Short Communication

Genetic Variation in the Androgen Receptor Gene and Endometrial Cancer Risk

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Abstract

Genetic variation in the androgen receptor (AR) gene may be associated with endometrial cancer risk based on the role of AR in regulating androgen levels. However, endometrial cancer studies reported inconsistent associations for a CAG repeat polymorphism in exon 1. Only one of these studies measured haplotype-tagging single nucleotide polymorphisms (htSNP) in AR and found statistically nonsignificant, decreased associations with endometrial cancer risk. In a population-based case-control study of 497 cases and 1,024 controls, we examined the CAG repeat polymorphism and six htSNPs (rs962458, rs6152, rs1204038, rs2361634, rs1337080, and rs1337082), which cover an estimated 80% of the known common variation in AR among Caucasian populations. CAG repeat length was not significantly associated with endometrial cancer [odds ratio per unit increase in the average number of repeats, 1.02 (95% confidence interval, 0.97-1.08); P_trend = 0.29]. Minor alleles in three correlated htSNPs (rs6152, rs1204038, and rs1337082; r² >0.6) were associated with increased risk for endometrial cancer. The strongest association was observed for rs6152, with the odds ratios (95% confidence interval) being 1.13 (0.89-1.44) for heterozygous and 2.40 (1.28-4.51) for homozygous minor genotypes (P_trend = 0.02) compared with homozygous major allele genotype. However, these associations were not statistically significant after permutation adjustment for multiple comparisons (P_trend > 0.09). Haplotype analyses did not reveal any additional associations with endometrial cancer. Results from our study, taken together with previously published studies, provide little evidence of a consistent association between common genetic variation in AR and endometrial cancer risk. (Cancer Epidemiol Biomarkers Prev 2009;18(2):585–9)

Introduction

Androgens are hypothesized to play a role in endometrial carcinogenesis. Although their underlying mechanisms are unresolved (1, 2), there is some epidemiologic evidence to support a link between endometrial cancer and androgens (3). For instance, higher serum androgen levels have been reported for women with endometrial cancer (4, 5). Androgens exert their effects by binding to androgen receptors (AR), which have been detected in normal human endometrium and endometrial carcinomas (1). Based on the role of AR in regulating androgen levels, genetic variation in the AR gene may be associated with endometrial cancer risk. AR is located at the Xq11-12, spans about 90 kb, contains 8 exons, and encodes ~920 amino acid proteins. The CAG trinucleotide repeat region at exon 1 (6) has been reported to be inversely related to the level of transactivation of AR (7, 8), which suggests that increased length of the CAG repeat is associated with decreased endometrial cancer risk. However, the putatively functional CAG repeat length polymorphism (9-11), as well as haplotype-tagging single nucleotide polymorphisms (htSNP; ref. 11), have been examined in association with endometrial cancer risk with inconclusive results.

In a population-based case-control study conducted in Poland, we assessed the association between common genetic variation of AR and endometrial cancer risk. We genotyped the CAG repeat length and six htSNPs (rs962458, rs6152, rs1204038, rs2361634, rs1337080, and rs1337082), which cover an estimated 80% of the known common variation in AR.

Materials and Methods

The design and conduct of this study have been described elsewhere (12, 13). Briefly, newly diagnosed invasive endometrial cancer cases were identified through hospitals and local cancer registries in Warsaw...
and Lodz, Poland from 2001 to 2003. Controls without a prior history of endometrial cancer at time of enrollment and with an intact uterus were randomly selected from a database of all residents and frequency-matched to cases by study site and age in 5-y categories. Controls were shared with a breast cancer study and thus did not have a prior history of breast cancer. Similarly, endometrial cancer cases did not have a history of breast cancer. A total of 551 cases (79% of the 695 eligible cases identified) and 1,925 controls (68% of the 2,843 eligible controls identified) provided an in-person interview on known and suspected risk factors. Trained interviewers collected venous blood from 85% of participating cases and 93% of participating controls. For genotyping studies, we selected all cases and age-frequency–matched controls who donated blood to a case/control ratio of ~1:2; thus, the analysis is based on 497 cases and 1,024 controls. The study protocol was reviewed and approved by local Polish and U.S. National Cancer Institute institutional review boards. All participants provided written informed consent.

