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Variations in Sex Hormone Metabolism Genes, Postmenopausal Hormone Therapy, and Risk of Endometrial Cancer

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Abstract

We investigated whether variants in sex steroid hormone metabolism genes modify the effect of hormone therapy (HT) on endometrial cancer risk in postmenopausal non-Hispanic white women. A nested-case control study was conducted within the California Teachers Study (CTS). We genotyped htSNPs in six genes involved in the hormone metabolism in 286 endometrial cancer cases and 488 controls. Odds ratio (OR) and 95% confidence interval (CI) were estimated for each haplotype using unconditional logistic regression, adjusting for age. The strongest interaction was observed between duration of estrogen therapy (ET) use and haplotype 1A in *CYP11A1* ($P_{\text{interaction}}=0.0027$; $P_{\text{interaction}}=0.027$ after correcting for multiple testing within each gene). The OR for endometrial cancer per copy of haplotype 1A was 2.00 (95%CI: 1.05-3.96) for long-term ET users and 0.90 (95% CI: 0.69-1.18) for never users. The most significant interaction with estrogen-progestin therapy (EPT) was found for two haplotypes on *CYP19A1* and EPT use (haplotype 4A, $P_{\text{interaction}}=0.024$ and haplotype 3B, $P_{\text{interaction}}=0.043$). However, neither this interaction, nor the ET or EPT interactions for any other genes, was statistically significant after correction for multiple testing. Variations in *CYP11A1* may modify the effect of ET use on risk of postmenopausal endometrial cancer; however, larger studies are needed to explore these findings further.

Keywords

menopausal hormone therapy; genetic polymorphism; hormone metabolism gene; endometrial cancer

Introduction

Endometrial cancer is the most common gynecological cancer in U.S women with an estimated 42,160 new cases diagnosed in the United States in 2009 ¹. Menopausal estrogen-

alone therapy (ET) is an established risk factor of endometrial cancer²⁻⁴. In the early 1980s, progestin was added to hormone therapy (HT) regimens in order to modify the risk of endometrial cancer associated with exposure to estrogen-alone therapy. Studies have generally found estrogen-progestin therapy (EPT) to be safe⁴⁻⁶. However, a few recent reports, including our own, suggest that long-term use of EPT may also increase the risk of endometrial cancer⁷⁻¹⁰. Whether this risk is modified by other factors, including a woman's ability to metabolize these hormones, is unknown.

Given the role of hormones in endometrial cancer, it is possible that inherited variation in genes encoding hormone metabolism enzymes or hormone receptors may affect the risk of endometrial cancer. It is also possible that such variants could modify the effect of hormone therapy (HT) on endometrial cancer risk. To answer these questions we performed a nested case-control study within the California Teachers Study (CTS) cohort.

Materials and Methods

Study Population

This nested case-control study has been described in detail elsewhere¹⁰. Briefly, the CTS is an ongoing cohort study of 133,479 current and former female public school teachers and administrators who were enrolled in the California State Teachers Retirement System and completed a self-administered questionnaire related to women's health in 1995-1996¹¹. Women who maintained California residence after joining the cohort, had not been previously diagnosed with endometrial cancer, and had not had a hysterectomy were eligible for the current case-control study.

Cases were identified by linkage of cohort participant data to the California Cancer Registry. Women were eligible for current study as cases if they were 50-85 years old when diagnosed with invasive endometrial cancer (ICD-O-3 codes C54.1 and C54.9) after cohort enrollment and before December 31, 2004. Controls were frequency matched to cases based on age (5-year age groups through 80+), race/ethnicity (African American, Asian/Pacific Islander, Hispanic, Native American, white, and other/mixed), and broad geographic region of residence within California. The interviews and collection of blood/buccal samples from endometrial cancer cases (N=401) and controls (N=682) were performed between February 2002 and May 2007.

The majority of CTS participants are non-Latino white (86%). Since the number of non-white participants who completed the interview and provided DNA sample was small (24 cases and 59 controls), this analysis was restricted to non-Hispanic white participants. We excluded patients with a history of breast cancer (33 cases and 54 controls) because of concern that breast cancer treatment could have influenced both a woman's chance of developing endometrial cancer as well as her decision to use HT. We also excluded from the present analysis, participants who were pre- or peri-menopausal at the time of diagnosis or reference date (24 cases and 40 controls); cases with in-situ or non-endometrioid cancers (N=15); women who did not provide a DNA sample or were not genotyped (11 cases and 17 controls); and women whose DNA samples had a call rate of <70% for all the SNPs (7 cases and 14 controls). The final analysis included 286 cases and 488 controls.

htSNP Selection and Genotyping

The SNPs included in this study were the same haplotype tagging SNPs (htSNPs) as those originally selected for the Multiethnic Cohort study (MEC) (<http://ccnt.hsc.usc.edu/MECGenetics>). The details of htSNP selection and linkage disequilibrium characterization for the genes have been described elsewhere¹²⁻¹⁶. In brief SNPs were identified to cover 20 kb upstream of transcription to 10 kb downstream of the

gene and the general principle was to select SNPs every 2-5 kb across the locus. Haplotype blocks were constructed using the method described by Gabriel et al.¹⁷, which uses the 90% confidence bounds of pairwise linkage disequilibrium (LD) D' statistics^{18, 19}. Haplotype frequencies were estimated using the expectation-maximization algorithm of Excoffier and Slatkin²⁰. The htSNPs in each haplotype block were selected using the TagSNP program¹⁵ to ensure the minimum of R_h^2 (i.e., the squared correlation between the true haplotypes and the estimated haplotypes) was greater than 0.80 in whites for all the genes.

After extracting DNA using the Qiagen 96 DNA Blood Kit, we genotyped the selected htSNPs using the TaqMan assay (Applied Biosystems, Foster City, CA). We included 89 random duplicates to assess reproducibility of genotyping. The concordance rate was 99.6%.

