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Progesterone receptor gene variants and risk of endometrial cancer

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Prolonged excessive estrogen exposure unopposed by progesterone is widely accepted to be a risk factor for endometrial cancer development. The physiological function of progesterone is dependent upon the presence of its receptor [progesterone receptor (PGR)] and several studies have reported single nucleotide polymorphisms (SNPs) in the *PGR* gene to be associated with endometrial cancer risk. We sought to confirm the associations with endometrial cancer risk previously reported for four different *PGR* polymorphisms. A maximum of 2888 endometrial cancer cases and 4483 female control subjects from up to three studies were genotyped for four *PGR* polymorphisms (rs1042838, rs10895068, rs11224561 and rs471767). Logistic regression with adjustment for age, study, ethnicity and body mass index was performed to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs) and *P*-values. Of the four SNPs investigated, only rs11224561 in the 3′ region of the *PGR* gene was found to be significantly associated with endometrial cancer risk. The *A* allele of the rs11224561 SNP was associated with increased risk of endometrial cancer (OR per allele 1.31; 95% CI 1.12–1.53, $P = 0.001$, adjusted for age and study), an effect of the same magnitude and direction as reported previously. We have validated the endometrial cancer risk association with a tagSNP in the 3′ untranslated region of *PGR* previously reported in an Asian population. Replication studies will be required to refine the risk estimate and to establish if this, or a correlated SNP, is the underlying causative variant.

Abbreviations: ANECS, Australian National Endometrial Cancer Study; BMI, body mass index; CI, confidence interval; OR, odds ratio; PGR, progesterone receptor; SNP, single nucleotide polymorphism; PRA, progesterone receptor A; PRB, progesterone receptor B; UTR, untranslated region.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract and its incidence is increasing in developed countries (1). It is well established that the development of endometrial cancer, especially the endometrioid subtype, is associated with risk factors suggesting excessive estrogen exposure unopposed by progesterone (reviewed by ref. 2). Furthermore, progesterone is recognized as being a natural agonist of estrogen-induced proliferation in the endometrium, and for this reason, an adequate progesterone response in the endometrium is essential to control normal cell proliferation (3). This is exemplified by the association of estrogen replacement therapy with elevated endometrial cancer risk and the observation that this increased risk can be abrogated by the addition of progesterone to hormone replacement therapy [(4) and reviewed by ref. 5].

The physiological effects of progesterone depend on the presence of progesterone receptor (PGR), which exists as two isoforms, progesterone receptor A (PRA) and progesterone receptor B (PRB), arising from two alternate promoters of the *PGR* gene (6). Indeed, response to progesterone therapy is dependent on the availability of functional PGR (7). This is confirmed by findings that responses to progesterone therapy are more successful for PGR-positive tumors than for PGR-negative tumors (reviewed by ref. 8). Additionally, PGR positivity in endometrial carcinoma was shown to be an independent prognostic factor for disease-free survival [(9) and reviewed by ref. 8].

Biologic function of PGR may be altered by genetic variation, thereby altering progesterone-mediated tumor suppression. It is therefore conceivable that polymorphisms located within the *PGR* gene may contribute to individual susceptibility to endometrial cancer. The current studies investigating *PGR* single nucleotide polymorphisms (SNPs) and endometrial cancer risk have used both a candidate SNP approach and a candidate gene SNP tagging approach. A case–control study of 187 cases and 397 controls nested within the Nurses' Health Study reported the rs10895068 SNP (331G>A) to be associated with an increased risk of endometrial cancer [331A carriers versus non-carriers; odds ratio (OR) 1.90; 95% confidence interval (CI) 1.10–3.29], with *in vitro* studies suggesting that this SNP caused increased expression of the PRB isoform. In addition, the estimated risk for carriers with a body mass index (BMI) >28 kg/m^2 was reported to be particularly elevated compared with lean non-carrier women (OR 4.71; 95% CI 1.87–11.87) (10). However, a population-based case–control study of 275 cases and 314 controls conducted in Sweden found no association with risk (OR 1.04; 95% CI 0.56–1.93) and no interaction between *PGR* genotype and BMI ($P = 0.35$) (11).