Genomic DNA was isolated from buffy coats by the Autopure LS DNA Purification System (Genta Systems, Inc.). We genotyped the CAG repeat length polymorphism and htSNPs, markers of common genetic variation of AR. htSNPs were selected based on the efforts of the Breast and Prostate Cohort Consortium (BPC3; ref. 14). CAG repeat length was determined by PCR followed by capillary electrophoresis, and htSNP genotypes by TaqMan assays, as described in Supplementary Laboratory Methods and http://snp500cancer.nci.nih.gov (15). Eighty blinded quality control pairs were inserted throughout the study plates and were found to be >98% concordant for each htSNP. Genotype frequencies among controls were in Hardy-Weinberg equilibrium (P > 0.16).

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression, adjusted for frequency matching variables age (≥5 y) and site (Lodz, Warsaw). For rare SNPs where no cases or controls were observed to carry the minor homozygous genotype, we combined women with the heterozygous and minor homozygous genotypes. P values for interactions were based on most established common susceptibility loci for complex diseases show a trend of increasing risk associated with increasing number of risk alleles. In these models, genotypes were coded as ordinal variables with 0, 1, and 2 values for number of minor alleles. Haploview was used to assess pairwise linkage disequilibrium among the Polish controls. Age- and study site–adjusted global score statistics were used to evaluate the overall and individual differences in haplotype frequencies between cases and controls using HaploStats (version 1.2.1; ref. 16). A permutation adjustment procedure (17) was carried out to correct P values by performing 10,000 permutations to obtain the empirical distribution of P values under the null hypothesis of no association. Permutation-adjusted P values for the trend test of each polymorphism were calculated as the proportion of the P values equal to or smaller than the observed P value.

We examined associations among all endometrial cases as well as among the endometrioid cases compared with other tumor types. Most cases were diagnosed with endometrioid tumors of which endometrioid adenocarcinoma was the most common (13). The histology was identified from the surgical pathology reports, which was confirmed by the study pathologist. The following histologic diagnoses were considered to be endometrioid: endometrioid adenocarcinoma, endometrioid with squamous differentiation, and endometrioid with other features.

We examined potential interactions between polymorphisms and endometrial cancer risk factors. Potential modifiers under study included age at reference (defined as the date of diagnosis for cases and date of interview for controls; ≤59, 60-69, ≥70 y of age categories), body mass index [body mass index = weight (kg)/height (m)^2; ≤25, 25-30, >30 categories], and use of menopausal hormone therapy including unopposed estrogen or estrogen plus progesterin use (ever/never). The log-additive model was assumed for analyses of gene-environment interactions to increase statistical power. For rare SNPs where no cases or controls were observed to carry the minor homozygous genotype, we combined women with the heterozygous and minor homozygous genotypes. P values for interaction were based on

### Table 1. Adjusted ORs (95% CIs) for the association between AR CAG repeats and endometrial cancer risk in a population–based case-control study in Poland

<table>
<thead>
<tr>
<th>Average repeat number</th>
<th>Case (n = 497)</th>
<th>Control (n = 1,024)</th>
<th>OR* (95% CI)</th>
<th>P_trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22</td>
<td>204 (41)</td>
<td>435 (42)</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>22.0-22.9</td>
<td>92 (19)</td>
<td>198 (19)</td>
<td>1.00 (0.74-1.34)</td>
<td></td>
</tr>
<tr>
<td>23.0-23.9</td>
<td>71 (14)</td>
<td>158 (15)</td>
<td>0.96 (0.69-1.33)</td>
<td></td>
</tr>
<tr>
<td>24.0-24.9</td>
<td>66 (13)</td>
<td>115 (11)</td>
<td>1.21 (0.86-1.71)</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>64 (13)</td>
<td>118 (12)</td>
<td>1.16 (0.85-1.64)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

One-unit increase in average repeat number

1.02 (0.97-1.08)

**NOTE:** Numbers of cases and controls genotyped vary due to missing values for genotypes.

*Unconditional logistic regression, adjusted for frequency matching variables age (≥5 y) and site (Lodz, Warsaw).