Age at Menopause and Postmenopausal Hormone Use

Study participants were interviewed in-person (91%) or by telephone using a structured questionnaire. For women who had not used oral contraceptives (OC) or HT within the 12 months before their last menstrual period, age at menopause was defined as the age at last menstrual period. For women who used HT within 12 months of their last reported menstrual period and had started using HT while still menstruating, age at menopause was defined as the age at which they started using HT. Eight women had used OCs through their last menstrual period, and their age at menopause was defined as their age at last OC use.

We collected detailed information on the date that each HT episode started and stopped, the brand name and dosage of the HT taken, the number of days per month of usage, and the reasons for use. We truncated the exposure data at 12 months before diagnosis for cases, or selection date for controls. The details of data collection and HT use are described in more detail elsewhere¹⁰.

For this analysis, we categorized HT use with <10 days/month of progestin as unopposed estrogen therapy (ET) and HT use with ≥ 10 days/month of progestin as estrogen-progestin therapy (EPT). Lifetime duration of HT use was calculated for each regimen. We categorized hormone use into three categories: no use (never use or use of <1 year of each regimen), 1-9 years of use, and 10+ years of use. We used the never use of HT category as the reference group in all analyses.

Statistical Analysis

We performed haplotype-based analyses using multivariable unconditional logistic regression models. We calculated odds ratios (ORs) and 95% confidence intervals (95% CI) of each haplotype within an LD block using the most common haplotype as the reference group (global model)²¹. We used likelihood ratio tests to calculate the p-values for each haplotype and the Bonferroni method to adjust the calculated p-values for multiple testing. We also examined the effect of each single haplotype by comparing the effect of the haplotype with all the other haplotypes in the block (single haplotype model). We performed the Armitage's trend test²² to assess single SNP associations for genes in the sex hormone pathway and risk of endometrial cancer, and reported Monte Carlo estimates of exact p-values. ORs and 95% CIs associated with each SNP were estimated using logistic regression models.

We adjusted the models for variables selected a priori. For the genetic analysis we only adjusted for age at diagnosis/selection. Additional adjustment for HT use, oral contraceptive (OC) use, body mass index (BMI), parity, and type of menopause did not change the results and thus we only present the results of the age-adjusted models.

We evaluated the effect of HT use on endometrial cancer using logistic regression models adjusted for matching factors (age at reference date, and broad geographic area of residence) and reference year. In addition, we adjusted these models for the following known or suspected confounders selected *a priori*: number of full-term pregnancies, age at the last full-term pregnancy, BMI at reference date, lifetime duration of OC use, and age at menopause. Additional adjustment for hypertension, other medication use, history of endometrial fibroadenoma, and number of previous dilations and curettages did not alter the results (data not shown). A detailed discussion of covariate selection is provided elsewhere ¹⁰.

To examine the interaction between genetic variation and different HT use regimens, we fitted a single haplotype model (comparing each haplotype to all the other haplotypes within each LD block) while including variables for ET and EPT use duration in the model. These interaction models were further adjusted for age at diagnosis/selection (continuous), age at menopause (continuous), BMI (continuous) and lifetime OC use (continuous in months). We assessed the statistical significance of the interaction between each haplotype and the respective HT variables by conducting likelihood ratio tests comparing the model with and without the haplotype and ET and EPT interaction terms. Since the effect of ET use was linear (on the log scale), we performed one degree of freedom (df) test, using ET variable as continuous variables. For EPT, we used a 2 df likelihood ratio test with EPT use included as a categorical variable. We used the Bonferroni method to correct the calculated p-values for multiple tests for interaction.

Results

All the htSNPs (see Supplementary Table 1 for complete list of htSNPs) conformed to Hardy-Weinberg equilibrium (HWE) among controls ($P > 0.01$). Only the 1D haplotype of *HSD17B2* was associated with risk of endometrial cancer (OR=1.26, 95% CI: 1.00-1.59) (Table 1). This association appeared to be driven by the T allele of rs4445895 in this haplotype with allele OR of 1.24 (95% CI: 1.00-1.54, $P = 0.046$) (Supplementary Table 1).

As previously reported from this study ¹⁰ both ET and EPT use were associated with risk of endometrial cancer. Among women who were included in the current study, the OR was 1.65 (95% CI: 1.41-1.93) per 5 years of ET use. We found a statistically significant increased risk of endometrial cancer with more than 10 years of EPT use. (OR: 1.76; 95% CI: 1.12-2.78) (Table 2).

We found some indication of an interaction between polymorphisms in these steroid hormone metabolizing genes and HT use (Tables 3). For ET use, the strongest interaction was observed between duration of ET use and the most common haplotype of *CYP11A1* (haplotype 1A; $P_{\text{interaction}} = 0.0027$). The OR for each copy of haplotype 1A (as compared to all the other haplotypes) was 2.00 (95% CI: 1.05-3.96) for long-term ET users and 0.90 (95% CI: 0.69-1.18) for never users. After Bonferroni adjustment of the P-value for multiple testing within each gene, this interaction was still statistically significant (adjusted $P_{\text{interaction}} = 0.027$). The interaction terms for all other genes and ET use were not statistically significant once Bonferroni adjustment was made.

For EPT use, the strongest indication of an interaction was for two haplotypes on *CYP19A1* and EPT use (haplotype 4A, $P = 0.024$ and haplotype 3B, $P = 0.043$). Neither these interactions nor interactions for any of the other genes were statistically significant after adjustment for multiple testing.

Discussion

In this nested case-control study, we evaluated the role of genetic variation in sex hormone metabolism genes using a haplotype-based approach, and the possible interaction between such variation and use of postmenopausal HT on the risk of endometrial cancer. Only the 1D haplotype of *HSD17B2* gene showed a direct association with endometrial cancer risk. We also observed an interaction between ET use and *CYP11A1* (haplotype 1A), such that those with the 1A haplotype were at increased risk with long-term ET use. Our results are for the most part consistent with the previous literature. In the following we discuss our findings in light of what others have found on the main effects and interactions for each gene.