Another candidate polymorphism investigated has been the PROGINS polymorphism, a 306 bp Alu insertion in intron 7 of the *PGR* gene, which is in complete linkage disequilibrium with a missense SNP in exon 4 (rs1042838; Val660Leu) and a silent SNP in exon 5 (rs1042839; His770His) and has been associated with affecting the stability of PGR isoforms (12). A Brazilian case–control study of 121 cases and 282 controls reported a higher incidence of homozygote insertion carriers of the PROGINS polymorphism among endometrial cancer patients compared with controls ($P = 0.012$) (13). It was also previously reported in a small study of 88 cases that carriers of the PROGINS allele exhibited an increased risk of endometrial cancer recurrence (14).

To date, two different studies of endometrial cancer have undertaken an SNP tagging approach using information from the International HapMap Project. A Chinese case–control study of 1204 cases and 1212 controls genotyped seven tag SNPs and identified two SNPs located in the 3′ flanking region of the gene (reported $r^2 = 0.11$) to be associated with endometrial cancer risk (15). Compared with the TT genotype, the rs11224561 CC genotype was significantly associated

with a reduced risk of endometrial cancer (OR 0.68; 95% CI 0.50–0.92, $P = 0.04$) (15). Carriers of the G allele of the rs 471767 SNP were also reported to be associated with a reduced risk of endometrial cancer, although this finding was of marginal statistical significance (OR per allele 0.77; 95% CI 0.58–1.01) (15). Very recently, another study assessed endometrial cancer risk associated with 17 tag SNPs in 583 cases and 1936 controls from two cohort studies, one multiethnic and the other US Caucasian (16). The tagset included rs10895068 (331G>A) and rs1042838 (Val660Leu). Overall, the findings suggested that a 3′ untranslated region (UTR) SNP rs608995 is associated with increased risk of endometrial cancer (OR per allele 1.20; 95% CI 1.06–1.59).

We initiated the current study to assess risk of endometrial cancer associated with four *PGR* polymorphisms for which there was existing evidence for association with endometrial cancer (rs10895068, rs1042838, rs11224561 and rs471767). All SNPs were assessed in our Australian dataset, and we identified independent case–control studies from the USA and Europe, with additional genotyping data for these SNPs, to conduct pooled analysis with increased statistical power.

Materials and methods

Study populations

Five studies from Australia, USA and Europe contributed existing data from SNP genotyping at each site to these analyses. Each study was approved by the relevant local institutional review committees, and participants provided informed consent to take part in research studies. Controls recorded as having had a hysterectomy were excluded from all analyses. Details of each study, numbers of samples and genotyping techniques used for each site are provided in Table I. The median age for cases was 63 years (26–80) and 59 years (19–80) for controls. The majority of subjects reported Caucasian ethnicity (87.1%). Most studies provided details on histology, BMI and ethnicity. The majority of endometrial cancer cases were of endometrioid histology (85.5%). Additional details about each study are provided below.

Australian National Endometrial Cancer Study and Australian Ovarian Cancer Study controls

The Australian National Endometrial Cancer Study (ANECS) is an Australian population-based case–control family study of cancer of the uterine corpus (17). Women aged 18–79 years, registered on the Electoral Roll and newly diagnosed with primary cancer of the endometrium between July 2005 and December 2007 were identified through major hospitals nationally and also from state-based cancer registries. Cases who reported a family history of cancer were also asked to invite their relatives (with and without cancer) to participate in the family component of the study. Relatives were not genotyped for this SNP study. Case participation rate was 63%. Female controls, with no personal history of endometrial cancer or hysterectomy, were recruited using two sources. A population-based control group comprised of women randomly selected using the Australian Electoral Roll (voting is compulsory in Australia) and matched to the age and geographic distribution of the cases (53% participation rate). A second control group of female blood donors were recruited with the aid of the Australian Red Cross Blood Service in Queensland (100% participation rate). All participants completed a detailed questionnaire providing clinical and epidemiological information including BMI and ethnicity. In addition, we also accessed available genotype data for two SNPs (rs1042838 and rs10895068) from controls only from the Australian Ovarian Cancer Study (AOCS, 44% participation rate). This is a national population-based case–control study of ovarian cancer with recruitment strategies almost identical to ANECS, the details of which have been previously published (18).

