Published in final edited form as:

Gynecol Oncol. 2011 April ; 121(1): 54–58. doi:10.1016/j.ygyno.2010.11.014.

Polymorphisms in genes hydroxysteroid-dehydrogenase-17b type 2 and type 4 and endometrial cancer risk

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Abstract

Objective—Hydroxysteroid-dehydrogenase-17b (*HSD17b*) genes control the last step in estrogen biosynthesis. The isoenzymes HSD17b2 and HSD17b4 in the uterus preferentially catalyze the conversion of estradiol, the most potent and active form of estrogen, to estrone, the inactive form of estrogen. Endometrial adenocarcinoma is linked to excessive exposure to estrogens. We hypothesized that single nucleotide polymorphisms (SNPs) in genes *HSD17b2* and *HSD17b4* may alter the enzyme activity, estradiol levels and risk of disease.

Methods—Pairwise tag SNPs were selected from the HapMap Caucasian database to capture all known common (minor allele frequency > 0.05) genetic variation with a correlation of at least 0.80. Forty-eight SNPs were genotyped in the case-control studies nested within the Nurses' Health Study (NHS) (cases=544, controls=1296) and the Women's Health Study (WHS) (cases=130, controls=389). The associations with endometrial cancer were examined using conditional logistic regression to estimate odds ratio and 95% confidence intervals adjusted for known risk factors. Results from the two studies were pooled using fixed effects models. We additionally investigated

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

All authors contributed to this study and approved the enclosed final manuscript. S.K. performed all analyses, assisted with study design, and prepared the manuscript; M.McG. assisted with study design, data analysis, and manuscript editing; and I.L., J.B, P.K, and I.DV. were involved in all stages of this project, including obtaining funding, study design, data collection, statistical support, and manuscript editing.

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whether SNPs are predictive of plasma estradiol and estrone levels in the NHS using linear regression.

Results—Four intronic SNPs were significantly associated with endometrial cancer risk (p-value <0.05). After adjustment for multiple testing, we did not observe any significant associations between SNPs and endometrial cancer risk or plasma hormone levels.

Conclusions—This is the first study to comprehensively evaluate variation in *HSD17b2* and *HSD17b4* in relation to endometrial cancer risk. Our findings suggest that variation in *HSD17b2* and *HSD17b4* does not substantially influence the risk of endometrial cancer in Caucasians.

Keywords

endometrial carcinoma; polymorphisms; *HSD17b2*; *HSD17b4*

Introduction

Hydroxysteroid dehydrogenase 17b (*HSD17b*) genes are involved in the synthesis and metabolism of sex steroid hormones. There are at least eleven human *HSD17b* isoenzymes expressed in a variety of tissues such as the ovary, placenta, uterus, liver, adipose tissue, prostate and testis(1). *HSD17b* Type 2 (*HSD17b2*) and *HSD17b* Type 4 (*HSD17b4*) are expressed in the uterus(2,3) and control the last step in the formation of estrogens. These enzymes preferentially catalyze the conversion of estradiol (E2), the most potent and active form of estrogen, to estrone (E1), the inactive form of estrogen (4). *HSD17b2* and *HSD17b4* are located on two different chromosomes, chromosome 16 and 5 respectively, span 63 Kb and 90 Kb each, and are composed of 5 and 24 exons respectively. *HSD17b2* and *HSD17b4* function as intracrine regulators modulating local estrogen levels (5).

Endometrial cancer is a disease linked to prolonged exposure to estrogen unopposed by progesterone. This mechanism is supported by studies demonstrating an association of reproductive factors and exogenous hormone use (oral contraceptives, postmenopausal hormones) with endometrial cancer (6). Family history of endometrial cancer has also been associated with sporadic endometrial cancer (7), suggesting genetic variability may play a role in the development of endometrial cancer. We hypothesized that genetic variation in the form of single nucleotide polymorphisms (SNPs) in estrogen metabolism genes *HSD17b2* and *HSD17b4* may influence enzyme activity, estradiol levels and risk of disease. A number of genes along the estrogen biosynthesis pathway have been previously examined in relation to endometrial cancer, however, no previous studies have examined *HSD17b2* and *HSD17b4* (8). In addition, only a small number of SNPs in these two genes have been investigated in relation to other health outcomes (9–15). We used the Nurses' Health Study (NHS) and Women's Health Study (WHS) nested case-control studies to comprehensively evaluate SNP variation in genes *HSD17b2* and *HSD17b4* and their association with endometrial cancer risk and circulating hormone levels.