CYP11A1

CYP11A1 is a gene encoding a rate-limiting enzyme CYP11A located upstream in sex hormone metabolism pathways, which converts cholesterol to pregnenolone²³. Early studies on variations of *CYP11A1* were mainly focused on the number of (TTTTA)_n repeats located in the 5' region in block 1. Haplotype 1A was associated with a smaller number of (TTTTA)_n repeats in data from the Multiethnic Cohort study¹³. The lower number of repeats has been associated with decreased risk of polycystic ovarian syndrome²⁴⁻²⁷, as well as breast and prostate cancer^{13, 28, 29} but not with risk of endometrial cancer in the only study that addressed this, which included 417 cases and 402 controls³⁰. In another recent study³¹, tagging SNPs of *CYP11A1* were not associated with endometrial cancer risk. In our study none of the haplotypes in *CYP11A1* was directly associated with risk of endometrial cancer. However, we found a possible interaction between ET use and haplotype 1A. This result could simply be a chance finding, although the finding remained statistically significant after Bonferroni adjustment for multiple testing. One possible mechanism for this interaction could be related to the endogenous estrogen/progesterone levels of these haplotype carriers. One study showed a lower levels of estradiol among postmenopausal women who carried 8 repeat alleles compared to those who did not carry this allele²⁸. One can hypothesize that the effect of exogenous estrogen among these women would be exaggerated as their baseline endogenous hormone levels were at a lower set point, and they may also have lower endogenous progesterone to oppose the adverse effect of exogenous estrogen on the endometrium.

CYP17A1

CYP17A1 encodes the enzyme, which converts pregnenolone to 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA) and also converts progesterone to 17-hydroxyprogesterone and androstenedione. The most studied polymorphism in *CYP17A1* is rs743572 [a T/C (A1/A2) SNP in the 5'UTR]. Although several previous studies with limited sample sizes reported a decreased risk of endometrial cancer associated with the A2 (C) allele³²⁻³⁵, in a large population-based study of 497 endometrial cancer cases and 1,024 controls in Poland, no association was observed for the A2 allele (p=0.15) or haplotypes in *CYP17A1*. Our results were consistent with the Polish study; we found no association between endometrial cancer risk and haplotypes 1D and 1E, which included the A2 (C) allele.

CYP19A1

CYP19A1, also known as the aromatase gene, encodes a rate-limiting enzyme involved in the conversion of androgens to estrogen. The association between *CYP19A1* SNPs and endometrial cancer risk has been previously reported from a large collaborative study³⁶, which included the data from this study. In the pooled analysis, carrying the A allele of rs749292 or rs727479 of *CYP19A1* was associated with increased risk of endometrial cancer (OR per copy of A-A haplotype: 1.15; 95% CI: 1.09-1.21) and no heterogeneity was

observed between studies. The minor allele of rs749292 is located on haplotype 3C, and the minor allele of rs727479 is located on 4A and 4B, respectively, in our study. Although these single SNPs were not associated with endometrial cancer risk in our study, CYP19A1 haplotype 3C was associated with a statistically non-significant 16% increased risk. Our sample size may have limited our statistical power to detect the association of the CYP19A1 SNPs and endometrial cancer risk. Alternatively, differences in the distribution of unidentified environmental effect modifiers may have influenced the magnitude of associations between CYP19A1 SNPs and endometrial cancer risk. However, our data suggest that hormone therapy use does not explain these different findings.

Three additional common genetic polymorphisms in *CYP19A1* have been previously studied³⁷. All three studied variants are in linkage disequilibrium (located in the LD block 4) and include: 1) (TTTA)_n repeat in intron 4, where the number of repeats varies between seven and 13, with seven repeats occurring most commonly; 2) a three base pair (TCT) deletion in close vicinity of the (TTTA)_n repeats, which has been found only with the 7-repeat allele³⁸; and 3) a T/C change in exon 10, (rs10046) which has been associated with an 8-repeat TTTA allele³⁹. While the data on the effect of the number of repeats on serum estrogen level is inconsistent^{12, 40}, longer TTTA repeats (>7) and the T-allele of rs10046 have been found to be associated with increased risk of endometrial cancer^{41, 42}. It has been also shown that not all the haplotypes carrying T-allele of rs10046 were associated with increased risk⁴², suggesting that rs10046 is not the causal allele or a direct marker of the causal allele. In a recent study utilizing tagging SNP approach, gene-based global test suggested that genetic variation in *CYP19A1* is associated with endometrial cancer risk, and the most strong association was with rs12595627³¹. In the current study, rs10046 (OR: 1.04 per copy of T-allele; Supplementary Table 1) was not associated with endometrial cancer risk, but the OR for haplotype 4A compared to all other haplotypes in block 4 combined was 1.12 (95% CI: 0.91-1.38; data not presented), which was stronger in EPT users. These results for block 4 of *CYP19A1*, although not statistically significant are compatible with these two studies^{41, 42}.

ESR2

Our observation that ESR2 genetic variations are not associated with risk of endometrial cancer is consistent with one of the two previous studies^{16, 43}. In a recent Australian study of 191 endometrial cancer cases⁴³, the G allele of two SNPs (rs1255998 and rs4986938) located in the 3' region of the gene were associated with elevated risk⁴³. However, in a nested case control study of 222 cases and 666 controls within the Nurses' Health Study (NHS), ESR2 variations (rs1256049 and rs1271572) were not associated with risk of endometrial cancer nor was there an interaction between HT use and ESR2 variants¹⁶, consistent with our findings. While the positive observations from the Australian study could be due to chance, it is possible that population differences in the distribution of unidentified effect modifiers may explain these inconsistencies.

HSD17B1 and HSD17B2

HSD17B1 encodes the enzyme 17 β -hydroxysteroid dehydrogenase 1, which reduces estrone (E1) to estradiol (a more biologically active form of estrogen than E1), and HSD17B2 encodes 17 β -hydroxysteroid dehydrogenase 2, which oxidizes estradiol back to estrone. Consistent with our observation of no association, Setiawan et al. found no overall association between *HSD17B1* SNPs or haplotypes and endometrial cancer risk in a nested case control study within the NHS⁴⁴. Our findings on *HSD17B2* were consistent with a recent study by Karageorgi et al.⁴⁵ and Low et al.³¹, which found no significant association between *HSD17B2* variations and endometrial cancer.

