Androgen Receptor Polymorphisms and the Incidence of Prostate Cancer[1]

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Abstract

The human *androgen receptor* gene contains polymorphic CAG and GGC repeats in exon 1. We investigated whether the number of CAG and/or GGC repeats is related to prostate cancer risk in a case-control study nested within the β Carotene and Retinol Efficacy Trial. Among 300 cases and 300 controls, we did not observe any increase in risk associated with fewer CAG or GGC repeats. We observed a nonsignificant decrease in risk associated with each unit of decrease in CAG length [odds ratio (OR), 0.98; 95% confidence interval (CI), 0.93–1.03). Men with CAG <22 had a relative risk of prostate cancer of 0.89 (95% CI, 0.65–1.23) compared with men with CAG ≥22. There was no appreciable difference in the mean number of GGC repeats between cases and controls; the estimated change in the risk of prostate cancer associated with one fewer GGC repeat was 0.97 (95% CI, 0.88–1.06). The risk in men at or below the mean number of GGC repeats (17) was 0.80 (95% CI, 0.57–1.12). In contrast to prior reports, men with both short CAG (<22) and short GGC (≤17) repeats were not at increased risk of prostate cancer (OR, 0.56; 95% CI, 0.32–0.98), compared with men with ≥22 CAG repeats and >17 GGC repeats. Our results do not support the hypothesis that a small number of CAG or GGC repeats in the *androgen receptor* gene increases a man's risk of prostate cancer.

Introduction

The growth and development of the human prostate gland, together with the maintenance of its physiological integrity, are dependent on the presence of circulating androgens and intact intracellular steroid signaling pathways (1). Androgens are generally required for prostate cancer development (2); administration of high doses of testosterone has induced prostate cancer in rodents (3, 4), and prostate cancer rarely occurs in castrated men. Prostate cancers often regress after androgen withdrawal (5–8).

The *AR*[3] gene is located on the X chromosome and spans more than 90 kb of genomic DNA (9). The AR protein has three major domains: an androgen-binding domain, a DNA-binding domain, and the NH_2-terminal domain (modulatory domain; Refs. 10, 11). Androgens, particularly dihydrotestosterone, bind to the AR with high affinity and stimulate the transcription of a cascade of androgen-responsive genes. The transactivation activity of the receptor resides in the NH_2-terminal domain of the protein, which is encoded in exon 1 and contains the polymorphic CAG and GGN repeats (12, 13). The CAG and GGC repeats encode for a polyglutamine tract and a polyglycine tract, respectively. In addition to stimulating expression of genes associated with the differentiated phenotype of the prostate, such as prostate-specific antigen (14), it has been reported that AR may regulate genes involved in cell-cycle control, *e.g.*, *CDK2*, *CDK4*, and *p16* (15). Extended polyglutamine tract interacts with caspase-8 and caspase-10 in nuclear aggregates (16). Antisense oligonucleotides targeting CAG repeats were found to be effective in inhibiting the growth of LNCaP prostate cancer cells (17). Longer CAG repeats of *AR* are associated with reduced transcriptional activities, even in the normal range of CAG repeats (18, 19). Increasing polyglutamine length negatively affects p160-mediated coactivation of the *AR* (20), and elimination of CAG repeats in *in vitro* systems in both human and rat *AR* results in a marked elevation of transcriptional activity (18), which suggests that the presence of this repeat is inhibitory to transactivation. The presence of more than 40 CAG repeats is related to a rare neuromuscular disorder, spinal and bulbar muscular atrophy (Kennedy syndrome), which is also associated with androgen insensitivity, decreased virilization, testicular atrophy, reduced sperm production, and infertility (21). These data raise the hypothesis that shorter CAG repeats of the *AR* gene are associated with increased risk of prostate cancer.