Singapore and Sweden Breast/Endometrial Cancer

Details of the population selection process for the Singapore and Sweden Breast/Endometrial Cancer Study (SASBAC) have been published previously (4). Briefly, this population-based case–control study was conducted among Swedish women aged 50–74 years, who were residing in Sweden between 1 January 1994 and 31 December 1995. Endometrial cancer cases were identified through the nationwide cancer registries in Sweden (75% participation rates). Controls, frequency matched for age, were randomly selected from the Swedish Registry of Total Population. Control participation rate was 79.9%. The study was restricted to postmenopausal women with an intact uterus and

Table I. Summary of the endometrial cancer case–control studies used in the analyses: details of recruitment, age, ethnicity, BMI and genotyping method

Study	Acronym	Ref	General setting	Controls	Cases (% endometrioid histological subtype)	Age range (median)	BMI range (median)	Ethnicity (%)				Genotyping platform
								Caucasian	African-American	Other	Missing	
Australian National Endometrial Cancer Study/ Australian Ovarian Cancer Study	ANECS/ AOCS	Spurdle *et al.* (17), Beesley *et al.* (18)	Australia; population-based case–control study	1126	1313 (80.1)	19–80 (60)	12.4–75.0 (27.3)	2696 (88.4)	0 (0)	103 (4.7)	210 (6.9)	Sequenom iPLEX
			Australia; population-based case–control ovarian cancer study (controls only)	632	—	20–80 (57)	16.0–64.9 (25.4)	612 (100)	0 (0)	0 (0)	0 (0)	Sequenom iPLEX
Singapore and Swedish Breast/Endometrial Cancer Study	SASBAC	Weiderpass *et al.* (4)	Sweden; population-based case–control study	1523	772 (86.9)	50–74 (63)	16.2–64.8 (25.3)	2295 (100)	0 (0)	0 (0)	0 (0)	Sequenom iPLEX
Women's Insight and Shared Experiences Study	WISE	Strom *et al.* (19)	USA; population-based case–control study	2144	561 (90.9)	50–79 (61)	15.0–51.2 (23.6)	1988 (73.5)	717 (26.5)	0 (0)	0 (0)	Polymerase chain reaction–restriction fragment length polymorphism
Leuven Endometrial Study	LES	None	Belgium; hospital-based case–control study	649	206 (71.8)	20–80 (48)	16.4–89.0 (24.9)	855 (100)	0 (0)	0 (0)	0 (0)	Sequenom iPLEX
Study of Epidemiology and Risk Factors in Cancer Heredity	SEARCH	http://www.ecric.org.uk/	England; population-based case–control study	1600	1455 (89.5)	35–76 (63)	16.0–73.0 (28.0)	3051 (99.9)	0 (0)	4 (0.1)	0 (0)	Taqman
Total				7674	4307 (85.5)	19–80 (60)	12.4–89 (25.6)	10030 (90.3)	717 (6.5)	147 (1.3)	210 (1.9)	

no previous diagnosis of endometrial cancer. All participants provided detailed questionnaire information. For endometrial cancer, histological specimens were reviewed and reclassified by the study pathologist. Genomic analyses are conducted by the Singapore node of the study.

Women's Insight and Shared Experiences Study

The Women's Insight and Shared Experiences Study (WISE) is a population-based case–control study conducted from among residents from a contiguous nine county region around Philadelphia and has been described previously (19). Eligible cases, identified by active surveillance at 61 hospitals, were African-American or Caucasian women aged 50–79 years, who were newly diagnosed with endometrial cancer between 1 July 1999 and 30 June 2002. Pathological reports and medical records were reviewed by trained abstractors and case status was validated by a pathology report that was compatible with primary, invasive epithelial endometrial adenocarcinoma of all stages (I–IV) and all grades. Frequency-matched control subjects were selected by random digit dialing and restricted to women with no history of endometrial cancer or hysterectomy. Telephone interviews to complete detailed questionnaires were conducted for all participants. The participation rates were 77% for both the case patients and control women.

Leuven Endometrial Study

The Leuven Endometrial Study is a hospital-based case–control study. Eligible cases, identified by active surveillance of electronic patient files at the Leuven University Hospital, were white women aged 27–80 years diagnosed with endometrial cancer. Clinical information of endometrial cancer patients was recorded during interview at the time of diagnosis and from pathology reports. All medical records were reviewed by trained abstractors and pathology reports compatible with primary, invasive epithelial endometrial adenocarcinoma of all stages (I–IV) and all grades were consulted. A control group of healthy female blood donors was recruited with the aid of the Red Cross Blood Service in the University Hospital. Participants completed a detailed questionnaire providing epidemiological information, including age, weight, height and self-reported Belgian (Flemish) ethnicity for three generations. Participation rates exceeded 95% for both cases and controls.

