Short Communication

Androgen Receptor and Prostate-Specific Antigen Gene Polymorphisms and Breast Cancer in African-American Women

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Abstract

Several previous studies have found the CAG repeat polymorphism in exon 1 of the androgen receptor (*AR*) gene to be associated with breast cancer risk among some groups of Caucasian and Asian women. In a population-based case-control study of 488 African-American women (239 cases and 249 controls), we examined this polymorphism along with a polymorphism (−158 G/A) in an androgen-regulated gene (*PSA*) whose expression has been correlated with breast cancer prognosis. Overall, we did not observe any significant association between the CAG repeat polymorphism and breast cancer risk. However, among women with a first-degree family history of breast cancer, longer CAG repeats were associated with a significantly increased risk. Women carrying at least one longer allele [(CAG)$n \geq 22$] had a 3-fold increased risk compared to those with two shorter alleles (odds ratio, 3.18; 95% confidence interval, 1.08-9.36). There was no significant association between the *PSA* gene polymorphism and breast cancer risk, nor was there significant gene-gene interaction. In summary, our results further support that shorter CAG repeats (stronger AR transactivation activity) may reduce the risk of breast cancer, at least among some groups of women. Our data, however, are unable to provide evidence that PSA is the pathway through which the protective effect of androgens operates. (Cancer Epidemiol Biomarkers Prev 2005;14(12):2990–4)

Introduction

The role of androgens in the etiology of breast cancer remains unclear. The tumor growth–inhibitory effects of testosterone and dihydrotestosterone have been observed in breast cancer cell lines and in animal models (1), whereas higher circulating androgen levels have been noted in breast cancer patients compared with controls (2, 3). Androgen and estrogen levels are highly correlated. Therefore, a positive association between androgen levels and breast cancer risk may reflect the effects of high concomitant estrogen levels and activities. Adjustment for circulating estrogen has attenuated the association with testosterone levels in some prospective studies (4-7), but not in others (8-10). However, because substantial conversion of androgens to estrogens occurs in breast adipose tissue (11), adjustment for circulating estrogen may not adequately adjust for local estrogen levels in the breast.

An alternative approach is to examine androgen receptor (*AR*) gene variants that alter the receptor function. A CAG repeat polymorphism in exon 1 encodes a variable-length polyglutamine tract in the transactivation domain of the protein. Long polyglutamine tract length reduces AR transactivation activity *in vitro* (12-14). Some (15-19), but not all (20-24) epidemiologic studies found longer CAG repeats associated with increased breast cancer risk.

The interaction with downstream genes in the androgen signaling pathway, such as the *PSA* gene (also named *KLK3*), may also be important. Prostate-specific antigen (PSA) protein, encoded by the *PSA* gene, is present in breast tissue (25), and may be a useful prognostic marker in breast cancer (26, 27). A guanine to adenine substitution (−158 G/A) in an androgen-responsive element I (ARE-I) of the *PSA* gene promoter has been associated with PSA levels in serum or in breast tissue in some (28-30), but not all studies (31, 32), and has also been associated with prognosis (30).

We examined the *AR* CAG length polymorphism and the single nucleotide polymorphism in the ARE-I of the *PSA* gene in relation to breast cancer risk in African-American women, a population with a notably shorter mean CAG repeat length and a wider CAG repeat length distribution compared with Whites and Asians (33).

Materials and Methods

Study Population. Study subjects were participants in a population-based case-control study conducted in the San Francisco Bay area (34). In brief, cases aged 35 to 79 years and newly diagnosed with invasive breast cancer between 1997 and 1999 were identified through the regional cancer registry. Controls were identified through random digit dialing (81% response to household enumeration). Two hundred and forty-nine cases and 255 controls completed a telephone screening interview (84% of cases and 86% of controls), and an in-person interview (87% of cases and 82% of controls), and provided a blood or mouthwash sample (85% of cases and 84% of controls). DNA was available for 246 cases and 255 controls. The study was approved by the Institutional Review Boards of both the University of Southern California and the Northern California Cancer Center.

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Laboratory Methods. The *AR* exon 1 CAG repeat variant was genotyped by simple sequence length polymorphism analysis. The genomic region containing the CAG repeat was PCR-amplified using the forward primer 5′-CGCGAAGT-GATCCAGAAC-3′ and the reverse primer 5′-CAGGAC-CAGGTAGCCTGTG-3′ (FAM-labeled; Applied Biosystems, Foster City, CA). Touchdown thermal cycling was performed. The resulting PCR product was run on the ABI 3700 capillary sequencer and allele sizes were scored using GeneScan software (version 3.5; Applied Biosystems). DNA samples from 12 male subjects with various CAG repeat lengths (determined from direct sequencing) were included in each run as controls. A standard curve was drawn based on these 12 control samples and was used to calculate CAG repeat number for study subjects.