Strengths and Weaknesses

The limitations of this study include a relatively low participation rate (around 50%) for providing a DNA sample. However, participation was similar for cases and controls and it is unlikely that genetic variation in steroid hormone genes differentially influenced participation. The effect of genetic variation on the choice to use HT and the duration of use, however, is not known. In addition, the allelic frequency distributions among controls in our study were similar to those reported in previous studies. Finally, as previously described¹⁰, the distribution of participants in this nested case-control study were similar to that of non-participating cohort members on a wide variety of risk factors assessed at baseline. Thus, selection bias may not play a critical role in our findings.

While the sample size in our study was similar or slightly larger than that of previous studies, we had only modest power to study gene-environment interactions. Assuming a log-additive model, two sided tests of significance, $OR_{ET}=3.0$, $OR_{EPT}=2.0$, $OR_G=1.2$, and $\alpha=0.05$, when the minimum allele frequency is 0.4-0.2, we had 80% power to detect interaction effects of 1.88-2.02 for EPT use and 2.18-2.25 for ET use. For the genetic main effects, we had 80% power to detect ORs ranging 1.33 to 1.40 (or 0.75 to 0.71) for alleles with minor allele frequency of 0.4 to 0.2.

Conclusion

In this nested case-control study within the CTS, we found mostly no convincing evidence that genetic haplotypes of sex hormone metabolism genes were associated with the risk of endometrial cancer. We also found some suggestion for possible interactions between variations in these genes, particularly *CYP11A1*, and the effect of postmenopausal ET use on risk of endometrial cancer; however, larger studies are needed to explore these findings further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009; 59:225-49. [PubMed: 19474385]
2. Brinton LA, Hoover RN. Estrogen replacement therapy and endometrial cancer risk: unresolved issues. The Endometrial Cancer Collaborative Group. *Obstet Gynecol*. 1993; 81:265-71. [PubMed: 8380913]

3. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol.* 1995; 85:304–13. [PubMed: 7824251]
4. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, Mack TM. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst.* 1997; 89:1110–6. [PubMed: 9262248]
5. Weiderpass E, Adami HO, Baron JA, Magnusson C, Bergstrom R, Lindgren A, Correia N, Persson I. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst.* 1999; 91:1131–7. [PubMed: 10393721]
6. Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet.* 1997; 349:458–61. [PubMed: 9040575]
7. Newcomb PA, Trentham-Dietz A. Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control.* 2003; 14:195–201. [PubMed: 12749724]
8. Jain MG, Rohan TE, Howe GR. Hormone replacement therapy and endometrial cancer in Ontario, Canada. *J Clin Epidemiol.* 2000; 53:385–91. [PubMed: 10785569]
9. Lacey JV Jr, Brinton LA, Lubin JH, Sherman ME, Schatzkin A, Schairer C. Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1724–31. [PubMed: 16030108]
10. Razavi P, Pike MC, Horn-Ross PL, Templeman C, Bernstein L, Ursin G. Long-term Postmenopausal Hormone Therapy and Endometrial Cancer. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:475–83. [PubMed: 20086105]
11. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, Pinder R, Reynolds P, Sullivan-Halley J, West D, Wright W, Ziogas A, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). *Cancer Causes Control.* 2002; 13:625–35. [PubMed: 12296510]
12. Haiman CA, Stram DO, Pike MC, Kolonel LN, Burtt NP, Altshuler D, Hirschhorn J, Henderson BE. A comprehensive haplotype analysis of CYP19 and breast cancer risk: the Multiethnic Cohort. *Hum Mol Genet.* 2003; 12:2679–92. [PubMed: 12944421]
13. Setiawan VW, Cheng I, Stram DO, Giorgi E, Pike MC, Van Den Berg D, Pooler L, Burtt NP, Le Marchand L, Altshuler D, Hirschhorn J, Henderson BE, et al. A systematic assessment of common genetic variation in CYP11A and risk of breast cancer. *Cancer Res.* 2006; 66:12019–25. [PubMed: 17178901]
14. Haiman CA, Dossus L, Setiawan VW, Stram DO, Dunning AM, Thomas G, Thun MJ, Albanes D, Altshuler D, Ardanaz E, Boeing H, Buring J, et al. Genetic variation at the CYP19A1 locus predicts circulating estrogen levels but not breast cancer risk in postmenopausal women. *Cancer Res.* 2007; 67:1893–7. [PubMed: 17325027]
15. Stram DO, Haiman CA, Hirschhorn JN, Altshuler D, Kolonel LN, Henderson BE, Pike MC. Choosing haplotype-tagging SNPS based on unphased genotype data using a preliminary sample of unrelated subjects with an example from the Multiethnic Cohort Study. *Hum Hered.* 2003; 55:27–36. [PubMed: 12890923]
16. Setiawan VW, Hankinson SE, Colditz GA, Hunter DJ, De Vivo I. Estrogen receptor beta (ESR2) polymorphisms and endometrial cancer (United States). *Cancer Causes Control.* 2004; 15:627–33. [PubMed: 15280642]
17. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, et al. The structure of haplotype blocks in the human genome. *Science.* 2002; 296:2225–9. [PubMed: 12029063]
18. Lewontin RC. The Interaction of Selection and Linkage. II. Optimum Models. *Genetics.* 1964; 50:757–82. [PubMed: 14221879]
19. Lewontin RC. The Interaction of Selection and Linkage. I. General Considerations; Heterotic Models. *Genetics.* 1964; 49:49–67. [PubMed: 17248194]
20. Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. *Mol Biol Evol.* 1995; 12:921–7. [PubMed: 7476138]