**Test for trend calculated using a single variable for CAG repeat number (using categories listed in the table).**
likelihood ratio tests comparing models with and without the interaction terms. Analyses were done with STATA (v9.0), unless otherwise stated.

Results

Associations with endometrial cancer risk factors and the reasons for nonparticipation of the cases and controls in the study population have previously been reported (12, 13). In brief, cases and controls had similar distribution of age at reference and majority of cases and controls were postmenopausal; cases, compared with controls, were more likely to ever use menopausal hormones and tended to be heavier.

The CAG repeat length was measured separately on each strand, and the shorter of the two strands was noted as the “short allele” whereas the other strand was considered the “long allele.” CAG repeat length ranged from 12 to 29 repeats among cases (mean ± SD, 20.6 ± 2.2) and 11 to 28 repeats among controls (20.5 ± 2.2) for the short allele and from 17 to 35 repeats among controls (23.9 ± 2.8) and controls (23.8 ± 2.5) for the long allele. Average CAG repeat length was not significantly associated with endometrial cancer [OR (95% CI) per unit increase in average repeat number, 1.02 (0.97-1.08); \( P_{\text{trend}} = 0.29 \) as presented in Table 1. We explored various classifications of the CAG repeats, including categorizations using a different threshold and quartiles of number of repeats (based on the control distribution) for the short and long alleles (Supplementary Table S1). These different ways of CAG repeat examination did not reveal risk associations according to allele length (\( P > 0.5 \)).

Three correlated htSNPs (rs6152, rs1204038, and rs1337082; \( D' > 0.93, r^2 > 0.6 \)) were positively associated with endometrial cancer. For rs6152, the ORs (95% CIs) were 1.13 (0.89-1.44) for the heterozygous genotype and 2.40 (1.28-4.51) for the homozygous minor genotype, compared with homozygous major allele genotype (\( P_{\text{trend}} = 0.02 \); Table 2). The associations between these three htSNPs and endometrial cancer risk, which were based on the log-additive model, were not statistically significant after permutation adjustment for multiple comparisons (\( P_{\text{trend}} > 0.09 \)). OR estimates for combined heterozygous and homozygous minor genotypes versus homozygous major genotype are presented in Supplementary Table S2. Associations between individual htSNP and risk were similar for endometrioid tumors (\( n = 416 \)) as for other tumor types (\( n = 81 \)) in case-only analyses (\( P \) for tumor heterogeneity >0.10). There was limited correlation between CAG repeats and htSNPs (Spearman correlation values ranged from −0.17 to 0.09).

In our study population, we identified a single linkage disequilibrium block with tight linkage (\( D' > 0.9 \) for all but one pairwise combination) among the htSNPs. Only 5 of 16 possible haplotypes in the block were common (>1%) among controls. Haplotype frequencies were marginally different between cases and controls (global \( P = 0.055 \); Table 3). A common haplotype (AAAAAG; 8%

### Table 2. Adjusted ORs (95% CIs) for the association between AR htSNPs and endometrial cancer risk in a population–based case-control study in Poland