There have been several epidemiological studies that have examined the association of CAG repeat lengths with prostate cancer risk. One found that the mean number of CAG repeats was smallest in African Americans, intermediate in Caucasians, and largest in Asians, who, respectively, have a high, intermediate, and low incidence of prostate cancer (22). Some case-control studies have observed an increase in prostate cancer risk

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[3] The abbreviations used are: AR, androgen receptor; OR, odds ratio; CI, confidence interval; CARET, β-Carotene and Retinol Efficacy Trial.

associated with short CAG alleles (22–27), although other studies did not find such an association (28–33).

The effect of the variation in the length of the GGN tract on AR activity is unclear. The GGN repeats are composed of a consensus sequence of 3 GGT, 1 GGG, 2 GGT, and a variable length of GGC repeats (34). Results from different studies of transient transfection of reporter constructs have shown that deletion of the GGN tract resulted in either no alteration or increased or decreased *AR* transcriptional activities (35, 36), whereas extension of the GGC repeats from 20 to 48 led to an inhibition (35). Epidemiological investigations of the association between the number of GGC repeats and prostate cancer risk have produced inconsistent results (22, 24, 26, 31, 34).

In the present study, we analyzed the risk of prostate cancer associated with CAG and/or GGC repeats of *AR* in a case-control study nested within the CARET study.

Materials and Methods

Study Population. The source population for this study was comprised of male participants in the CARET, a double-blind, randomized placebo-controlled trial of β-carotene (30 mg/day) and retinol palmitate (25,000 IU/day) among two populations of individuals at high risk of lung cancer: asbestos-exposed workers and heavy smokers (37). Individuals eligible for the asbestos-exposed population were men, ages 45–69, who were current or former smokers with either occupational exposure to asbestos at least 15 years before randomization or a chest X-ray positive for asbestos-related lung disease. Eligible for the heavy-smoker population were men and women 50–69 years of age who were current or recent (quit less than 6 years) cigarette smokers with at least 20 pack-years of cigarette smoking. A total of 18,314 participants were enrolled in the CARET study at six study centers (Fred Hutchinson Cancer Research Center, Seattle, WA, Univ. of California, San Francisco, CA, Univ. of California, Irvine, CA, Univ. of Maryland, Baltimore, MD, Yale University, New Haven, CT, Kaiser Permanente, Portland, OR) from 1985 to 1994 and were followed routinely (as frequently as every 3 months or as infrequently as every year) for end points thereafter. When a CARET participant reported a new cancer diagnosis at a follow-up visit or telephone contact, the diagnosis was confirmed by requesting a pathology report and clinical notes. Those records were reviewed by the members of the end point review committee and the diagnosis confirmed. In many cases, the only records that were available were pathology reports from a needle biopsy. The race of the men was self-identified.

A total of 300 participants with prostate cancer, reported from 1987 to 1998 and confirmed by August 1999, were selected for the present study. Fifty-three others potentially were eligible, but limited availability of blood samples from these men precluded their inclusion in this study. All of the cases were free of lung cancer. A medical oncologist (G. G.) reviewed all of the available clinical records of patients with prostate cancer and determined the grade and stage of the tumor, using the American Joint Committee on Cancer Staging for prostate-cancer 1992 staging system. Complete clinical and pathological staging was missing on 126 cases because the diagnoses were made only by the available pathology and clinical notes. A blinded re-review of a number of cases showed that there was 100% agreement in pathological staging from surgical specimens. For this analysis, "aggressive" cancers were defined as those stage C or D (extraprostatic) or as those stage A or B either with Gleason score ≥7 or with poorly differentiated tumors. Approximately 46% of the cases had a tumor that met our criteria for being aggressive.

Controls were chosen from male CARET participants who were alive and free of lung and prostate cancer as of August 31, 1999, and were matched to the cases on race, age at enrollment (within 5 years), enrollment study center, and year of randomization. Three cases had no suitable controls with the same year of randomization. For these, we selected a control that had been randomized within a year of the case. Controls also had been followed up in the CARET study through the date of diagnosis of the paired case, at a minimum. All of the participants provided informed consent, and the Institutional Review Offices of all of the participating centers approved the study.

