	1.33	0.93	1.97	0.81	5.08E-01
CYP11B1_2	rs11787475	8	143946223	0.14	All	Parity	2.05	7.76	1.01	0.95	0.23	1.83	2.64E-04	2.00	7.38	1.21	1.01	0.23	1.50	1.83E-02	2.20	9.00	1.23	0.97	0.29	2.64	1.77E-02
ESR1	rs11155811	6	152077846	0.48	All	EPP MHT Use	-1.09	0.34	1.03	1.13	1.54	0.51	9.19E-04	-0.82	0.44	1.07	1.16	1.52	0.63	6.71E-02	-1.49	0.23	1.01	1.13	2.00	0.00	6.05E-02
FSHR	rs1024776	2	49170035	0.21	All	Parity	0.92	2.50	1.08	0.97	0.53	1.16	3.86E-04	0.89	2.44	1.00	0.94	0.57	1.00	2.78E-02	0.32	1.38	1.09	1.04	0.53	0.94	4.80E-01
HSD17B3	rs10125001	9	99023237	0.44	All	Breast Fed	-1.05	0.35	0.93	0.94	2.17	0.73	7.58E-04	-1.11	0.33	0.92	0.91	1.98	0.60	8.06E-03	-2.02	0.13	1.00	1.01	3.58	0.40	4.65E-03
HSD17B3	rs8190534	9	99018281	0.22	All	Estrogen Use	-2.50	0.08	1.09	1.09	0.93	0.05	5.78E-04	-4.42	0.01	1.09	1.06	0.87	0.00	3.00E-03	-0.84	0.43	1.03	1.20	1.00	0.10	4.76E-01
IGF1R	rs1815007	15	99480263	0.39	All	OC Use	0.68	1.98	1.08	0.94	0.81	1.32	6.14E-04	0.64	1.89	1.12	0.95	0.83	1.22	2.26E-02	0.57	1.77	1.13	0.89	1.03	1.79	1.43E-01
IGFBP2_5	rs869564	2	217500111	0.11	All	Parity	-2.34	0.10	0.90	1.04	5.78	0.52	1.43E-05	-2.56	0.08	0.78	1.08	7.49	0.69	1.12E-03	-1.22	0.30	0.97	1.12	1.99	1.02	1.98E-01
INSR	rs7257990	19	7180910	0.12	All	Endometriosis	2.29	9.85	1.06	1.19	0.70	15.31	6.68E-04	2.28	9.74	1.05	1.09	0.78	57.15	4.87E-03	2.68	14.63	1.20	1.50	0.58	8.00E+25	1.08E-02
IRS2	rs1755724	13	110417837	0.14	All	Parity	-1.63	0.20	0.66	1.07	2.45	0.73	3.92E-04	-1.75	0.17	0.66	0.98	4.22	0.70	1.08E-02	-1.50	0.22	0.61	1.20	1.30	0.72	7.38E-02
LHCGR	rs12052559	2	48982174	0.18	All	EPP MHT Use	1.53	4.62	0.98	1.07	0.70	6.34	8.96E-04	1.32	3.75	0.98	1.08	0.65	5.78	1.77E-02	1.76	5.78	0.95	1.13	0.62	6.55	6.18E-02
SST	rs62277773	3	187372426	0.12	All	EPP MHT Use	2.01	7.45	1.11	0.96	0.80	14.78	5.25E-04	2.13	8.43	1.13	0.82	1.45	28.29	2.40E-03	2.37	10.66	1.47	0.97	0.59	234.16	3.62E-02
UGT1A134567910	rs2011404	2	234627937	0.15	All	Estrogen Use	-1.98	0.14	0.97	1.28	1.10	0.09	1.81E-04	-2.65	0.07	0.90	1.12	1.02	0.00	3.01E-04	-0.45	0.64	1.16	1.36	0.54	2.17	6.60E-01
HSD17B2	rs3887358	16	82136566	0.12	Endometrioid	Parity	0.37	1.44	1.06	1.01	0.95	1.04	3.11E-01	-0.02	0.98	0.89	1.07	0.70	0.95	9.67E-01	2.24	9.40	1.53	0.92	0.52	2.57	9.67E-04
INSR	rs150197522	19	7249994	0.18	Endometrioid	OC Use	-1.26	0.28	0.84	1.12	1.49	0.65	1.52E-03	-1.14	0.32	0.83	1.18	1.25	0.77	4.44E-02	-3.81	0.02	1.03	1.17	1.60	0.06	1.81E-04
INSR	rs8102954	19	7288771	0.37	Endometrioid	Parity	-0.31	0.73	1.10	1.05	1.19	0.84	3.24E-01	0.20	1.23	1.25	1.09	0.70	0.76	6.60E-01	-2.56	0.08	0.95	1.17	3.28	0.28	8.35E-06