<table>
<thead>
<tr>
<th>rs no</th>
<th>Genotype</th>
<th>MAF*</th>
<th>Case (( n = 497 ))</th>
<th>Control (( n = 1,024 ))</th>
<th>OR (^{2} ) (95% CI)</th>
<th>( P_{\text{trend}} ) (^{1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs962458</td>
<td>AA</td>
<td><strong>G = 0.07</strong></td>
<td>427 (86)</td>
<td>883 (86)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>19024C&gt;G</td>
<td>AG</td>
<td>68 (14)</td>
<td>134 (13)</td>
<td>1.06 (0.78-1.46)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>0.99 (0.73-1.34)</td>
<td>0.94 (1.00)</td>
<td></td>
</tr>
<tr>
<td>rs6152</td>
<td>GG</td>
<td><strong>A = 0.16</strong></td>
<td>328 (66)</td>
<td>718 (70)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>Ex1-978G&gt;A</td>
<td>AG</td>
<td>146 (29)</td>
<td>285 (28)</td>
<td>1.13 (0.89-1.44)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>21 (4)</td>
<td>20 (2)</td>
<td>2.40 (1.28-4.51)</td>
<td>0.02 (0.09)</td>
<td></td>
</tr>
<tr>
<td>rs1204038</td>
<td>GG</td>
<td><strong>A = 0.16</strong></td>
<td>326 (66)</td>
<td>717 (70)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>IVS1-458G&gt;A</td>
<td>AG</td>
<td>147 (30)</td>
<td>286 (28)</td>
<td>1.14 (0.90-1.45)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>21 (4)</td>
<td>20 (2)</td>
<td>2.41 (1.28-4.53)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>rs2361634</td>
<td>GG</td>
<td><strong>A = 0.07</strong></td>
<td>434 (88)</td>
<td>885 (87)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>IVS2-255A&gt;G</td>
<td>AG</td>
<td>59 (12)</td>
<td>132 (13)</td>
<td>0.90 (0.65-1.29)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>2 (0)</td>
<td>6 (1)</td>
<td>0.69 (0.14-3.47)</td>
<td>0.46 (0.93)</td>
<td></td>
</tr>
<tr>
<td>rs1337080</td>
<td>GG</td>
<td><strong>A = 0.07</strong></td>
<td>426 (86)</td>
<td>882 (86)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>IVS3+15670G&gt;A</td>
<td>AG</td>
<td>69 (14)</td>
<td>136 (13)</td>
<td>1.06 (0.78-1.46)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>0.99 (0.73-1.34)</td>
<td>0.95 (1.00)</td>
<td></td>
</tr>
<tr>
<td>rs1337082</td>
<td>AA</td>
<td><strong>G = 0.21</strong></td>
<td>284 (58)</td>
<td>644 (63)</td>
<td>1.00 (Reference)</td>
<td>NE</td>
</tr>
<tr>
<td>40331 bp 3' of STP</td>
<td>AG</td>
<td>182 (37)</td>
<td>336 (33)</td>
<td>1.24 (0.99-1.56)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>27 (5)</td>
<td>42 (4)</td>
<td>1.49 (0.90-2.47)</td>
<td>NE</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Numbers of cases and controls genotyped for each htSNP varies due to missing values for genotypes.

*Minor allele frequency among controls.

1Unconditional logistic regression, adjusted for frequency matching variables age (±5 y) and site (Lodz, Warsaw).

\(^{2}\)Test for trend per allele calculated using a single variable for the number of minor alleles present (permutation-adjusted \( P \) values for trend test, adjusting for SNPs and CAG average repeat number).

\(^{1}\)\( D' \geq 0.93 \) and \( r^2 \geq 0.6 \).
among controls), marked by the three correlated htSNPs, was associated with increased risk of endometrial cancer (OR, 1.51; 95% CI, 1.17-1.96); however, another haplotype containing the three correlated htSNPs (GAAAGG; 7% among controls) was not associated with endometrial cancer risk (OR, 1.00; 95% CI, 0.74-1.37) compared with the most common haplotype (AAGGAA; 68% among controls). Adjustment for the repeat polymorphism did not substantially change the associations between AR haplotypes and endometrial cancer (data not shown). We also examined two alternative haplotype block definitions [two blocks: all SNPs, except for rs1337082, in block 1; rs1337082 in block 2 (14); three blocks: rs962458 and rs6152 in block 1; rs1204038, rs2361634, and rs1337080 in block 2; rs1337082 in block 3 (11)] to facilitate comparison of our results with those of previous studies and did not find any additional associations from those discussed above.

We combined heterozygous and homozygous minor genotypes and compared them to homozygous major genotypes to examine interactions with a few established endometrial cancer risk factors. We did not observe statistically significant modification of associations between htSNPs and endometrial cancer by age, body mass index, or use of menopausal hormone therapy (Supplementary Table S3).

**Discussion**

Based on observations that lower transactivation of AR is related to increasing CAG repeat length (7, 8), we hypothesized that longer length would be associated with lower endometrial cancer risk; however, no statistically significant decreased associations were found in our data from 497 cases and 1,024 population-based controls. Initial reports based on small (n = 58 and 79 cases) studies among Ashkenazi (9) and Japanese (10) women suggested an increased risk with longer CAG repeat length. However, a report from McGrath et al. (11) using data from two nested case-control studies (n = 137 and 222 cases) of U.S. Caucasian women and our results do not support these findings. The study among Ashkenazi women (9) reported that the longer CAG allele ranged from 11 to 33 repeats (mean ± SD, 19.8 ± 2.7) among cases and 10 to 22 repeats (17.9 ± 1.9) among controls. This mean repeat length of the longer allele from this populations differs from Caucasian women in our study and another U.S. study (11), which supports previous observations that CAG repeat length may vary by ethnicity (18, 19). The genetic ancestry of the study populations may contribute to inconsistencies between studies.