Studies of Epidemiology and Risk factors in Cancer Heredity

The Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH) is an ongoing population-based study with cases ascertained through the Eastern cancer Registration and Information Center (http://www.ecric.org.uk). All women diagnosed with endometrial cancer between the ages of 18–69 years (average age diagnosis 58 years) from 31 July 2001 to 1 September 2007 were eligible for inclusion. Approximately 54% of eligible patients have enrolled in the study. Women taking part in the study were asked to provide a 20 ml blood sample for DNA analysis and to complete a comprehensive epidemiological questionnaire. Controls were also drawn from SEARCH (http://www.srl.cam.ac.uk/search/Homepage.htm) but had no prior history of cancer at the time of recruitment. They were female, also between the ages of 18–69 at the time of recruitment and matched to cases in geographical profile. Approximately 35% of eligible controls enrolled in the study. There were 1127 endometrial cases and 1600 controls available for genotyping analysis at the time of this study.

Genotyping

For three studies (ANECS/AOCS, SASBAC and Leuven Endometrial Study), genotyping was performed using matrix-assisted laser desorption/ionization time of flight mass spectrometry for the determination of allele-specific primer extension products using Sequenom's MassARRAY system and iPLEX technology (Sequenom, San Diego, CA). Oligonucleotides were designed using MassARRAY Assay Design software (version 3.1; Sequenom) and results analyzed using TYPER software (version 3.4; Sequenom). For WISE, the rs10895068 polymorphism was assessed using polymerase chain reaction–restriction fragment length polymorphism analysis. Reactions of 50 µl containing 15 ng genomic DNA, 25 pmol of each primer (forward primer 5′-gtacggagccagcagaagtc-3′ and reverse primer 5′-gaggactggagacgcagagt-3′) and 20 µl Eppendorff Master Mix were cycled at 95°C for 3 min, followed by 35 cycles of 94°C for 30 s, 59°C for 30 s, 72°C for 30 s and a final cycle of 72°C for 7 min. Amplicons were digested at 37°C for 4 h in a 25 µl reaction mixture that contained 1 U restriction endonuclease *Nla*IV (New England Biolabs, Beverley, MA), 10 µl of polymerase chain reaction-amplified DNA, 0.25 µl of bovine serum albumin and 1× NEB buffer 4 (New England Biolabs). Genotypes were visualized on 3% ethidium bromide-stained NuSieve gels (Cambrex Bio Science, Rockland, ME). For SEARCH, genotyping was carried out by nuclease assay (Taqman; Applied Biosystems, Foster City, CA). Taqman genotyping reagents were design by Applied Biosystems (http://www.appliedbiosystems.com/) as Assays-by-Design. The sequence for the Assay-by-Design primers and probes are as follows: rs10895068—F-primer, cacgagtttgatgccagagaaaa; R-primer, tgcgacggcaatttagtgaca; G-Allele, CGGCTCCTTTATCTC and A-Allele, CGGCTCTTTTATCTC and rs1042838—F-primer, ttcaataaagtcagagttgtgagagca; R-primer, agggcttggctttcatttgga; C-Allele, ACAGCCAGTGGGCGT and A-Allele, ACAGCCATTGGGCGT. Genotyping was performed using the ABI Prism 7900HT Sequence Detection Systems according to the manufacturer's instructions.

All studies complied with quality control standards by including two or more no DNA template controls per 384-well assay plate and at least 2% of samples in duplicate. A genotyping call rate >95% and at least 98% concordance between duplicated samples for each SNP assay was required. No significant evidence of departure from Hardy–Weinberg equilibrium was observed for subjects from each center using chi-squared test (1 d.f.). There was no difference in minor allele frequency for any SNP across the different studies and thus no evidence for inter-laboratory variability for genotyping.

Statistical analyses

Logistic regression models were used to estimate ORs and 95% CIs. ORs and 95% CIs were adjusted for age (as a continuous variable) and study (as a categorical variable). Additional analyses included adjustment for ethnicity (Caucasian versus other) or BMI (as a continuous variable). The extent of heterogeneity across studies was measured by the likelihood ratio test. All statistical analyses were performed using the Statistical Packages for Social Sciences for Windows, version 17 (SPSS, Chicago, IL), except heterogeneity testing and forest plots that were undertaken using R version 2.10 software (www.r-project.org). The major homozygote genotype or allele was used as the reference for all SNP analyses.