IRS1	rs6725330	2	227666857	0.11	Endometrioid	Parity	-1.00	0.37	0.92	0.96	1.77	0.68	1.11E-02	-1.34	0.26	0.95	0.95	2.32	0.46	3.61E-02	-2.84	0.06	0.72	1.06	2.43	0.16	2.77E-04
IRS2	rs75453923	13	110418023	0.28	Endometrioid	Parity	-0.58	0.56	0.86	1.04	1.35	0.94	2.73E-02	-0.28	0.76	0.78	1.03	0.89	1.07	4.83E-01	-1.57	0.21	0.74	1.06	1.93	0.46	6.46E-04
PGR	rs600677	11	100887598	0.30	Endometrioid	Parity	-0.47	0.63	0.96	1.00	1.47	0.93	4.15E-02	-0.20	0.82	1.03	0.95	1.40	0.96	5.55E-01	-1.47	0.23	1.02	1.15	3.44	0.63	3.41E-04
AKR1C1_2_3	rs4881390	10	5108821	0.30	High Grade Serous	Breast Fed	0.45	1.57	0.97	1.03	0.70	1.26	9.16E-02	1.25	3.48	1.06	1.10	0.54	1.93	4.71E-04	-0.61	0.54	0.71	0.97	0.87	0.69	2.94E-01
COMT	rs72195121	22	20017857	0.50	High Grade Serous	Endometriosis	-1.01	0.36	0.98	1.10	1.09	0.37	1.32E-02	-2.29	0.10	1.01	1.21	1.13	0.06	2.31E-04	-0.46	0.63	1.06	0.95	1.21	9.97E+13	5.38E-01
CYP11B1_2	rs113759408	8	143958342	0.22	High Grade Serous	OC Use	1.02	2.77	0.99	1.03	0.51	1.73	1.25E-03	1.79	5.97	1.03	0.96	0.46	3.24	4.68E-05	0.74	2.11	0.98	1.05	0.45	1.10	2.43E-01
GNRHR	rs148964181	4	68607384	0.12	High Grade Serous	OC Use	0.52	1.68	1.08	1.00	0.81	1.33	1.67E-01	1.81	6.10	0.98	0.92	0.40	2.33	7.86E-04	-1.12	0.33	1.03	1.08	1.70	0.89	1.45E-01
IGF1R	rs8034564	15	99190601	0.43	High Grade Serous	EPP MHT Use	1.48	4.38	0.93	1.06	0.58	3.94	3.47E-04	2.16	8.63	0.93	1.08	0.50	7.86	2.35E-04	0.47	1.59	0.92	1.03	0.66	1.01	5.91E-01
IGF1R	rs12591120	15	99236869	0.25	High Grade Serous	Tubal Ligation	-0.46	0.63	1.00	1.02	1.10	0.79	8.03E-02	-1.20	0.30	1.04	1.00	1.48	0.47	9.65E-04	-0.36	0.70	1.11	1.22	0.75	0.61	6.63E-01
IGFBP2_5	rs56024880	2	217495408	0.30	High Grade Serous	EPP MHT Use	1.73	5.64	1.08	1.02	0.73	4.70	1.16E-03	1.77	5.84	1.06	1.20	0.74	7.44	9.55E-04	2.91	18.39	1.00	0.93	0.23	4.54	1.39E-02
INHBB	rs11902591	2	121106003	0.11	High Grade Serous	Tubal Ligation	1.37	3.95	0.94	1.07	0.86	4.47	9.77E-03	2.63	13.87	0.98	0.73	0.44	6.42	1.78E-04	1.04	2.82	0.85	2.38	0.98	451.13	4.59E-01
IRS2	rs12586052	13	110391499	0.43	High Grade Serous	Parity	-0.35	0.71	1.08	1.06	1.25	0.86	1.73E-01	-1.53	0.22	1.04	1.05	4.30	0.75	1.28E-04	0.28	1.32	1.47	1.14	0.78	0.63	5.44E-01
UGT1A134567910	rs2011404	2	234627937	0.15	High Grade Serous	Estrogen Use	-1.98	0.14	0.97	1.28	1.10	0.09	1.81E-04	-2.65	0.07	0.90	1.12	1.02	0.00	3.01E-04	-0.45	0.64	1.16	1.36	0.54	2.17	6.60E-01
UGT2B17	rs59678213	4	69434357	0.44	High Grade Serous	Parity	0.40	1.49	1.12	0.98	0.72	0.83	2.55E-01	1.81	6.09	1.14	0.95	0.22	1.04	7.61E-04	-0.83	0.44	1.27	0.96	1.29	0.44	1.79E-01