Methods

Study populations

The NHS case-control study of endometrial cancer is nested within the NHS prospective cohort study established in 1976 when 121,700 married female nurses aged between 30–55 years and residing in 11 US states, agreed to participate in the study. The nurses were followed every two years by completing a self-administered mailed questionnaire with detailed information on lifestyle factors and disease status (6). In 1989–90, 32,826 women completed a blood questionnaire and provided a blood sample. In 2000–2002, 33,040 women who had not provided a blood sample completed a buccal cell questionnaire and

provided a buccal cell sample. Cases in this study consisted of women who provided a blood or buccal cell sample, were diagnosed with invasive endometrial cancer between 1976 through June 1, 2004 and were confirmed by medical records. Controls were randomly selected participants from the cohort who provided a blood or buccal cell sample, and had no previous report of hysterectomy and cancer through the questionnaire cycle in which the case was diagnosed. Controls were matched to cases, using a 2:1 or 3:1 ratio, on age, menopausal status at specimen collection and prior to diagnosis, postmenopausal hormone use at specimen collection, date of specimen collection, type of biospecimen, and fasting status at blood draw.

The WHS case-control study of endometrial cancer is nested within the completed WHS randomized clinical trial that examined the use of low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease. The trial consists of 39,876 female health professionals across the US, aged 45 years or older when randomization began in April 1993 (16,17). Upon randomization, every six months for the first year, and annually thereafter, participants completed a detailed questionnaire that provided information on known or potential risk factors for endometrial cancer (18). From 1993–95, 28,345 women in the WHS provided blood samples. The cases in this analysis included women who provided a blood sample and were diagnosed with endometrial cancer from blood collection through June 1, 2002. Only cases confirmed by a pathologist were considered. Controls were randomly selected from the rest of the participants who provided a blood sample, and had no previous report of cancer and hysterectomy. Controls were matched to cases, using a 3:1 ratio, on age, menopausal status and postmenopausal hormone use at specimen collection, date of specimen collection and fasting status at blood draw.

SNP selection

SNPs were selected using data from the HapMap population sample with European ancestry (CEU) (phase I+II release 24). SNP data were downloaded from a region including the gene and 20Kb upstream and 10Kb downstream of the gene, in order to capture 5' and 3' regulatory regions. We excluded SNPs with Minor Allele Frequency (MAF) <0.05. Following exclusions, a total of 71 SNPs were listed in HapMap in gene *HSD17b2* and a total of 87 SNPs in gene *HSD17b4*. All SNPs within the genes were in introns except 3 non-synonymous SNPs in *HSD17b4*. One SNP was in the 5' untranslated region (UTR) of *HSD17b2*. Using the software Haploview and taking advantage of the linkage disequilibrium structure between SNPs, we randomly selected pairwise tag SNPs correlated with a minimum r^2 of 0.80 with all remaining SNPs in the regions of interest. We forced certain SNPs to be chosen as tag SNPs, for comparability of results between studies and because of possible functional significance. These included tag SNPs identified by the Breast and Prostate Cohort Consortium (personal communication), non-synonymous SNPs (n=3), SNPs in regulatory regions (n=1), and SNPs previously reported to be associated with other diseases (n=2 of which one SNP overlapped with an exonic SNP) (14,15).

Power calculations were estimated using the program Quanto. The sample size of ~700 case-control pairs in this study provided more than 82% power to detect a minimum log-additive odds ratio of 1.3 for an allele with 20% or higher frequency at the 0.05 level.