21. Zaykin DV, Westfall PH, Young SS, Karnoub MA, Wagner MJ, Ehm MG. Testing association of statistically inferred haplotypes with discrete and continuous traits in samples of unrelated individuals. *Hum Hered.* 2002; 53:79–91. [PubMed: 12037407]
22. Armitage P. Tests for linear trends in proportions and frequencies. *Biometrics.* 1955; 11:375–86.
23. Gasteiger E, Gattiker A, Hoogland C, Ivanyi I, Appel RD, Bairoch A. ExPASy: The proteomics server for in-depth protein knowledge and analysis. *Nucleic Acids Res.* 2003; 31:3784–8. [PubMed: 12824418]
24. Franks S, Gharani N, Waterworth D, Batty S, White D, Williamson R, McCarthy M. The genetic basis of polycystic ovary syndrome. *Hum Reprod.* 1997; 12:2641–8. [PubMed: 9455828]
25. Gharani N, Waterworth DM, Batty S, White D, Gilling-Smith C, Conway GS, McCarthy M, Franks S, Williamson R. Association of the steroid synthesis gene CYP11a with polycystic ovary syndrome and hyperandrogenism. *Hum Mol Genet.* 1997; 6:397–402. [PubMed: 9147642]
26. Gaasenbeek M, Powell BL, Sovio U, Haddad L, Gharani N, Bennett A, Groves CJ, Rush K, Goh MJ, Conway GS, Ruokonen A, Martikainen H, et al. Large-scale analysis of the relationship between CYP11A promoter variation, polycystic ovarian syndrome, and serum testosterone. *J Clin Endocrinol Metab.* 2004; 89:2408–13. [PubMed: 15126571]
27. Diamanti-Kandarakis E, Bartzis MI, Bergiele AT, Tsianateli TC, Kouli CR. Microsatellite polymorphism (tttta)(n) at –528 base pairs of gene CYP11alpha influences hyperandrogenemia in patients with polycystic ovary syndrome. *Fertil Steril.* 2000; 73:735–41. [PubMed: 10731534]
28. Zheng W, Gao YT, Shu XO, Wen W, Cai Q, Dai Q, Smith JR. Populationbased case-control study of CYP11A gene polymorphism and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:709–14. [PubMed: 15159300]
29. Kumazawa T, Tsuchiya N, Wang L, Sato K, Kamoto T, Ogawa O, Nakamura A, Kato T, Habuchi T. Microsatellite polymorphism of steroid hormone synthesis gene CYP11A1 is associated with advanced prostate cancer. *Int J Cancer.* 2004; 110:140–4. [PubMed: 15054879]
30. Olson SH, Orlow I, Bayuga S, Sima C, Bandera EV, Pulick K, Faulkner S, Tommasi D, Egan D, Roy P, Wilcox H, Asya A, et al. Variants in hormone biosynthesis genes and risk of endometrial cancer. *Cancer Causes Control.* 2008
31. Low YL, Li Y, Humphreys K, Thalamuthu A, Darabi H, Wedren S, Bonnard C, Czene K, Iles MM, Heikkinen T, Aittomaki K, Blomqvist C, et al. Multi-variant pathway association analysis reveals the importance of genetic determinants of estrogen metabolism in breast and endometrial cancer susceptibility. *PLoS Genet.* 2010; 6:e1001012. [PubMed: 20617168]
32. Haiman CA, Hankinson SE, Colditz GA, Hunter DJ, De Vivo I. A polymorphism in CYP17 and endometrial cancer risk. *Cancer Res.* 2001; 61:3955–60. [PubMed: 11358812]
33. McKean-Cowdin R, Feigelson HS, Pike MC, Coetzee GA, Kolonel LN, Henderson BE. Risk of endometrial cancer and estrogen replacement therapy history by CYP17 genotype. *Cancer Res.* 2001; 61:848–9. [PubMed: 11221867]
34. Berstein LM, Imyaninov EN, Kovalevskij AJ, Maximov SJ, Vasilyev DA, Buslov KG, Sokolenko AP, Iyevleva AG, Chekmariova EV, Thijssen JH. CYP17 and CYP19 genetic polymorphisms in endometrial cancer: association with intratumoral aromatase activity. *Cancer Lett.* 2004; 207:191–6. [PubMed: 15072828]
35. Aban M, Arslan M, Tok E, Tekes S, Budak T, Altintas A. CYP17 genetic polymorphism in patients with endometrial hyperplasia and cancer. *Int J Gynecol Cancer.* 2006; 16(Suppl 1):448–51. [PubMed: 16515644]
36. Setiawan VW, Doherty JA, Shu XO, Akbari MR, Chen C, De Vivo I, Demichele A, Garcia-Closas M, Goodman MT, Haiman CA, Hankinson SE, Henderson BE, et al. Two estrogen-related variants in CYP19A1 and endometrial cancer risk: a pooled analysis in the Epidemiology of Endometrial Cancer Consortium. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:242–7. [PubMed: 19124504]
37. Olson SH, Bandera EV, Orlow I. Variants in estrogen biosynthesis genes, sex steroid hormone levels, and endometrial cancer: a HuGE review. *Am J Epidemiol.* 2007; 165:235–45. [PubMed: 17110639]
38. Baxter SW, Choong DY, Eccles DM, Campbell IG. Polymorphic variation in CYP19 and the risk of breast cancer. *Carcinogenesis.* 2001; 22:347–9. [PubMed: 11181459]