Genotyping of the single nucleotide polymorphism in the *PSA* gene was performed by the TaqMan assay (Applied Biosystems). The two labeled oligonucleotide probes were 5′-FAM-CAGAACAGCAAGTACTAGCTCTCCCTC-3′ and 5′-CY3-AGAACAGCAAGTGCTAGCTCTCCC-3′. In both probes, the thymidines were replaced with Propyne-dU to increase the T_m of the probe ~1°C for every addition (Biosearch Technologies, Inc., Novato, CA). The forward primer was 5′-GGTGCATCCAGGGTGATCTAG-3′ and the reverse primer was 5′-CACACCCAGAGCTGTGGAAG-3′. Nine previously sequenced DNA samples (three of each genotype) were included as genotyping controls. Ambiguous genotyping results were confirmed by sequencing. Concordance for duplicates (5% random sample of all blood specimens) was 100%.

Statistical Analysis. We refer to the two *AR* CAG alleles carried by each woman as the smaller allele (the shorter of the two) and the larger allele (the longer of the two). SAS PROC

Table 1. Characteristics of African-American study participants, by case-control status

	Cases (n = 239)*	Controls (n = 249)*	P
Age			
Mean (SD)	55.6 (11.5)	55.3 (11.6)	0.79
Median (interquartile range)	54 (47-64)	54 (46-65)	0.78
Menopausal status			
Premenopausal	72 (30.1%)	82 (32.9%)	
Postmenopausal	146 (61.1%)	146 (58.6%)	0.80
Undetermined	21 (8.8%)	21 (8.4%)	
Education (y)			
<12	42 (17.6%)	46 (18.5%)	
12	53 (22.2%)	64 (25.7%)	
13-16	94 (39.3%)	101 (40.6%)	
≥17	50 (20.9%)	38 (15.3%)	0.41
First-degree family history			
Yes	35 (14.6%)	32 (12.8%)	
No	204 (85.4%)	217 (87.2%)	0.57
Benign breast disease			
Yes	61 (25.5%)	38 (15.4%)	
No	178 (74.5%)	209 (84.6%)	0.006
Age at menarche			
<12	52 (21.9%)	55 (22.4%)	
12-13	133 (55.9%)	130 (52.9%)	
≥14	53 (22.3%)	61 (24.8%)	0.76
Age at menopause			
Mean (SD)	46.4 (7.02)	46.4 (8.08)	0.97
Median (interquartile range)	48 (44-51)	48 (43-51)	0.78
Number of full-term pregnancies			
Nulliparous	44 (18.4%)	34 (13.7%)	
1	42 (17.6%)	47 (18.9%)	
2	54 (22.6%)	55 (22.1%)	
3	43 (18.0%)	48 (19.3%)	
≥4	56 (23.4%)	65 (26.1%)	0.68
Age at first full-term pregnancy			
<20	83 (42.6%)	93 (43.3%)	
20-24	59 (30.3%)	79 (36.7%)	
25-29	27 (13.9%)	27 (12.6%)	
≥30	26 (13.3%)	16 (7.4%)	0.18
History of oral contraceptive use			
Yes	160 (67.5%)	163 (66.0%)	
No	77 (32.5%)	84 (34.0%)	0.72
History of hormone replacement therapy use (postmenopausal women)			
Yes	70 (48.0%)	83 (58.0%)	
No	76 (52.0%)	60 (42.0%)	0.09
Body mass index in premenopausal women			
Mean (SD)	30.1 (6.21)	32.4 (8.20)	0.05
Median (interquartile range)	29.3 (25.0-34.5)	30.5 (25.5-39.9)	0.11
<25	18 (25.0%)	16 (19.5%)	
25-29	20 (27.8%)	23 (28.1%)	
≥30	34 (47.2%)	43 (52.4%)	0.69
Body mass index in postmenopausal women			
Mean (SD)	31.2 (6.34)	31.5 (7.17)	0.71
Median (interquartile range)	30.5 (26.6-35.2)	30.8 (26.5-34.6)	0.97
<25	24 (16.6%)	26 (17.8%)	
25-29	44 (30.3%)	40 (27.4%)	
≥30	77 (53.1%)	80 (54.8%)	0.85

*The numbers in the table do not add up due to missing values.

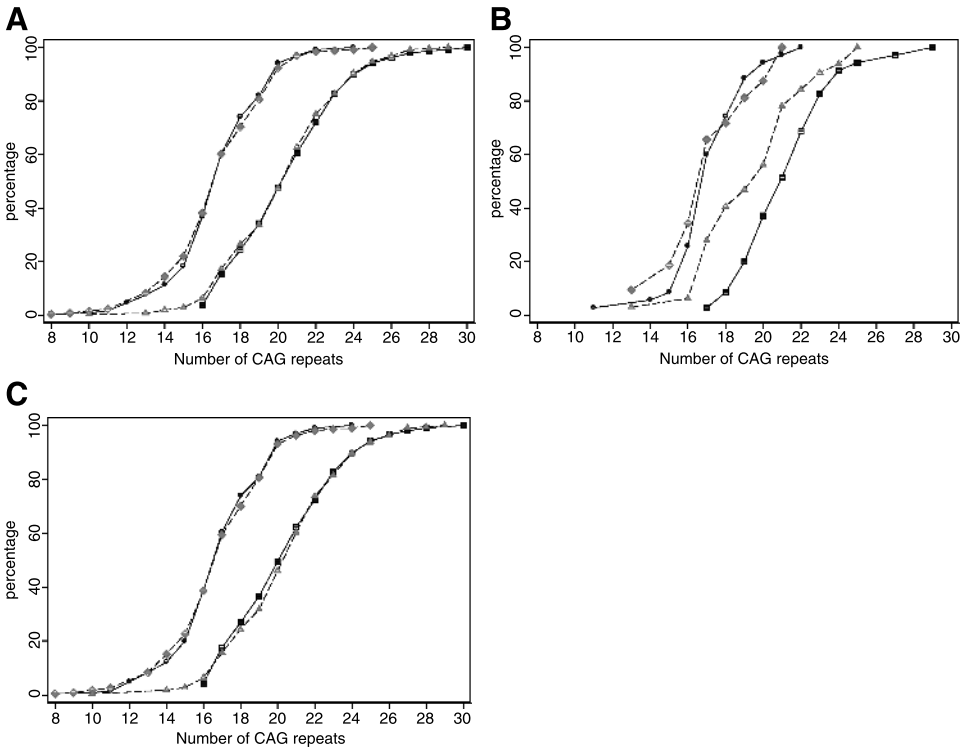

Figure 1. The cumulative distribution curves of the CAG repeat lengths for the smaller and the larger allele of the two alleles carried by each woman. **A,** in all cases (n = 239) and controls (n = 249); *, P = 0.94 (smaller allele), P = 0.64 (larger allele). **B,** in cases (n = 35) and controls (n = 32) with a first-degree family history of breast cancer; P = 0.62 (smaller allele) and P = 0.008 (larger allele). **C,** in cases (n = 204) and controls (n = 217) without a first-degree family history of breast cancer; P = 0.93 (smaller allele), P = 0.62 (larger allele); *, P values are for Wilcoxon tests. ——◆——, case_smaller; ——■——, case_larger; – – ◆ – –, control_smaller; – – ▲ – –, control_larger.

ALLELE was used to assess Hardy-Weinberg equilibrium of the CAG length distribution among controls (SAS Institute, Inc., Cary, NC). Wilcoxon rank sum test was used to compare the distributions of the repeat lengths (for the smaller and the larger allele separately). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the effect of *AR* CAG repeat length on breast cancer risk. CAG repeat lengths were dichotomized into short and long using a cutoff point (CAG = 22) commonly used in previous publications (17, 18, 20). Other cutoff points, including the median, were also examined. Women with one or two alleles ≥22 were combined given the few women with two alleles ≥22. For the *PSA* gene, ORs and 95% CIs were estimated by comparing genotypes A/A and G/A to G/G. A test of trend was performed by including in the logistic model a variable coded as 0, 1, or 2 for the number of ''at-risk'' alleles.

All models were adjusted for age (continuous). Adjustment for other known breast cancer risk factors (see Table 1) did not, either individually or jointly, change the OR estimates by >10%. We considered menopausal status (defined as in ref. 17), hormone replacement therapy use, and first-degree family history of breast cancer as potential effect modifiers. Formal tests of effect modification were performed by including the appropriate interaction terms in the logistic model. To assess possible interactions between the *AR* and *PSA* genes, ORs were estimated for each *AR/PSA* genotype combination.

Power for detecting a shift of two CAG repeats between the distributions of CAG repeat lengths in cases and controls with a positive family history was estimated by bootstrap (35). With each bootstrap sample comprising 67 observations (32 cases and 35 controls), 1,000 samples were drawn with replacement from the empirical distribution of controls in our data set, with two CAG repeats being added to the sampled value for each case. Wilcoxon rank-sum tests were performed on each sample and the percentage of significant results were calculated.

Results

Genotyping results were missing for 13 subjects (seven cases and six controls) due to PCR failure (Table 1). The CAG repeat lengths ranged from 8 to 30 (median = 19) and the distribution in controls did not show significant departure from Hardy-Weinberg equilibrium (P = 0.14). Overall, the distributions of the CAG repeat lengths in cases and controls were almost identical (P = 0.94 for the smaller allele; P = 0.64 for the larger allele; Fig. 1A). Compared with women having no allele with (CAG)n ≥22 (corresponding to the SS genotype in the literature), women who carried one or two alleles with (CAG)n ≥22 (SL and LL genotypes, respectively) had an OR of 1.09 (95% CI, 0.75-1.57; Table 2). Similar results were obtained when other cutoff points were used. Mean age at diagnosis of cases did not differ by their CAG repeat genotypes (data not shown). The association between CAG repeat genotypes and breast cancer risk did not differ significantly by menopausal status (Table 2), and, among postmenopausal women, did not differ significantly by hormone replacement therapy use (P for interaction = 0.48, data not shown).

Cases and controls without a first-degree family history of breast cancer had nearly identical distributions (for both the smaller and the larger alleles), whereas among subjects with a family history, the distribution of the larger allele was noticeably shifted to the right among cases compared with controls (P = 0.008; Fig. 1B and C). Among women with a family history, having one or two alleles with 22 or more CAG repeats was associated with a significantly increased risk (OR, 3.18; 95% CI, 1.08-9.36), whereas no association was observed among women without a family history (OR, 0.92; 95% CI, 0.62-1.37; P for interaction, 0.03; Table 2). Similar results were obtained when other cutoff points were used (data not shown).

The distribution of the *PSA* −158 A/G genotype frequencies did not show significant departure from Hardy-Weinberg equilibrium among controls (P = 0.29). There was no significant association between breast cancer risk and *PSA* genotype overall. Nor was there any significant interaction with menopausal status (P = 0.10), or family history (P = 0.82; Table 2).

There was no evidence for a significant gene-gene interaction when the effects of *PSA* genotype were estimated within strata defined by the *AR* genotypes (OR, 1.08; 95% CI, 0.64-1.83 for AG versus AA and OR, 0.80; 95% CI, 0.42-1.54 for GG versus AA among women with SS genotype and OR, 0.85; 95%

CI, 0.42-1.72 for AG versus AA and OR, 1.64; 95% CI, 0.66-4.09 for GG versus AA among women with SL or LL genotypes (P for interaction = 0.15; data not shown). We were not able to test for interaction between the *AR* and the *PSA* genotypes among women with a positive family history due to small sample size.

Discussion

Among African-American women with a first-degree family history of breast cancer, a significant increase in breast cancer risk was associated with carrying one or two *AR* CAG long alleles. Our results agree with the Nurses' Health Study that reported a reduced risk with shorter CAG repeats only among women with a positive family history of breast cancer (17), and with a study by Rebbeck et al. in *BRCA1* mutation carriers that found a significant risk reduction associated with shorter CAG repeats (15). A statistical interaction between *AR* genotype and *BRCA1* mutation status is strongly supported by *in vitro* studies suggesting that BRCA1 protein is an *AR* coactivator (36, 37). We had no information available on *BRCA1* mutation status to investigate this interaction. However, the number of *BRCA1* mutation carriers is likely to be small (38). It is possible that the interaction between family history and *AR* CAG genotype observed in our study and in the Nurses' Health Study is due, at least in part, to variant(s) in other gene(s) or to some other familial risk factor(s).

Three other studies (22-24), however, did not confirm the finding by Rebbeck et al. (15), possibly due to small sample size. Our family history–positive stratum was also small. But by examining the entire distribution curve rather than relying solely on cutpoints, we had reasonable power (74%) to detect a shift of two CAG repeats between cases and controls with a family history. Nevertheless, confirmation by studies with larger numbers of *BRCA1* mutation carriers and/or family history–positive subjects is needed.

Unlike previous studies, we explored the possible mechanism of the androgen effect by examining a genetic variation in the *PSA* gene, an *AR* downstream gene, together with the *AR* CAG polymorphism. Some (28, 29) but not all (31, 32) studies have suggested that a polymorphism in the ARE-I of the *PSA* gene (−158 G/A) may contribute to interindividual variations in serum PSA levels in men. The only study in females found the A allele to be associated with lower PSA concentration in breast tumor tissue (30). Cases with the AA genotype (lower PSA) also had worse survival than cases with GG or GA genotypes (30).

We found no association with this *PSA* polymorphism, possibly because it is not functional. In an *in vitro* study, the two alleles showed no differences in *PSA* gene promoter activity (32). We speculate that the association of the ARE-I polymorphism with serum PSA found in some studies may be a result of its linkage disequilibrium with other functional polymorphisms in the *PSA* gene. Several polymorphisms in the 5′ enhancer region of the *PSA* gene have recently been

Table 2. The association between the *AR* CAG and *PSA* ARE-I −158 G/A polymorphisms and breast cancer in African-American women

	CAG length (S <22; L ≥22)	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)
All women	SS	145 (60.7)	156 (62.7)	1.0
	SL or LL	94 (39.3)	93 (37.3)	1.09 (0.75-1.57)
Menopausal status				
Premenopausal	SS	43 (59.7)	51 (62.2)	1.0
	SL or LL	29 (40.3)	31 (37.8)	1.11 (0.58-2.12)
Postmenopausal	SS	90 (61.6)	90 (61.6)	1.0
	SL or LL	56 (38.4)	56 (38.4)	1.01 (0.63-1.61)
				P for interaction = 0.82
First-degree family history				
Yes	SS	18 (51.4)	25 (78.1)	1.0
	SL or LL	17 (48.6)	7 (21.9)	3.18 (1.08-9.36)
No	SS	127 (62.3)	131 (60.4)	1.0
	SL or LL	77 (37.7)	86 (39.6)	0.92 (0.62-1.37)
				P for interaction = 0.03
	ARE-I genotypes	**Cases *n* (%)**	**Controls *n* (%)**	**OR (95% CI)**
All women	AA	65 (27.2)	68 (27.3)	1.0
	AG	125 (52.3)	132 (53.0)	0.98 (0.65-1.50)
	GG	49 (20.5)	49 (19.7)	1.04 (0.62-1.76)
				P for trend = 0.90
Menopausal status				
Premenopausal	AA	26 (36.1)	28 (34.1)	1.0
	AG	31 (43.1)	44 (53.7)	0.75 (0.37-1.52)
	GG	15 (20.8)	10 (12.2)	1.81 (0.68-4.84)
				P for trend = 0.46
Postmenopausal	AA	32 (21.9)	37 (25.3)	1.0
	AG	86 (58.9)	74 (50.7)	1.33 (0.76-2.35)
	GG	28 (19.2)	35 (24.0)	0.92 (0.47-1.84)
				P for trend = 0.86
				P for interaction = 0.10
First-degree family history				
Yes	AA	10 (28.6)	8 (25.0)	1.0
	AG	18 (51.4)	19 (59.4)	0.80 (0.25-2.51)
	GG	7 (20.0)	5 (15.6)	1.05 (0.24-4.68)
				P for trend = 0.99
No	AA	55 (27.0)	60 (27.6)	1.0
	AG	107 (52.5)	113 (52.1)	1.04 (0.66-1.63)
	GG	42 (20.6)	44 (20.3)	1.05 (0.60-1.84)
				P for trend = 0.86
				P for interaction = 0.82

associated with serum PSA levels (39). Three of them were also found to be functional in reporter gene assays (39). However, the region containing these polymorphisms did not seem to be critical in stimulating *PSA* gene transcription in breast cancer cells (40), suggesting that this enhancer region might be tissue-specific.

Our finding adds to the literature suggesting that androgen protects against breast cancer in some groups of women. Although we could not rule out the involvement of the PSA pathway in family history–positive women (as we could not examine any possible gene-gene interaction between *AR* and *PSA* in this small subgroup), we were unable to provide any evidence that PSA is the pathway through which the protective effect of androgen operates. Other androgen target genes need to be investigated. We realize that our study has small sample size, especially when examining interactions. Our results (both positive and negative) need to be taken with caution.

This is the first study to examine the *AR* CAG polymorphism in African-American women.

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