Genotyping

DNA was extracted from leukocyte cell and buccal cell samples with the QIAGEN-QIAamp 96 DNA Blood Kit. The SNPs were genotyped using Taqman assay on Biotrove OpenArray® Real-Time qPCR system (Woburn, MA). Laboratory personnel were blinded to case status, and a random 5% of the samples were repeated for genotyping quality control. The concordance for the duplicate samples was 100%. Missing data was less than 10%.

Both DNA extraction and genotyping were performed at the Harvard Partners Genotyping Facility at the Dana–Farber/Harvard Cancer Center High Throughput Genotyping Core.

Plasma hormone level measurements

In a previous study of breast cancer risk in the NHS, estradiol and estrone plasma levels were measured in 643 postmenopausal control women with no history of cancer (except non-melanoma skin cancer) and no prior PMH use in the last three months (19). A subset of our tag SNPs ($n=23/48$; RS2042429, RS4445895, RS2955163, RS996752, RS2955162 in *HSD17b2* and RS25640, RS32646, RS382719, RS442923, RS463513, RS2455466, RS2457221, RS2636961, RS2678070, RS3797371, RS3850201, RS6897978, RS10064000, RS10478424, RS11748477, RS11749784, RS12653702, RS17388769 in *HSD17b4*) was previously genotyped in these controls (unpublished data). For our analysis we restricted to women at risk for endometrial cancer (intact uterus) ($n=471$) and who had genotype data available for *HSD17b2* and *HSD17b4* SNPs.

Statistical analysis

Genotype frequencies among controls were tested for Hardy-Weinberg equilibrium using a chi-square test. The success rate (SR) for each SNP was calculated as the percent of successfully genotyped samples for each SNP. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between *HSD17b2* and *HSD17b4* SNP genotypes and endometrial cancer risk. We used the additive model modeling the number of minor alleles as a continuous variable. Individuals homozygous for the more common allele were coded as having zero copies of the minor allele, individuals heterozygous as having one copy, and individuals homozygous for the rare allele as having two copies. We conducted analysis adjusted for the matching factors only and separate analysis additionally adjusted for age at menarche, parity and age at first birth, body mass index at diagnosis (BMI; kg/m^2), smoking status at diagnosis, postmenopausal hormone use at diagnosis, age at menopause at diagnosis, and ever oral contraceptive use. We used the fixed effects model to combine results from the two cohorts after testing for heterogeneity. We adjusted for multiple testing by controlling the false discovery rate (20). All analyses were restricted to Caucasians (98%). We used linear regression adjusted for age and laboratory batch to evaluate the association between the number of copies of minor allele and log-transformed hormone levels. SAS Version 9.1 software (SAS Institute, Cary, NC) was used for all analyses.

Results

The NHS comprised of 544 cases (300 blood, 244 buccal cell) and 1,296 controls (817 blood, 479 buccal cell), and the WHS study of 130 cases and 389 matched controls. The complete nested case-control study was composed of 686 endometrial cancer cases and 1,729 matched controls. The basic characteristics of the two study populations are described in previous studies (21).

For gene *HSD17b2* pairwise tagging yielded 24 tag SNPs that captured all 71 SNPs in the region of interest with a mean r^2 of 0.95. For gene *HSD17b4* pairwise tagging yielded 24 tag SNPs that captured all 87 SNPs in the region of interest with a mean r^2 of 0.96. One SNP in *HSD17b4* failed genotyping, however, this SNP only tagged itself, therefore coverage of the region remained high. We successfully genotyped a total of 47 SNPs; 24 SNPs in *HSD17b2* and 23 SNPs in *HSD17b4*.