Our data suggested that variant alleles of three correlated htSNPs (rs6152, rs1204038, and rs1337082) might be associated with endometrial cancer risk. Specifically, the minor alleles for rs6152 and rs1204038 (less so for rs1337082) were positively associated with endometrial cancer. However, McGrath et al. reported that haplotypes marked by minor alleles of rs6152, rs1204038, and rs1337082 were not associated with endometrial cancer (OR, 0.93; 95% CI, 0.67-1.30). For rs6152, compared with homozygous major allele genotype, the OR (95% CI) was 0.73 (0.29-1.63) for homozygous minor genotypes in the pooled data from McGrath et al. Estimated minor allele frequencies for the htSNPs among controls were nearly identical for both studies [for pooled data from McGrath et al. (11)] to those among our study population. Differences in the linkage structure of the study populations are unlikely to explain the differences because both studies are among Caucasian women and same linkage disequilibrium blocks were observed for measured markers.

As noted by Tran et al. (20), genotyping of variable number repeat polymorphisms, such as the CAG repeat polymorphism in AR, may have led to misclassification of the number of trinucleotides, particularly for the longer allele. However, we verified the fragment sizes by sequencing and genotyping the exact number of repeats for the SNPs Cancer 102 samples. X chromosome inactivation, which occurs early in female embryos, may distort results for genetic variation in AR, as noted by Cox et al. (14). Examination of somatic DNA would need to be analyzed to determine the inactivated allele, which is beyond the scope of this report.

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*Table 3. Adjusted ORs (95% CIs) for the association between AR haplotypes and endometrial cancer risk in a population based case-control study in Poland*

<table>
<thead>
<tr>
<th>Haplotype*</th>
<th>Percentage of cases (n = 497)</th>
<th>Percentage of controls (n = 1,024)</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>G</td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Rare haplotypes1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global P‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Percentage of cases (n = 497)</th>
<th>Percentage of controls (n = 1,024)</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Loci of AR htSNPs are written 5′ to 3′.

1Unconditional logistic regression, adjusted for frequency matching variables age (±5 y) and site (Lodz, Warsaw).

1One haplotype block structure based on Polish endometrial cancer study population. All htSNPs were included. The nucleotide in bold indicates the minor allele and the normal script indicates the major allele.

1Haplotypes with frequencies < 0.01 categorized into a group of rare haplotypes.

2†Global test for entire set of haplotypes matched on age (±5 y) and site (Lodz, Warsaw).

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M. McGrath, personal communication, September 2008.
Our study has some of the highest participation rates attained in molecular epidemiologic studies with the collection of DNA (21). Selection bias is unlikely because carrier status is probably not associated with reasons for nonparticipation. In addition, the frequencies of alleles (Table 1), as well as the ORs of most of the well-defined endometrial cancer risk factors (12), were consistent with previous studies of women of European descent. Cases and controls were collected from the two largest cities in Poland, a genetically homogenous population, which minimizes concerns of population stratification.

In conclusion, we observed weak evidence of an association between common genetic variations, marked by rs6152, rs1204038, or rs1337082, and increased endometrial cancer risk that was not statistically significant after adjustment for multiple comparisons. No association was found with length of the CAG repeat polymorphism in this study population. Based on the weak evidence from our study as well as the inconsistent results between this and previous studies, we are circumspect that common genetic variation in AR is related to endometrial cancer risk.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
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References
20. Tran N, Bharaj BS, Diamandis EP, Smith M, Li BD, Yu H. Short tandem repeat polymorphism and cancer risk: Influence of labora-
Genetic Variation in the Androgen Receptor Gene and Endometrial Cancer Risk

Hannah P. Yang, Montserrat Garcia-Closas, James V. Lacey, Jr., et al.


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