DNA Extraction and Genotype Determination. Genomic DNA was extracted from whole blood (251 cases and 283 controls) or serum (49 cases and 17 controls) samples that had previously been collected and frozen at −80°C with the use of QIAamp DNA blood Midi kits (Qiagen, Valencia, CA). DNA concentration was determined spectrophotometrically using a Beckman DU-650 spectrophotometer.

To determine the number of CAG repeats in the *AR* gene, two PCR amplifications (primary and secondary) were performed. The forward and reverse primers used for the primary and secondary PCR were: CAGF1, 5′-GTG CGC GAA GTG ATC CAG AA-3′; CAGR1, 5′-TCT GGG ACG CAA CCT CTC TC-3′; CAGF2, 5′-AGA GGC CGC GAG CGC AGC ACC TC-3′; and CAGR2, 5′-GCT GTG AAG GTT GCT GTT CCT CAT-3′. The primary and secondary reactions contained 0.25 μM respective primers pair, 0.25 mM each dNTP, 1.5 mM $MgCl_2$, 1× Qiagen buffer, and 0.25 units of Taq polymerase per μl of reaction. Primary cycling parameters included an initial denaturation of 2 min at 95°C, 17 cycles of 94°C for 1 min, 55°C for 1 min, 72°C for 2 min, and a final extension at 72°C for 10 min. The secondary PCR used 1 μl of the primary PCR products as a template and a fraction (0.05 μM) of the Hex-labeled CAGF2 forward primer. Secondary cycling included an initial denaturation of 2 min at 95°C, 35 cycles of 95°C for 1 min, 66°C for 1 min, 72°C for 2 min, and a final extension of 72°C for 10 min.

To determine the number of GGC repeats in the *AR* gene, two PCR amplifications were performed. The forward and reverse primers for the primary PCR were identical to those described by Sleddens *et al.* (13). The PCR primers for the secondary reaction have been previously reported by Irvine *et al.* (22). We elected to use the Advantage-GC genomic PCR kit produced by Clontech, which gave better efficiency in amplification than using plaque-forming units of polymerase and high denaturing temperatures to overcome the GC-rich nature of the template. For the primary PCR, 5 ng of genomic DNA isolated from whole blood or 2 μl (equivalent to 1/40 of DNA recovered from 1 ml of serum) of DNA isolated from the serum was used as template for the 10-μl primary PCR. The 10-μl secondary PCR used 1 μl of the primary PCR product as a template and contained 0.2 μM each primer, 0.2 mM dNTP, 1.1 mM magnesium acetate, and reagents from Clontech (Palo Alto, CA) Advantage® GC Genomic PCR kit that included a reaction buffer [with final concentrations at 40 mM tricine-KOH (pH 9.3), 15 mM potassium acetate, 3.5 mM magnesium acetate, 5% DMSO], 1.5 M GC-melt, 0.1–0.12 units/μl Tth polymerase, 0.01 μg/μl Tth Start antibody, 1.0% glycerol, 0.2 mM Tris-HCl (pH 7.5), 4.6 mM KCl, 1.5 μM EDTA, 15 μM DTT, 3.75 μg/ml BSA, and 0.0625 μM forward primer labeled with 6-carboxyfluorescein (6FAM). Cycling conditions included an initial denaturation of 2 min at 95°C, followed by 35 cycles of 94°C

Table 1 Characteristics of men with prostate cancer and controls

	Cases (n = 300)			Controls (n = 300)		
	Mean (SD)	n	%	Mean (SD)	n	%
Age, years	61.2 (5.7)			60.8 (5.9)		
Race						
% white		281	93.7		281	93.7
% black		8	2.7		8	2.7
% other (nonmissing)		11	3.7		11	3.7
Height (cm)	174.8 (7.3)			174.9 (7.6)		
Weight (kg)	86.0 (13.7)			84.9 (14.9)		
Body mass index (kg/m^2)	28.2 (4.1)			27.7 (4.5)		
% married[a]		247	82.9		256	85.9
% with greater than high school education[b]		122	55.2		121	55.3
Smoking history at baseline						
% smokers		291	97.0		284	94.7
% former smoker		149	49.7		134	44.7
% current smokers		142	50.3		150	50.0
Intervention arm						
Placebo		149	49.7		142	47.3
β carotene/retinol		151	50.3		158	52.7
Clinical stage						
Localized (stage 0–2)		154	51.3			
Regional (stage 3)		7	2.3			
Distant (stage 4)		13	4.3			
Histologic grade						
Well differentiated (Gleason 2–4)		30	10.0			
Moderately differentiated (Gleason 5–6)		135	45.0			
Poorly differentiated (Gleason 7–10)		111	37.0			
Could not be assessed		24	8.0			
Gleason score						
<7		165	55.0			
≥ 7		111	37.0			