Genotype frequencies in controls were in accordance with Hardy-Weinberg equilibrium. Success rates were above 90% except for seven SNPs ($\text{SR} > 85\%$), and one SNP (rs

2911422) failed genotyping. MAFs in our study were similar to MAFs listed in HapMap. All of the SNPs but 10 (see Table 2 footnote) had P-values greater than 0.05 for the test of heterogeneity comparing the NHS and WHS findings. Results adjusted for the matching factors only were similar to results additionally adjusted for other factors (data not shown). In the pooled analysis, we observed a total of four intronic SNPs in genes *HSD17b2* and *HSD17b4* with a p-value <0.05 (Table 1, 2). However, after adjustment for multiple testing (47 tests) we did not observe any statistically significant associations with the polymorphisms in *HSD17b2* and *HSD17b4* and endometrial cancer risk. In the individual studies, a small number of SNPs in *HSD17b4* including a non-synonymous SNP were found to be significant in the WHS, however, this is likely attributed to chance given the number of tests conducted, the smaller sample size in the WHS, and the fact that these SNPs had a low MAF (0.08–0.09). Among a group of NHS controls (n=471) with plasma hormone measurements, SNPs in *HSD17b2* and *HSD17b4* were not associated with estradiol or estrone levels (data not shown).

Discussion

This is the first study to examine genetic variation in *HSD17b2* and *HSD17b4* genes in relation to endometrial cancer risk. We evaluated the association between 47 tag SNPs that efficiently covered the genes *HSD17b2* and *HSD17b4* and endometrial cancer risk, in two case-control studies nested within the NHS and WHS. After combining results from the two studies, we observed no significant associations between polymorphisms in *HSD17b2* and *HSD17b4* and endometrial cancer risk among Caucasians.

Previous studies have examined a small number of SNPs (n<3) in *HSD17b2* in relation to mammographic density (12), prostate cancer (10), human spermatogenic defect (11) and circulating sex hormones (9,12). None of these studies observed any significant associations. Similarly, a handful of studies have examined a select number of SNPs (n<13) in *HSD17b4* in relation to testicular germ cell tumors (13), ovarian cancer (14), and androgen deprivation prostate cancer therapy (15). The study by Beesly *et al.* (14) observed a borderline association of non-synonymous SNP rs17145454 with the clear cell subtype of ovarian cancer but not with overall ovarian cancer suggesting the association maybe due to chance. The study by Ross *et al.* (15) observed a significant association of intronic SNP rs24543 with androgen deprivation prostate cancer therapy. We genotyped these two SNPs as well as newly discovered non-synonymous SNPs in our genes of interest and SNPs in known regulatory regions. We also included SNPs genotyped in the Breast and Prostate Cancer Consortium where no association was observed with breast and prostate cancer (personal communication). We did not observe an association with any of the above selected SNPs nor with the remaining tag SNPs we genotyped.

Mice knock-out studies on *HSD17b2* and *HSD17b4* highlight the importance of these genes for survival to birth and adulthood. Mice lacking the gene *HSD17b2* exhibit placenta structural abnormalities and die at the embryo stage (22). Mice overexpressing *HSD17b2* show growth retardation, ovarian dysfunction and mammary gland hyperplasia (23). Mice lacking the gene *HSD17b4* do not die at the embryo stage but exhibit growth retardation and structural abnormalities in several organs such as the eye (atrophic retina), brain, and testis (infertility) (24). *HSD17b4* in addition to sex steroid metabolism plays a central role in fatty acid metabolism. Humans deficient in *HSD17b4*, also named multifunctional protein or D-bi-functional protein (DBP), are diagnosed with a developmental syndrome known as Zellweger syndrome otherwise called DBP deficiency. Patients die within their first to third year of life, and have brain abnormalities and seizures (24). The deficiency is caused by point mutations, deletions or truncations that severely affect the structure and activity of *HSD17b4* (25). We observed that all known SNPs in these genes as listed in the HapMap

database were located in introns, except 3 non-synonymous SNPs in *HSD17b4*. Taken together all of the above observations underscore the important role these two genes play in biological function and support that these proteins are more likely to be functionally conserved (26).

We also did not observe any association between a subset of our tag SNPs and plasma hormone levels suggesting that variation in these genes does not influence levels of circulating hormones. It is possible that circulating hormone levels may not accurately reflect local hormone levels which may be influenced by variation in *HSD17b2* and *HSD17b4*.