Results

Results for the association of *PGR* polymorphisms with endometrial cancer risk are shown in Table II. In addition to the Australian sample set, genotyping data were available from one or two replication cohorts for each SNP as indicated in Table II. The minimum pooled sample size was 1386 cases and 1640 controls and the maximum was 2888 cases and 4483 controls. We estimated ORs based on all data combined for risk of endometrial cancer overall and also for risk of endometrioid cancer subtype only.

No associations were observed for three of the SNPs investigated (rs1042838, rs10895068 and rs 471767). Adjustment for ethnicity did not alter interpretation of results for any of these SNPs. For example, the per allele OR for rs10895068 was 1.00 (95% CI 0.86–1.16; $P = 0.99$). Similarly, risk estimates were little different after adjustment for BMI: the per allele OR for rs1042838 was 1.03 (95% CI 0.91–1.17; $P = 0.60$). To specifically investigate the previous report of risk associated with rs10895068 within BMI subgroups by De Vivo *et al.* (10), the interaction between genotype and BMI was evaluated for this SNP; however, no significant interaction was found ($P = 0.111$).

The rs11224561 3′ UTR SNP was found to be significantly associated with endometrial cancer risk. There was no evidence of heterogeneity in ORs across the two studies ($P = 0.568$). The effect is in the same direction and of the same magnitude as that previously reported by the original study of Chinese women. Using the GG genotype as reference since this is the most common genotype in our Caucasian sample (and in HapMap), we observed an OR per allele of 1.31 (95% CI 1.12–1.53; $P = 0.001$), whereas the original Chinese study used the common Asian genotype AA as reference and reported a protective effect (OR 0.68; 95% CI 0.50–0.92). Risk estimates differed little with adjustment for ethnicity (OR per allele 1.26; 95% CI 1.08–1.49; $P = 0.005$) or BMI (OR per allele 1.29; 95% CI 1.08–1.53; $P = 0.004$). Excluding non-endometrioid subtypes from the analyses did not appreciably alter the association results observed for any of the investigated SNPs. For example, the per allele OR for rs11224561 became 1.23 (95% CI 1.03–1.47; $P = 0.03$). When stratified by age (<50 or ≥50 years), a commonly used surrogate for menopausal status, no meaningful difference was observed. For example, the per allele OR for rs11224561 became 1.29 (95% CI 1.09–1.53; $P = 0.003$).

Discussion

In this study, we were unable to demonstrate previously reported associations with endometrial cancer risk for two *PGR*

Table II. Estimated ORs and 95% CIs for four PGR polymorphisms and endometrial cancer risk

rs number	Genotype	Pooled adjusted OR (95% CI)[a]	*P*-value	No. of cases	No. of controls	No. of cases	No. of controls	No. of cases	No. of controls
rs1042838				ANECS/AOCS		SASBAC		SEARCH	
V660L				1220	1354	582	1538	1086	1591
	CC	1.00 (ref)		867 (71.1)	933 (68.9)	414 (71.1)	1147 (74.6)	765 (70.4)	1123 (70.6)
	CA	1.00 (0.89–1.12)	0.97	323 (26.5)	383 (28.3)	151 (25.9)	361 (23.5)	294 (27.1)	434 (27.3)
	AA	1.15 (0.83–1.60)	0.40	30 (2.4)	38 (2.8)	17 (2.9)	30 (2.0)	27 (2.5)	34 (2.1)
	Per allele	1.02 (0.93–1.13)	0.68						
rs10895068				ANECS/AOCS		WISE		SEARCH	
331 G>A				1213	1348	455	1701	1089	1593
	GG	1.00 (ref)		1058 (87.2)	1185 (87.9)	412 (90.5)	1567 (92.1)	966 (88.7)	1392 (87.4)
	AG	1.00 (0.85–1.18)	0.97	148 (12.2)	160 (11.9)	41 (9.0)	121 (7.1)	119 (10.9)	192 (12.1)
	AA	1.06 (0.51–2.21)	0.88	7 (0.6)	3 (0.2)	2 (0.4)	13 (0.8)	4 (0.4)	9 (0.6)
	Per allele	1.01 (0.87–1.17)	0.92						
rs11224561				ANECS		LES		—	
3′ UTR tagSNP				1188	997	205	648		
	GG	1.00 (ref)		838 (70.5)	750 (75.2)	145 (70.7)	475 (73.3)		
	AG	1.24 (1.03–1.50)	0.02	311 (26.2)	225 (22.6)	52 (25.4)	162 (25.0)		
	AA	2.10 (1.27–3.48)	0.004	39 (3.3)	22 (2.2)	8 (3.9)	11 (1.7)		
	Per allele	1.31 (1.12–1.53)[b]	0.001						
rs 471767				ANECS		LES		-	
3′ UTR tagSNP				1182	992	204	648		
	TT	1 (ref)		584 (49.4)	487 (49.1)	97 (47.5)	300 (46.3)		
	TC	0.92 (0.78–1.09)	0.32	485 (41.0)	416 (41.9)	82 (40.2)	299 (46.1)		
	CC	1.18 (0.89–1.57)	0.26	113 (9.6)	89 (9.0)	25 (12.3)	49 (7.6)		
	Per allele	1.02 (0.90–1.15)	0.78						