39. Haiman CA, Hankinson SE, Spiegelman D, Brown M, Hunter DJ. No association between a single nucleotide polymorphism in CYP19 and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2002; 11:215–6. [PubMed: 11867511]
40. Tworoger SS, Chubak J, Aiello EJ, Ulrich CM, Atkinson C, Potter JD, Yasui Y, Stapleton PL, Lampe JW, Farin FM, Stanczyk FZ, McTiernan A. Association of CYP17, CYP19, CYP1B1, and COMT polymorphisms with serum and urinary sex hormone concentrations in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:94–101. [PubMed: 14744739]
41. Bernstein LM, Imyanitov EN, Suspitsin EN, Grigoriev MY, Sokolov EP, Togo A, Hanson KP, Poroshina TE, Vasiljev DA, Kovalevskij AY, Gamajunova VB. CYP19 gene polymorphism in endometrial cancer patients. *J Cancer Res Clin Oncol.* 2001; 127:135–8. [PubMed: 11216915]
42. Paynter RA, Hankinson SE, Colditz GA, Kraft P, Hunter DJ, De Vivo I. CYP19 (aromatase) haplotypes and endometrial cancer risk. *Int J Cancer.* 2005; 116:267–74. [PubMed: 15800924]
43. Ashton KA, Proietto A, Otton G, Symonds I, McEvoy M, Attia J, Gilbert M, Hamann U, Scott RJ. Estrogen receptor polymorphisms and the risk of endometrial cancer. *BJOG.* 2009; 116:1053–61. [PubMed: 19438492]
44. Setiawan VW, Hankinson SE, Colditz GA, Hunter DJ, De Vivo I. HSD17B1 gene polymorphisms and risk of endometrial and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:213–9. [PubMed: 14973105]
45. Karageorgi S, McGrath M, Lee IM, Buring J, Kraft P, De Vivo I. Polymorphisms in genes hydroxysteroid-dehydrogenase-17b type 2 and type 4 and endometrial cancer risk. *Gynecol Oncol.* 2010

Table 1

Association between haplotypes in sex hormone metabolism genes and risk of endometrial cancer

Gene	Block	Haplotype	Haplotype Frequency %		OR (95%CI) *	P-Value †
			Case (N=286)	Control (N=488)		
CYP11A1						
Block 1	1A	GGGT	62	60	1 (Referent)	-
	1B	GGCT	7	8	0.87 (0.57-1.29)	0.48
	1C	GGCC	17	16	1.00 (0.75-1.32)	0.98
	1D	AACC	13	14	0.88 (0.64-1.19)	0.41
CYP17A1						
Block 1	1A	CTAGG	37	36	1 (Referent)	-
	1B	CCAGT	18	18	0.96 (0.71-1.29)	0.78
	1C	TTGGG	11	10	1.05 (0.73-1.50)	0.79
	1D	TTGAG	30	31	0.91 (0.71-1.17)	0.47
Block 2	2A	TAAA	28	30	1 (Referent)	-
	2B	CACA	23	22	1.16 (0.87-1.56)	0.31
	2C	CACG	16	17	1.06 (0.77-1.48)	0.71
	2D	CAAA	16	16	1.13 (0.81-1.58)	0.47
	2E	CGCA	16	16	1.10 (0.80-1.51)	0.55
CYP19A1						
Block 1	1A	AGTTGA	50	53	1 (Referent)	-
	1B	AGCTAA	4	5	0.75 (0.42-1.28)	0.30
	1C	AGCCAA	22	21	1.08 (0.83-1.41)	0.58
	1D	TCCTAT	8	7	1.23 (0.81-1.86)	0.33
	1E	TCCCGA	5	5	1.08 (0.67-1.71)	0.75
Block 2	2A	AAGCG	78	75	1 (Referent)	-
	2B	GAGCG	8	10	0.82 (0.56-1.18)	0.29
Block 3	3A	GCG	41	44	1 (Referent)	

Gene	Block	Haplotype	Haplotype Frequency %			P-Value [†]
			Case (N=286)	Control (N=488)	OR (95%CI) *	
ESR2	Block 1	3B GGA	13	14	1.04 (0.74-1.44)	0.82
		3C AAA	44	41	1.16 (0.92-1.46)	0.21
	Block 4	4A AAGGGAC	46	43	1 (Referent)	-
		4B AGGAGA	9	10	0.90 (0.62-1.30)	0.58
		4C CGGGGGC	19	19	0.94 (0.71-1.26)	0.69
		4D CGGGGGA	16	17	0.91 (0.67-1.22)	0.51
	Block 1	1A CGCC	44	44	1 (Referent)	-
		1B CACC	9	9	0.91 (0.60-1.36)	0.63
		1C CACT	8	10	0.77 (0.50-1.16)	0.21
		1D TACC	7	5	1.25 (0.77-2.02)	0.35
		1E TACT	28	27	1.01 (0.78-1.30)	0.93
HSD17B1	Block 1	1A CGAT	41	43	1 (Referent)	-
		1B CAGC	27	26	1.08 (0.83-1.40)	0.56
		1C AAGC	27	25	1.14 (0.88-1.48)	0.32
	Block 1	1A CAT	50	54	1 (Referent)	-
		1B CAC	5	5	1.07 (0.65-1.73)	0.79
		1C CGC	4	7	0.67 (0.40-1.08)	0.11
HSD17B2	Block 1	1D TGC	37	31	1.26 (1.00-1.59)	0.046
		2A GCAT	50	49	1 (Referent)	-
		2B GCAC	11	9	1.23 (0.86-1.75)	0.24
	Block 2	2C GCGC	7	8	0.82 (0.53-1.24)	0.35
		2D GTGC	27	29	0.90 (0.70-1.14)	0.37

* Odds ratios per copy of the haplotype, adjusted for age

[†]Wald P-value

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval

Table 2

Association between duration of postmenopausal hormone therapy (HT) use and risk of endometrial cancer by HT type

HT type	Duration	N Ca(Co)	OR (95% CI) *
ET	No ET use	175 (374)	1 (Referent)
	1-9y	63 (79)	2.27 (1.52-3.39)
	10+y	48 (35)	5.28 (3.09-9.01)
	Per 5-year		1.65 (1.41-1.93) [†]
EPT	No EPT use	174 (280)	1 (Referent)
	1-9y	65 (130)	0.89 (0.61-1.31)
	10+y	47 (78)	1.76 (1.12-2.78)
	Per 5-year		1.25 (1.10-1.42) [†]

* Mutually adjusted ORs: adjusted for age, referent year, geographic area of residence, menopause age, number of full-term pregnancies, age at the last full-term pregnancy, lifetime oral contraceptive use duration and body mass index. Variables for duration of ET use and EPT use were included in one model.