This is the first report to investigate genetic variation in *HSD17b2* and *HSD17b4* in relation to endometrial cancer risk. The main strengths of this study include the comprehensive evaluation of SNPs in *HSD17b2* and *HSD17b4* in two prospective case-control studies. We selected 47 tagging SNPs that provided complete coverage across the genes and regulatory regions. In addition, we investigated SNPs with possible functional significance and we replicated findings from previous studies on other health outcomes. The use of two prospective case-control studies in which to validate our findings and the homogeneous population are among other strengths of the study. However, our study was limited to Caucasians therefore the results may not be generalized to other ethnicities. We also did not examine rare variants and may not have had sufficient power to detect weak associations. The lack of significant associations does not rule out the possibility that polymorphisms in these genes may have a larger impact when they interact with other genes or lifestyle factors. Our findings suggest that common genetic variation in *HSD17b2* and *HSD17b4* does not substantially influence the risk of endometrial cancer in Caucasian women.

Research Highlights

- Comprehensive examination of SNPs in estrogen metabolism genes *HSD17b2* and *HSD17b4*
- Examined in two prospective case-control studies nested within the NHS and WHS
- Novel findings reported in relation to endometrial cancer risk
- Endometrial cancer is a model of estrogen carcinogenesis
- SNP variation in these genes may not influence the risk of endometrial cancer

Acknowledgments

Funding

This work was supported by the National Institute of Health (grant numbers: CA87969, CA49449, CA82838, CA047988, HL043851, NICHD K12 HD051959-01); the American Cancer Society (grant number: RSG-00-061-04-CCE); and the HSPH-Cyprus Initiative for the Environment and Public Health funded by the Republic of Cyprus (to S.K).

We thank J. Prescott, K. Terry, H. Ranu, and P. Soule, for assistance, and we thank the participants in the Nurses' Health Study and the Women's Health Study for their dedication and commitment.

References

1. Peltoketo H, Luu-The V, Simard J, Adamski J. 17 β -hydroxysteroid dehydrogenase (HSD)/17-ketosteroid reductase (KSR) family; nomenclature and main characteristics of the 17HSD/KSR enzymes. *J Mol Endocrinol*. 1999; 23:1–11. [PubMed: 10431140]
2. Husen B, Psonka N, Jacob-Meisel M, Keil C, Rune GM. Differential expression of 17 β -hydroxysteroid dehydrogenases types 2 and 4 in human endometrial epithelial cell lines. *J Mol Endocrinol*. 2000; 24:135–44. [PubMed: 10657005]
3. Yang S, Fang Z, Gurates B, et al. Stromal PRs mediate induction of 17 β -hydroxysteroid dehydrogenase type 2 expression in human endometrial epithelium: a paracrine mechanism for inactivation of E2. *Mol Endocrinol*. 2001; 15:2093–105. [PubMed: 11731611]
4. Luu-The V. Analysis and characteristics of multiple types of human 17 β -hydroxysteroid dehydrogenase. *J Steroid Biochem Mol Biol*. 2001; 76:143–51. [PubMed: 11384872]
5. Labrie F, Luu-The V, Lin SX, et al. The key role of 17 β -hydroxysteroid dehydrogenases in sex steroid biology. *Steroids*. 1997; 62:148–58. [PubMed: 9029730]
6. Karageorgi S, Hankinson SE, Kraft P, De Vivo I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976–2004. *Int J Cancer*. 2010; 126:208–16. [PubMed: 19551854]
7. Parazzini F, La Vecchia C, Moroni S, Chatenoud L, Ricci E. Family history and the risk of endometrial cancer. *Int J Cancer*. 1994; 59:460–2. [PubMed: 7960212]
8. 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]
9. Dunning AM, Dowsett M, Healey CS, et al. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. *J Natl Cancer Inst*. 2004; 96:936–45. [PubMed: 15199113]
10. Mononen N, Seppala EH, Duggal P, et al. Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors. *Cancer Res*. 2006; 66:743–7. [PubMed: 16424004]
11. Su MT, Chen CH, Kuo PH, et al. Polymorphisms of estrogen-related genes jointly confer susceptibility to human spermatogenic defect. *Fertil Steril*. 2010; 93:141–9. [PubMed: 18980759]
12. Warren R, Skinner J, Sala E, et al. Associations among mammographic density, circulating sex hormones, and polymorphisms in sex hormone metabolism genes in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:1502–8. [PubMed: 16896040]
13. Figueroa JD, Sakoda LC, Graubard BI, et al. Genetic variation in hormone metabolizing genes and risk of testicular germ cell tumors. *Cancer Causes Control*. 2008; 19:917–29. [PubMed: 18415690]
14. Beesley J, Jordan SJ, Spurdle AB, et al. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:2557–65. [PubMed: 18086758]
15. Ross RW, Oh WK, Xie W, et al. Inherited variation in the androgen pathway is associated with the efficacy of androgen-deprivation therapy in men with prostate cancer. *J Clin Oncol*. 2008; 26:842–7. [PubMed: 18281655]
16. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *Jama*. 2005; 294:56–65. [PubMed: 15998891]
17. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005; 352:1293–304. [PubMed: 15753114]
18. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *Jama*. 2005; 294:47–55. [PubMed: 15998890]

19. Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE. Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. *J Natl Cancer Inst.* 2004; 96:1856–65. [PubMed: 15601642]
20. Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behav Brain Res.* 2001; 125:279–84. [PubMed: 11682119]
21. McGrath M, Lee IM, Buring J, Hunter DJ, De Vivo I. Novel breast cancer risk alleles and endometrial cancer risk. *Int J Cancer.* 2008; 123:2961–4. [PubMed: 18785201]
22. Rantakari P, Strauss L, Kiviranta R, et al. Placenta defects and embryonic lethality resulting from disruption of mouse hydroxysteroid (17-beta) dehydrogenase 2 gene. *Mol Endocrinol.* 2008; 22:665–75. [PubMed: 18048640]
23. Shen Z, Saloniemi T, Ronnblad A, Jarvensivu P, Pakarinen P, Poutanen M. Sex steroid-dependent and -independent action of hydroxysteroid (17beta) Dehydrogenase 2: evidence from transgenic female mice. *Endocrinology.* 2009; 150:4941–9. [PubMed: 19797119]
24. Huyghe S, Mannaerts GP, Baes M, Van Veldhoven PP. Peroxisomal multifunctional protein-2: the enzyme, the patients and the knockout mouse model. *Biochim Biophys Acta.* 2006; 1761:973–94. [PubMed: 16766224]
25. Moller G, van Grunsven EG, Wanders RJ, Adamski J. Molecular basis of D-bifunctional protein deficiency. *Mol Cell Endocrinol.* 2001; 171:61–70. [PubMed: 11165012]
26. Breitling R, Marijanovic Z, Perovic D, Adamski J. Evolution of 17beta-HSD type 4, a multifunctional protein of beta-oxidation. *Mol Cell Endocrinol.* 2001; 171:205–10. [PubMed: 11165031]

Table 1

Association between SNPs in gene *HSD17b2* and risk of endometrial cancer

SNP [†]	MAF	NHS		WHS		Pooled [‡]	
		OR [†]	95% CI	p-value	OR [†]	95% CI	p-value [*]
RS4243229	0.01	2.10	(1.08–4.09)	0.03	8.19	(0.85–79.22)	0.07
RS4404064	0.07	1.45	(1.09–1.92)	0.01	0.87	(0.51–1.49)	0.61
RS6564958	0.34	0.86	(0.73–1.02)	0.08	0.89	(0.64–1.22)	0.47
RS8191175	0.04	0.79	(0.53–1.16)	0.23	0.76	(0.36–1.60)	0.48
RS723012	0.35	1.13	(0.97–1.32)	0.12	0.92	(0.68–1.25)	0.59
RS295163	0.04	1.11	(0.77–1.59)	0.57	1.41	(0.72–2.75)	0.32
RS2955162	0.26	1.08	(0.91–1.27)	0.38	1.06	(0.77–1.47)	0.72
RS2042429	0.47	0.93	(0.80–1.08)	0.34	0.99	(0.73–1.33)	0.93
RS9923501	0.06	0.84	(0.58–1.21)	0.35	0.99	(0.55–1.78)	0.98
RS989019	0.48	0.95	(0.82–1.11)	0.55	0.92	(0.69–1.23)	0.58
RS11649253	0.05	1.21	(0.87–1.67)	0.26	0.70	(0.32–1.52)	0.37
RS11150438	0.07	0.94	(0.68–1.29)	0.71	1.55	(0.93–2.58)	0.09
RS8191225	0.08	0.95	(0.69–1.31)	0.76	0.88	(0.46–1.67)	0.69
RS2966245	0.43	0.97	(0.83–1.13)	0.68	0.99	(0.74–1.33)	0.96
RS11643002	0.38	1.04	(0.90–1.21)	0.59	0.96	(0.71–1.29)	0.78
RS10514524	0.49	1.00	(0.86–1.16)	0.98	1.09	(0.81–1.45)	0.58
RS4291899	0.09	0.98	(0.75–1.29)	0.90	0.94	(0.59–1.51)	0.81
RS996752	0.34	1.02	(0.86–1.20)	0.84	0.88	(0.65–1.21)	0.44
RS10514527	0.36	1.01	(0.87–1.19)	0.86	0.89	(0.66–1.21)	0.47
RS3887358	0.10	0.95	(0.74–1.22)	0.69	1.12	(0.69–1.81)	0.65
RS9889094	0.04	0.93	(0.63–1.36)	0.70	1.55	(0.70–3.41)	0.28
RS9934209	0.39	1.01	(0.86–1.19)	0.86	0.97	(0.70–1.34)	0.85
RS4445895 [§]	0.38	1.02	(0.87–1.18)	0.84	0.95	(0.71–1.29)	0.75

NHS, Nurses' Health Study; WHS, Women's Health Study; OR, Odds Ratio; CI, Confidence Interval; SNP, Single Nucleotide Polymorphism; HSD17b2, Hydroxysteroid-dehydrogenase-17b Type 2; MAF, Minor Allele Frequency; 5'-UTR, 5'-UnTranslated Region

* Results sorted by pooled p-value

¹ OR adjusted for matching factors only; age, date of specimen collection, fasting status at blood draw, menopausal status at specimen collection and prior to diagnosis, and postmenopausal hormone use at specimen collection

² combined results from NHS and WHS using fixed effects model

[†] Intronic SNP unless otherwise noted

[§] 5'-UTR SNP

[‡] All SNPs had a p-value for the test of heterogeneity of less than 0.05

Table 2

Association between SNPs in gene *HSD17b4* and risk of endometrial cancer

SNP [†]	MAF	NHS		WHS		Pooled	
		OR [‡] (95% CI)	p-value	OR [‡] (95% CI)	p-value	OR [‡] (95% CI)	p-value [*]
RS17388769	0.15	1.19 (0.99–1.44)	0.07	1.22 (0.82–1.84)	0.33	1.20 (1.01–1.42)	0.04
RS2636961	0.44	1.22 (1.04–1.41)	0.01	0.91 (0.66–1.25)	0.56	1.15 (1.00–1.32)	0.04
RS11749784 [‡]	0.23	0.97 (0.81–1.16)	0.73	0.58 (0.39–0.87)	0.01	0.89 (0.75–1.05)	0.16
RS11205 [#]	0.40	0.88 (0.75–1.02)	0.09	1.02 (0.76–1.38)	0.88	0.91 (0.79–1.04)	0.16
RS6897978	0.21	0.96 (0.80–1.17)	0.71	0.65 (0.45–0.96)	0.03	0.89 (0.75–1.06)	0.19
RS2457221	0.50	0.91 (0.79–1.05)	0.18	1.04 (0.78–1.39)	0.78	0.93 (0.82–1.06)	0.28
RS12653702 [‡]	0.09	1.01 (0.77–1.31)	0.96	0.31 (0.15–0.64)	0.001	0.88 (0.69–1.12)	0.30
RS463513 [‡]	0.48	0.88 (0.76–1.01)	0.07	1.24 (0.92–1.66)	0.15	0.94 (0.82–1.07)	0.32
RS11241507 [‡]	0.32	0.85 (0.72–1.01)	0.06	1.23 (0.92–1.66)	0.17	0.93 (0.81–1.08)	0.34
RS257977	0.06	1.25 (0.93–1.70)	0.14	0.76 (0.42–1.37)	0.36	1.13 (0.86–1.48)	0.38
RS2678070 [‡]	0.47	0.88 (0.76–1.01)	0.07	1.29 (0.96–1.71)	0.09	0.95 (0.83–1.07)	0.39
RS6898518	0.14	0.98 (0.78–1.21)	0.83	0.74 (0.49–1.13)	0.17	0.92 (0.76–1.12)	0.41
RS10478424	0.24	0.99 (0.83–1.18)	0.92	0.74 (0.51–1.06)	0.10	0.94 (0.80–1.10)	0.42
RS382719	0.45	1.04 (0.90–1.21)	0.56	1.02 (0.76–1.38)	0.88	1.04 (0.91–1.18)	0.56
RS11539471 [#] [‡]	0.08	1.09 (0.83–1.43)	0.55	0.35 (0.18–0.69)	0.002	0.93 (0.72–1.20)	0.56
RS25640 [#] [‡]	0.44	0.88 (0.75–1.02)	0.10	1.34 (1.01–1.78)	0.05	0.96 (0.84–1.10)	0.59
RS3850201 [‡]	0.08	1.08 (0.83–1.40)	0.58	0.36 (0.18–0.71)	0.003	0.93 (0.73–1.20)	0.59
RS2455466	0.30	0.91 (0.77–1.07)	0.25	1.21 (0.89–1.65)	0.21	0.97 (0.84–1.12)	0.67
RS2455463 ^{//}	0.47	1.10 (0.94–1.29)	0.23	0.82 (0.61–1.09)	0.17	1.03 (0.90–1.18)	0.69
RS10064000 [‡]	0.34	0.90 (0.77–1.05)	0.17	1.37 (1.01–1.86)	0.04	0.98 (0.85–1.12)	0.75
RS3797371	0.13	1.00 (0.80–1.26)	0.98	0.87 (0.57–1.31)	0.50	0.97 (0.79–1.18)	0.77
RS32646	0.38	0.95 (0.81–1.11)	0.50	1.24 (0.93–1.65)	0.15	1.01 (0.88–1.16)	0.92
RS11748477 [‡]	0.08	1.13 (0.87–1.47)	0.36	0.35 (0.17–0.73)	0.01	0.99 (0.77–1.27)	0.93
RS442923	0.15	1.01 (0.82–1.23)	0.96	1.00 (0.67–1.50)	0.99	1.00 (0.84–1.20)	0.96

NHS, Nurses' Health Study; WHS, Women's Health Study; OR, Odds Ratio; CI, Confidence Interval; SNP, Single Nucleotide Polymorphism; HSD17b4, Hydroxysteroid-dehydrogenase-17b Type 4; MAF, Minor Allele Frequency

* Results sorted by pooled p-value

/ OR per minor allele (additive model)

/ OR adjusted for matching factors only; age, date of specimen collection, fasting status at blood draw, menopausal status at specimen collection and prior to diagnosis, and postmenopausal hormone use at specimen collection

2 combined results from NHS and WHS using fixed effects model

† Intronic SNP unless otherwise noted

Non-synonymous SNP

// SNP previously associated with a disease

‡ These 10 SNPs had p-value for the test of heterogeneity of greater than 0.05; all remaining SNPs had a p-value of less than 0.05