[a]Adjusted for age and study.
[b]This equates to a 0.76-fold risk for the G allele. Risk estimates showed little difference when adjusted additionally for ethnicity (Caucasian versus other) e.g. (per allele OR 1.26; 95% CI 1.08–1.49, $P = 0.005$).

polymorphisms (rs10895068 and rs1042838) reported to have functional effects (10,13). Similar to Dossus *et al.* (11), we were also unable to provide evidence for interaction of rs10895068 with BMI.

We also did not confirm the borderline association with endometrial cancer risk previously reported for tagSNP rs 471767 in a Chinese population (15). We have demonstrated the association of the rs11224561 genotype and endometrial cancer risk, originally reported in the same Chinese study (15). It is important to note that the frequency of the minor allele (A) in our largely Caucasian study, which was 16.4% among our population controls and 12.5% in the HapMap Caucasian population, was the most common allele (66.7%) among HapMap Chinese (available at http://www.hapmap.org accessed February 2010). This result remained statistically significant after adjustment for multiple comparisons using the very rigorous Bonferroni correction method [significance threshold $P = 0.0125$, (0.05/4)] for all SNPs included in this study.

The SNP rs11224561 is located in the 3′ flanking region of the *PGR* gene; thus, it is possible that this polymorphism, or others in high linkage disequilibrium with it, may regulate the translation of the *PGR* gene and therefore increase the anti-proliferative activity of progesterone. Of note, the very recent publication by Lee *et al.* (16) identified another 3′ UTR SNP rs608995 to be associated with a similar level of increased risk (OR per allele 1.20; 95% CI 1.06–1.59). There is currently no publically available information available about the correlation between rs608995 and rs11224561, but the SNPs are located only 767 bp apart.

Based on the ANECS dataset, which had data available for all four SNPs included in this analysis, none of the SNPs in this study were in linkage disequilibrium. The maximum R2 observed was between rs10890568 and rs11224561 ($r^2 = 0.2073$).

This study represents the largest to date investigating the association of *PGR* SNPs and endometrial cancer. Our results do not confirm the previously reported associations for rs10895068, rs1042838 and rs471767. Although we acknowledge that very large studies would be required to exclude the outer limits of the estimates previously reported, we had more than sufficient power to exclude risk estimates previously reported. For example, our pooled sample had >90% power to detect an OR of 1.3 associated with the rare allele of rs10895068, previously reported in the literature to be associated with an OR of 1.90 (10). Likewise, we had 95% power to detect an OR of 0.77 reported for carriers of the rs471767 C allele (15). Our findings do support an association of the 3′ UTR *PGR* gene SNP rs11224561 with endometrial cancer risk, previously demonstrated in Chinese women by Xu *et al.* (15). Given the recent report that yet another 3′ UTR PGR SNP rs608995 is associated with increased risk of endometrial cancer (16), there is incentive to conduct further studies that refine the risk estimate for rs608995, rs11224561 and other SNPs in the relevant linkage disequilibrium block and to identify and prioritize probably causal variants for further functional studies.

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Full membership of the Australian Ovarian Cancer Study Group is listed at http://www.aocstudy.org/.

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