[†] OR per 5-year use

Abbreviations: ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy; OR: Odds Ratio; CI: Confidence Interval; Ca: Case; Co: Control; HT: Hormone Therapy

Table 3
Odds ratios and 95% confidence intervals of risk of endometrial cancer per copy of haplotype by duration of hormone use

Gene	Block	Haplotype	E ^T *			EPT*			P Interaction [‡]
			No E ^T use [†] 175 (374)	1-9 years 63 (79)	10+ years 48 (35)	No EPT use [†] 174 (280)	1-9 years 65 (130)	10+ years 47 (78)	
CYP11A1									
Block 1	1A	GGGT	0.90 (0.69-1.18)	1.25 (0.77-2.06)	2.00 (1.05-3.96)	1.16 (0.86-1.56)	1.04 (0.68-1.58)	0.81 (0.46-1.41)	0.54
	1B	GGCT	1.15 (0.66-1.95)	0.60 (0.25-1.38)	0.78 (0.21-3.02)	0.93 (0.52-1.65)	0.89 (0.39-1.93)	0.99 (0.27-3.23)	0.98
	1C	GGCC	1.25 (0.88-1.76)	0.88 (0.44-1.73)	0.87 (0.29-2.77)	1.07 (0.72-1.60)	1.16 (0.66-1.99)	1.38 (0.64-3.00)	0.85
	1D	AACC	0.89 (0.59-1.31)	1.07 (0.55-2.07)	0.39 (0.14-1.05)	0.73 (0.48-1.09)	1.04 (0.51-2.06)	1.23 (0.53-2.80)	0.45
CYP17A1									
Block 1	1A	CTAGG	1.01 (0.77-1.32)	1.22 (0.73-2.02)	1.52 (0.77-3.16)	1.02 (0.75-1.38)	1.38 (0.87-2.18)	1.01 (0.61-1.68)	0.53
	1B	CCAGT	0.89 (0.62-1.27)	1.09 (0.61-1.92)	1.16 (0.45-3.09)	0.96 (0.66-1.38)	0.98 (0.51-1.87)	0.93 (0.46-1.85)	0.99
	1C	TTGGG	1.28 (0.81-2.00)	0.74 (0.34-1.54)	0.60 (0.22-1.72)	1.00 (0.62-1.59)	0.84 (0.41-1.66)	1.94 (0.63-5.94)	0.45
	1D	TTGAG	1.02 (0.76-1.35)	0.98 (0.58-1.63)	0.70 (0.35-1.37)	1.03 (0.77-1.39)	0.87 (0.51-1.45)	0.83 (0.44-1.53)	0.74
Block 2	2A	TAAA	0.92 (0.68-1.24)	1.00 (0.59-1.69)	0.69 (0.34-1.40)	0.97 (0.71-1.31)	0.94 (0.55-1.60)	0.63 (0.32-1.21)	0.50
	2B	CACA	1.04 (0.75-1.44)	1.52 (0.83-2.84)	1.12 (0.54-2.38)	1.04 (0.72-1.49)	1.43 (0.85-2.40)	1.05 (0.57-1.93)	0.59
	2C	CACG	0.92 (0.62-1.34)	1.11 (0.61-1.98)	0.86 (0.32-2.30)	0.94 (0.63-1.39)	0.92 (0.48-1.76)	1.09 (0.54-2.20)	0.93
	2D	CAAA	1.21 (0.83-1.76)	0.75 (0.39-1.42)	0.73 (0.31-1.74)	1.03 (0.70-1.52)	0.80 (0.44-1.43)	1.74 (0.71-4.27)	0.37
	2E	CGCA	0.94 (0.65-1.34)	0.73 (0.36-1.43)	3.95 (1.23-16.08)	1.01 (0.70-1.46)	0.88 (0.42-1.79)	1.05 (0.51-2.13)	0.93
CYP19A1									
Block 1	1A	AGTTGA	0.86 (0.66-1.12)	0.96 (0.59-1.55)	1.05 (0.56-2.00)	0.91 (0.68-1.22)	1.16 (0.74-1.83)	0.61 (0.36-1.02)	0.17
	1B	AGCTAA	1.09 (0.55-2.09)	0.46 (0.13-1.45)	-	0.77 (0.35-1.61)	0.81 (0.24-2.38)	1.13 (0.23-4.95)	0.90
	1C	AGCCAA	0.94 (0.68-1.31)	1.93 (1.00-3.81)	1.05 (0.49-2.32)	1.15 (0.81-1.63)	1.03 (0.59-1.79)	0.93 (0.47-1.80)	0.84
	1D	TCCTAT	1.45 (0.87-2.39)	0.74 (0.23-2.20)	1.15 (0.31-4.67)	1.59 (0.87-2.88)	0.93 (0.40-2.06)	1.10 (0.36-3.15)	0.56
	1E	TCCCGA	0.81 (0.41-1.53)	0.89 (0.30-2.55)	1.25 (0.44-4.09)	0.87 (0.46-1.62)	0.49 (0.15-1.30)	4.02 (0.97-20.56)	0.060
Block 2	2A	AAGCG	1.02 (0.73-1.42)	2.00 (1.11-3.71)	0.95 (0.46-1.91)	0.99 (0.70-1.39)	1.44 (0.83-2.59)	1.54 (0.82-3.00)	0.33
	2B	GAGCG	1.05 (0.66-1.66)	0.45 (0.17-1.05)	0.71 (0.22-2.37)	0.72 (0.41-1.21)	1.62 (0.74-3.53)	0.57 (0.22-1.38)	0.15
Block 3									
3A	GGG		0.83 (0.63-1.10)	1.22 (0.73-2.03)	0.95 (0.49-1.85)	0.93 (0.69-1.24)	0.89 (0.56-1.41)	0.90 (0.50-1.59)	0.98