[a] Marital status was missing for two cases and two controls.
[b] Education status was missing for 79 cases and 81 controls. It was not collected in the pilot studies of CARET.

for 1 min, 68°C for 3 min, and a final extension at 68°C for 10 min.

After PCR amplification, PCR products for CAG repeats and GGC repeats from each sample were mixed at a ratio of 1:5, then a 2.5-μl aliquot was added to 0.5 μl of Tamra Internal Size-Standard 500 (Applied Biosystems Inc., Foster City, CA) and 12 μl of deionized formamide. The mixture was denatured at 95°C for 5 min and chilled on ice, then run on a Perkin Elmer Applied Biosystems 310 Genetic Analyzer, using Pop-4 polymer. The GeneScan software (Applied Biosystems Inc., Foster City, CA) determined electrophoretic parameters (mobility, peak color, peak height, and peak area). The GeneScan data were analyzed by the Genotyper software to determine the number of CAG or GGC repeats of the unknown samples.

Included in each 96-well plate of samples was a negative control that contained all of the reagents except the genomic DNA and a set of positive controls with a known number of CAG or GGC repeats. If the GeneScan result of the negative control showed a peak in any of the sample bins, sample results from that batch were excluded from analysis, and the samples were retested. The positive controls were created by the purification of the PCR products from a number of homozygous individuals covering a range of CAG or GGC repeats using Pharmacia Sephaglas Band Prep kits (Pharmacia, Piscataway, NJ), cloning the purified products using Novagen pT7Blue Perfectly Blunt Cloning kits (Novagen, Madison, WI) and sequencing the cloned PCR products using Amersham Thermo Sequenase kits (Amersham-Pharmacia, Piscataway, NJ) on a 5% denaturing polyacrylamide gel to determine the exact number of CAG or GGC repeats. These clones were analyzed on a number of runs on the ABI310 Genetic Analyzer; their relative mobility units were used to set Genotyper sample bins. The number of CAG or GGC repeats in the unknown samples was determined by the comparison of their relative mobility units with those of the cloned standards. This system reliably distinguished fragments that differed by a single basepair in length.

Data Analysis. Univariate t test was used in univariate comparisons of allele frequencies among cases and controls. ORs associated with the different genotypes were estimated by logistic regression. These analyses were adjusted for age and race of the participants.

Results

Table 1 presents selected characteristics of prostate cancer cases and controls. The mean age at entry into the trial was 61.2 years (SD, 5.7) for cases and was 60.8 years (SD, 5.9) for controls. The case and control group each had 281 Caucasians (94%), 8 African Americans (3%), and 11 (4%) men with other ethnic origins. The cases and controls were similar in height, weight, body mass index, educational level, and marital status. Among both cases and controls, ~50% were former and 50% were current smokers of cigarettes at baseline. There was an equal proportion of cases and controls randomized into the placebo and active arm.

The number of *AR* CAG repeats ranged from 7 to 33, with 21 being the most common among both cases and controls (Table 2). The mean number of CAG repeats was 22.00 $\pm$ 3.20 and 21.79 $\pm$ 3.07 among cases and controls, respectively; the median was 22 among cases and 21 in controls.

Table 2 Distribution of *AR*-CAG repeats in prostate cancer patients and controls

No. of repeats	Cases (n = 300)		Controls (n = 300)	
	n	%	*n*	%
7	0	0.0	1	0.3
8	1	0.3	0	0.0
9	1	0.3	0	0.0
12	2	0.7	0	0.0
14	2	0.7	2	0.7
15	1	0.3	2	0.7
16	3	1.0	3	1.0
17	0	0.0	6	2.0
18	21	7.0	18	6.0
19	25	8.3	34	11.3
20	34	11.3	29	9.7
21	54	18.0	58	19.3
22	22	7.3	33	11.0
23	41	13.7	34	11.3
24	30	10.0	31	10.3
25	26	8.7	20	6.7
26	19	6.3	10	3.3
27	5	1.7	7	2.3
28	8	2.7	4	1.3
29	1	0.3	4	1.3
30	1	0.3	2	0.7
31	3	1.0	0	0.0
32	0	0.0	1	0.3
33	0	0.0	1	0.3
Median	22		21	
Mean (±SD)	22.00 (±3.20)		21.79 (±3.07)	

Table 3 Distribution of *AR*-GGC repeats[a] in prostate cancer cases and controls

No. of repeats	Cases (n = 300)		Controls (n = 300)	
	n	%	*n*	%
5	2	0.7	1	0.3
9	0	0.0	2	0.7
10	1	0.3	1	0.3
11	1	0.3	1	0.3
12	2	0.7	0	0.0
13	14	4.7	12	4.0
14	3	1.0	2	0.7
15	2	0.7	3	1.0
16	4	1.3	5	1.7
17	156	52.0	173	57.7
18	96	32.0	91	30.3
19	10	3.3	7	2.3
20	1	0.3	0	0.0
21	6	2.0	2	0.7
22	1	0.3	0	0.0
23	1	0.3	0	0.0
Median	17		17	
Mean (±SD)	17.11 (±1.81)		17.02 (±1.57)	

[a] No. of GGC repeats + 6 = no. of GGN repeats.

The number of GGC repeats ranged from 5 to 23 (Table 3). There was no appreciable difference in the mean number of GGC repeats between cases (17.11 ± 1.81) and controls (17.02 ± 1.57). The median number of GGC repeats was 17 for both cases and controls.

Although there was a suggestion that the risk of prostate cancer decreased with decreasing length of the CAG repeat (Table 4), the association was inconsistent across categories and weak overall (OR, 0.98 per unit decrease in length; 95% CI, 0.93–1.03). There also was little association seen when a dichotomy was formed; having <22 CAG repeats was associated with an OR of 0.89 (95% CI, 0.65–1.23; Table 4). The association between the number of CAG repeats and risk of prostate cancer was weak or absent irrespective of body mass index (data not shown) or the aggressiveness of the tumor (Table 4).

There was little association between prostate cancer risk and the number of GGC repeats. The risk of prostate cancer associated with each decreasing GGC repeat was 0.97 (95% CI, 0.88–1.06). The OR was 0.80 (95% CI, 0.57–1.12) for men with GGC ≤17 when compared with men with GGC >17 (Table 5). A similar result was obtained when men with 17 GGC repeats were compared with those with a greater or smaller number, combined (OR, 0.79; 95% CI, 0.57–1.09). When the analysis was restricted to cases with aggressive disease, the results were similar (Table 5).

Among men under 60 years of age, the race-adjusted OR associated with CAG <22 was 1.48, but the CI was wide (95% CI, 0.62–3.56; Table 6). The corresponding OR for men ages 60–69 was 0.74 (95% CI, 0.48–1.15), and for men ≥70 years, it was 0.96 (95% CI, 0.54–1.69). There was no association between prostate cancer risk and GGC repeat lengths among men under 70 years of age. Among men older than this, there was a suggestion that having GGC ≤17 was associated with a reduced risk, compared with men with GGC >17.

Compared with men having both a large number of CAG and GGC repeats in the *AR* (CAG ≥22 and GGC >17), there was ~2-fold reduction in risk among men with other *AR* genotypes (Table 7).

Discussion

The association of CAG repeat length in exon 1 of the *AR* gene and prostate cancer risk has been examined in 12 other case-control studies (Refs. 22–33; Table 7). Whereas some studies found the shorter CAG repeat lengths to be associated with an increase in prostate cancer risk (22–27), others (including ours) did not (28–33). Several of these studies observed the association with shorter CAG repeat lengths to be restricted to (25), or relatively more prominent in (23, 29, 30), prostate cancers of higher grade and/or stage. Thus, one possible basis for the disparity of results across studies could be a difference in the proportions of men with more advanced lesions who were included in the case group. However, neither our study nor four of the others (24, 26, 28, 33) found evidence of a relationship of CAG repeat length to severity of prostate cancer.

Three studies observed that men with prostate cancer at relatively young ages at diagnosis tended to have a relatively short CAG repeat length (29, 33, 38). In three other studies, there was a suggestion of an association in relatively younger men (ORs for CAG <22 repeats ranging from 1.38 to 1.72 among men less than 60 years in two studies and less than 66 years in the third), but virtually no association at all in older men (24, 30, 31). We also observed a modest increase in risk (OR, 1.48) among men <60 years with <22 CAG repeats, but the confidence limits were quite wide (0.62–3.56), and in men 60–69 years there was a reduced risk of approximately equal size.

There have been several earlier studies investigating the association of *AR*-GGC repeat length and prostate cancer risk, and these have produced somewhat conflicting results (Table 7). Two studies examined the risk of prostate cancer associated with GGC repeat lengths by age of diagnosis (24, 31). Stanford *et al.* (24) observed men with GGC ≤16 to be at increased risk regardless of age at diagnosis [OR for ≤16

Table 4 Risk of prostate cancer in relation to the number of CAG repeats in exon 1 of the *AR*

	No. of CAG repeats									
	≥26	24–25	22–23	21	20	19	18	<18	≥22	<22
Controls	29	51	67	58	29	34	18	14	147	153
Cases										
All (n = 300)	37	56	63	54	34	25	21	10	156	144
OR[a]	1.0	0.86	0.75	0.74	0.93	0.57	0.92	0.56	1.0	0.89
95% CI	Referent	(0.46–1.59)	(0.41–1.36)	(0.40–1.37)	(0.46–1.86)	(0.28–1.17)	(0.42–2.05)	(0.21–1.45)	Referent	(0.65–1.23)
High-grade/stage only[b] (n = 139)	18	31	32	26	10	9	8	5	81	58
OR[a]	1.0	0.98	0.77	0.73	0.56	0.43	0.70	0.56	1.0	0.63
95% CI	Referent	(0.47–2.05)	(0.37–1.59)	(0.34–1.53)	(0.22–1.42)	(0.17–1.10)	(0.25–1.96)	(0.17–1.83)	Referent	(0.39–1.02)

[a] OR adjusted for age and race.
[b] High-grade/stage = Gleason score ≥7 or stage C/D.

Table 5 Risk of prostate cancer in relation to the number of GGC repeats in exon 1 of the *AR*

	Number of GGC repeats			
	>17	≤17	not 17	equals 17
Controls	100	200	127	173
Cases				
All (n = 300)	115	185	144	156
OR[a]	1.0	0.80	1.0	0.79
95% CI	Referent	(0.57–1.12)	Referent	(0.57–1.09)
High-grade/stage only[b] (n = 139)	49	90	63	76
OR[a]	1.0	0.92	1.0	0.89
95% CI	Referent	(0.6–1.40)	Referent	(0.59–1.33)

[a] OR adjusted for age and race.
[b] High-grade/stage = Gleason score ≥7 or stage C/D.

Table 6 Risk of prostate cancer associated with *AR*-CAG or *AR*-GGC repeats, by age at diagnosis

Age at diagnosis, yrs	No. of repeats	Cases		Controls		OR[a]	95% CI
		n	%	n	%		
CAG repeats							
<60	≥22	18	43.9	22	53.7	1	Referent
	<22	23	56.1	19	46.3	1.48	(0.62–3.56)
60–69	≥22	87	53.4	75	46.0	1	Referent
	<22	76	46.6	88	54.0	0.74	(0.48–1.15)
≥70	≥22	51	53.1	50	52.1	1	Referent
	<22	45	46.9	46	47.9	0.96	(0.54–1.69)
GGC repeats							
<60	>17	15	36.6	14	34.1	1	Referent
	≤17	26	63.4	27	65.9	0.9	(0.36–2.23)
60–69	>17	62	38.0	62	38.0	1	Referent
	≤17	101	62.0	101	62.0	1	(0.64–1.56)
≥70	>17	38	39.6	24	25.0	1	Referent
	≤17	58	60.4	72	75.0	0.51	(0.27–0.94)
<60	Not 17	19	46.3	17	41.5	1	Referent
	17	22	53.7	24	58.5	0.82	(0.34–1.97)
60–69	Not 17	79	48.5	77	47.2	1	Referent
	17	84	51.5	86	52.8	0.95	(0.62–1.47)
≥70	Not 17	46	47.9	33	34.4	1	Referent
	17	50	52.1	63	65.6	0.57	(0.32–1.02)

[a] OR adjusted for race.

repeats was 1.40 (95% CI, 0.83–2.39) in men <60 and 2.23 (95% CI, 1.14–4.42) in men 60–64 years]. The other found a reduced risk among men diagnosed at age <66 (OR, 0.36; 95% CI 0.1–1.33) and an increased risk among men diagnosed at age ≥66 (OR, 1.56; 95% CI, 0.59–4.13 Ref. 31). The present study observed a reduced risk associated with ≤17 repeats in men 70 years and older (OR, 0.51; 95% CI, 0.27–0.94) and no evidence of any association in men younger than this.

When we examined the association of prostate cancer risk in relation to combined CAG and GGC repeats, we found a reduction in prostate cancer risk among men with CAG <22

Table 7 Comparison of case-control studies of *AR*-CAG and *AR*-GGC/*N* polymorphism and prostate cancer risk

Study (reference no.)	*n* (case/control)	CAG comparison	OR/RR[a]	95% CI
Current study	156/147	≥22	1.0	Referent
	144/153	<22	0.89	0.65–1.23
Irvine *et al.* (22)	19/25	≥22	1.0	Referent
	38/24	<22	1.25	0.88–1.73
Ingles *et al.* (23)	19/68	≥22	1.0	Referent
	14/56	20–21	0.89	0.41–1.94
	24/45	<20	1.91	0.94–3.88
Stanford *et al.* (24)	136/140	≥22	1.0	Referent
	145/126	<22	1.23	0.88–1.73
Giovannucci *et al.* (25)	60/72	≥26	1.0	Referent
	98/115	24–25	1.02	0.66–1.58
	116/119	22–23	1.17	0.76–1.80
	113/101	21	1.325	0.87–2.09
	69/65	20	1.28	0.79–2.08
	62/61	19	1.22	0.75–2.00
	69/55	≤18	1.52	0.92–2.49
Correa-Cerro *et al.* (30)	39/28	≥24	1.0	Referent
	30/22	22–23	1.02	0.49–2.13
	34/35	20–21	1.43	0.73–2.82
	29/20	≤19	0.96	0.45–2.03
Edwards *et al.* (28)	74/178	>21	1.0	Referent
	88/212	≤21	1.0	0.96–1.03
Bratt *et al.* (29)	92/93	1 CAG decrement	0.97	0.91–1.04
Hsing *et al.* (26)	74/154	≥23	1.0	Referent
	116/146	<23	1.65	1.14–2.39
	52/108	≥24	1.0	Referent
	79/113	22–23	1.45	0.93–2.25
	59/79	<22	1.55	0.96–2.49
Xu *et al.* (27)	33/114	>20	1.0	Referent
	24/42	<20	1.97	1.05–3.72
Miller *et al.* (31)	71/34	≥22	1.0	Referent
	66/35	<22	1.13	0.54–2.37
Latil *et al.* (32)	41/30	>24	1.0	Referent
	55/36	23–24	1.12	0.59–2.10
	61/45	21–22	0.99	0.54–1.82
	68/45	≤20	1.11	0.60–2.02
Beilin *et al.* (33)	456/456	Mean CAG repeats = 21.95 in both cases and controls		

Study (reference no.)	*n* (case/control)	GGC/*N* Comparison	OR/RR	95% CI
Present study	115/100	>17	1.0	Referent
	185/200	≤17	0.8	0.57–1.12
	144/127	Not 17	1.0	Referent
	156/173	17	0.79	0.57–1.09
Irvine *et al.* (22)	10/21	16	1.0	Referent
	27/16	Not 16	1.18	Not given
Stanford *et al.* (24)	56/75	>16	1.0	Referent
	201/175	≤16	1.60	1.07–2.41
Platz *et al.* (34)	244/369	Not 23	1.0	Referent
	338/425	23	1.2	0.97–1.49
Edwards *et al.* (28)	64/116	>16	1.0	Referent
	98/168	≤16	1.06	0.57–1.96
Hsing *et al.* (26)	147/239	≥23	1.0	Referent
	39/56	<23	1.12	0.71–1.78
Miller *et al.* (31)	51/25	>16	1.0	Referent
	82/44	≤16	0.98	0.46–2.06

Table 7 Continued

Study (reference no.)	*n* (case/control)	CAG and GGC/*N* comparison	OR/RR	95% CI
Present study	49/29	≥22, >17	1.0	Referent
	107/118	≥22, ≤17	0.54	0.32–0.91
	66/71	<22, >17	0.55	0.31–0.98
	78/82	<22, ≤17	0.56	0.32–0.98
Irvine *et al.* (22)	34/28	≥22, 16	1.0	Referent
	23/9	<22, not 16	2.1	Not given
Stanford *et al.* (24)	22/32	≥22, >16	1.0	Referent
	32/41	≥22, ≤16	1.15	0.56–2.35
	97/93	<22, >16	1.54	0.83–2.86
	98/77	<22, ≤16	2.05	1.09–3.84
Platz *et al.* (34)	66/119	>23, not 23	1.0	Referent
	90/133	>23, 23	1.17	0.77–1.77
	75/116	21–23, not 23	1.39	0.93–2.06
	152/185	21–23, 23	1.22	0.82–1.83
	103/134	<21, not 23	1.49	1.02–2.15
	96/107	<21, 23	1.62	1.07–2.44
Hsing *et al.* (26)	53/120	≥23, ≥23	1.0	Referent
	19/29	≥23, <23	1.48	0.76–2.88
	94/115	<23, ≥23	1.85	1.21–2.82
	20/26	<23, <23	1.75	0.9–3.41
Miller *et al.* (31)	21/8	≥22, >16	1.0	Referent
	45/26	≥22, ≤16	0.63	0.18–2.2
	29/17	<22, >16	0.69	0.17–2.74
	35/17	<22, ≤16	1.06	0.25–4.46

[a] RR, relative risk.

and GGC ≤17, or CAG <22 and GGC >17, or CAG ≥22 and GGC ≤17 when compared with men with CAG >22, GGC >17 (Table 5). Our results contrast with those of a study of Caucasians (24) and a study of Chinese (26), both of which found having a short repeat length for either or both CAG and GGC alleles was associated with increased risk. Similar to our results were those of a sibship study of Caucasians with a family history of prostate cancer. That study found a reduction of risk was associated with a short CAG or GGC allele (Ref. 31; Table 7). The reasons for the observed differences and similarities among the studies are unclear.

In conclusion, we observed little or no association between the length of CAG and/or GGC repeat sequence in exon 1 of the *AR* gene and prostate cancer risk in a predominantly Caucasian population. To the extent that we did observe any association, *e.g.*, an increased risk associated with a long sequence for both of these, they were in the direction that was opposite to that observed in some of the prior studies. The aggregate of studies of this question suggests that it is doubtful that, as an independent factor, the commonly observed variation in CAG or GGC repeat length in exon 1 of the *AR* is associated with the incidence of prostate cancer.

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