Supplementary Table 6: Sample Sizes by Low/High status across environmental factors.

Young Adult BMI			
	Low or Normal (< 25)	High or Obese (>25)	Totals
Controls	7607	679	8286
All Invasive Cases	4427	508	4935
High Grade Serous	2103	193	2296
Endometrioid	680	98	778
Totals	12034	1187	13221

Parity			
	1 or less childbirth	More than 1 child birth	Totals
Controls	2837	6812	9649
All Invasive Cases	2352	3429	5781
High Grade Serous	940	1764	2704
Endometrioid	446	441	887
Totals	5189	10241	15430

Oral Contraceptive Use			
	Less than 2 years	More than 2 years	Totals
Controls	4895	5428	10323
All Invasive Cases	3487	2616	6103
High Grade Serous	1716	1237	2953
Endometrioid	538	407	945
Totals	8382	8044	16426

Breast Fed			
	Never	Ever	Totals
Controls	2312	5320	7632
All Invasive Cases	1641	2467	4108
High Grade Serous	834	1227	2061
Endometrioid	235	336	571
Totals	3953	7787	11740

Endometrioisis			
	Never	Ever	Totals
Controls	8738	568	9306
All Invasive Cases	4802	533	5335
High Grade Serous	2366	212	2578
Endometrioid	701	114	815
Totals	13540	1101	14641

MHT Combination Use			
	Never	Ever	Totals
Controls	3420	1631	5051
All Invasive Cases	2105	765	2870
High Grade Serous	1024	452	1476
Endometrioid	301	104	405
Totals	5525	2396	7921

HRT Estrogen Use			
	Never	Ever	Totals
Controls	3986	1068	5054
All Invasive Cases	2250	631	2881
High Grade Serous	1124	356	1480
Endometrioid	328	77	405
Totals	6236	1699	7935

Supplementary Table 7: Sample Sizes by young adult BMI (Low/High) and Environmental (Low/High) status across 7 environmental factors.

Parity					
	Low BMI		High BMI		
	1 or less childbirth	More than 1 child birth	1 or less childbirth	More than 1 child birth	Totals
Controls	2090	5516	231	447	8284
All Cases	1643	2783	232	276	4934
High-Grade Serous	659	1444	69	124	2296
Endometrioid	307	373	58	40	778
Totals	3733	8299	463	723	13218

Oral Contraceptive Use					
	Low BMI		High BMI		
	Less than 2 years	More than 2 years	Less than 2 years	More than 2 years	Totals
Controls	3716	3858	327	349	8250
All Cases	2493	1898	312	195	4898
High-Grade Serous	1208	872	120	72	2272
Endometrioid	388	288	52	46	774
Totals	6209	5756	639	544	13148

Breast Feeding					
	Low BMI		High BMI		
	Never	Ever	Never	Ever	Totals
Controls	1960	4467	191	354	6972
All Cases	1395	2091	145	200	3831
High-Grade Serous	711	1048	62	89	1910
Endometrioid	202	291	25	29	547
Totals	3355	6558	336	554	10803

Endometriosis					
	Low BMI		High BMI		
	Never	Ever	Never	Ever	Totals
Controls	6610	434	598	34	7676
All Cases	3682	416	433	39	4570
High-Grade Serous	1806	161	168	15	2150
Endometrioid	531	88	79	9	707
Totals	10292	850	1031	73	12246

Tubal Ligation					
	Low BMI		High BMI		
	No	Yes	No	Yes	Totals
Controls	5419	1604	479	170	7672
All Cases	3599	697	408	75	4779
High-Grade Serous	1656	395	146	42	2239
Endometrioid	578	80	86	5	749
Totals	9018	2301	887	245	12451

Estrogen Plus Progesterone MHT					
	Low BMI		High BMI		
	Never	Ever	Never	Ever	Totals
Controls	2404	1215	215	78	3912
All Cases	1542	567	157	33	2299
High-Grade Serous	741	319	61	20	1141
Endometrioid	214	76	28	6	324
Totals	3946	1782	372	111	6211

Estrogen only MHT					
	Low BMI		High BMI		
	Never	Ever	Never	Ever	Totals
Controls	2793	828	228	65	3914
All Cases	1593	525	166	26	2310
High-Grade Serous	771	292	73	9	1145
Endometrioid	225	65	28	6	324
Totals	4386	1353	394	91	6224