Gene	Block	Haplotype	E _T [*] N cases (controls)				E _{PT} [*] N cases (controls)				P Interaction [‡]	P Interaction [‡]
			No E _T use [†] 175 (374)	1-9 years 63 (79)	10+ years 48 (35)		No E _{PT} use [†] 174 (280)	1-9 years 65 (130)	10+ years 47 (78)			
ESR2	3B	GGA	1.03 (0.68-1.54)	0.64 (0.30-1.35)	1.28 (0.55-3.18)	0.94	1.37 (0.89-2.09)	0.56 (0.26-1.14)	0.59 (0.25-1.30)	0.043		
	3C	AAA	1.23 (0.94-1.63)	0.90 (0.55-1.48)	0.85 (0.43-1.65)	0.070	0.90 (0.66-1.20)	1.61 (1.02-2.58)	1.36 (0.76-2.46)	0.083		
	4A	AAGGGAC	1.13 (0.85-1.49)	1.11 (0.69-1.79)	0.91 (0.47-1.77)	0.37	0.86 (0.64-1.15)	1.82 (1.14-2.94)	1.27 (0.72-2.25)	0.024		
	4B	AGGGAGA	0.89 (0.56-1.39)	1.69 (0.64-4.57)	1.09 (0.43-2.78)	0.76	1.08 (0.66-1.74)	0.89 (0.40-1.89)	0.96 (0.36-2.42)	0.91		
	4C	CGGGGGC	1.03 (0.73-1.45)	0.94 (0.49-1.78)	1.52 (0.67-3.65)	0.51	1.05 (0.71-1.52)	1.24 (0.69-2.20)	0.92 (0.48-1.74)	0.79		
ESR2	4D	CGGGGGA	0.95 (0.65-1.37)	0.80 (0.42-1.54)	1.27 (0.52-3.40)	0.19	1.16 (0.79-1.71)	0.59 (0.28-1.17)	0.81 (0.39-1.62)	0.22		
	Block 1	1A	CGCC	0.94 (0.71-1.24)	1.03 (0.65-1.64)	1.04 (0.54-1.99)	0.31	1.08 (0.80-1.46)	0.81 (0.53-1.24)	0.90 (0.51-1.56)	0.52	
	1B	CACC	0.72 (0.41-1.22)	0.84 (0.31-2.20)	3.03 (0.97-11.42)	0.17	0.92 (0.52-1.61)	1.38 (0.68-2.76)	0.18 (0.02-0.80)	0.052		
	1C	CACCT	0.91 (0.55-1.49)	0.48 (0.16-1.29)	0.48 (0.14-1.51)	0.046	0.68 (0.38-1.18)	0.85 (0.37-1.82)	0.84 (0.26-2.49)	0.89		
	1D	TACC	1.19 (0.64-2.18)	0.83 (0.30-2.16)	-	0.76	1.63 (0.81-3.26)	0.71 (0.23-1.86)	0.97 (0.29-3.03)	0.37		
HSD17B1	1E	TACT	1.09 (0.80-1.46)	1.40 (0.77-2.60)	0.66 (0.30-1.41)	0.55	0.93 (0.66-1.29)	1.35 (0.82-2.21)	1.27 (0.69-2.36)	0.39		
	Block 1	1A	CGAT	0.92 (0.70-1.20)	0.65 (0.39-1.07)	1.20 (0.61-2.40)	0.72	0.89 (0.67-1.19)	0.65 (0.40-1.02)	1.37 (0.78-2.44)	0.13	
	1B	CAGC	1.06 (0.78-1.44)	1.52 (0.90-2.59)	0.49 (0.21-1.11)	0.27	1.05 (0.75-1.46)	1.21 (0.73-2.00)	0.97 (0.54-1.74)	0.84		
	1C	AAGC	1.12 (0.83-1.51)	1.06 (0.58-1.92)	1.24 (0.55-2.92)	0.46	1.16 (0.83-1.61)	1.14 (0.68-1.89)	0.96 (0.50-1.82)	0.87		
HSD17B2	Block 1	1A	CAT	0.96 (0.74-1.25)	0.74 (0.44-1.22)	0.92 (0.47-1.77)	0.77	0.76 (0.56-1.01)	1.14 (0.73-1.80)	1.21 (0.73-2.02)	0.15	
	1B	CAC	0.95 (0.49-1.78)	1.84 (0.58-6.08)	0.80 (0.22-2.81)	0.59	1.51 (0.80-2.86)	0.47 (0.12-1.42)	0.68 (0.14-2.71)	0.17		
	1C	CGC	0.88 (0.50-1.49)	0.12 (0.01-0.80)	0.08 (0.01-0.49)	0.043	0.51 (0.25-1.01)	0.79 (0.27-2.13)	0.65 (0.20-1.91)	0.78		
	1D	TGC	1.15 (0.86-1.53)	1.30 (0.77-2.21)	1.39 (0.70-2.85)	0.75	1.42 (1.04-1.95)	1.04 (0.65-1.68)	0.86 (0.48-1.51)	0.25		
	Block 2	2A	GCAT	1.19 (0.91-1.55)	0.89 (0.54-1.46)	1.07 (0.58-1.99)	0.93	1.20 (0.90-1.58)	1.38 (0.87-2.20)	0.62 (0.36-1.07)	0.067	
HSD17B2	2B	GCAC	1.23 (0.79-1.92)	1.03 (0.49-2.23)	1.62 (0.55-5.87)	0.97	1.12 (0.70-1.79)	1.12 (0.51-2.37)	1.83 (0.77-4.38)	0.60		
	2C	GCGC	0.74 (0.42-1.27)	1.88 (0.71-5.06)	0.25 (0.06-0.86)	0.30	0.73 (0.42-1.26)	0.73 (0.25-1.86)	1.26 (0.35-4.27)	0.73		
	2D	GTGC	0.81 (0.59-1.10)	0.95 (0.55-1.62)	1.14 (0.61-2.14)	0.63	0.80 (0.58-1.10)	0.87 (0.53-1.41)	1.25 (0.69-2.27)	0.43		

* Odds ratio (95% confidence interval) per copy of haplotype adjusted for age, body mass index, age at menopause, lifetime oral contraceptive use and the other type of hormone therapy

[†]No use included hormone never users and < 1 year of use

[‡]P for interaction for ET based on 1 df likelihood ratio test with ET as continuous variable and for EPT based on 2 degree of freedom likelihood ratio test with EPT as categorical variable as presented in the table.

Abbreviations: ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy