Short Communication

The Polymorphic Exon 1 Androgen Receptor CAG Repeat in Men with a Potential Inherited Predisposition to Prostate Cancer[1]

Ethan M. Lange, Hong Chen, Kristin Brierley, Heather Livermore, Kirk J. Wojno, Carl D. Langefeld, Kenneth Lange, and Kathleen A. Cooney[2]

Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48105 [E. M. L., C. D. L.]; Departments of Internal Medicine [E. M. L., H. C., K. B., H. L., K. A. C.], Surgery [K. A. C.], and Pathology [K. J. W.], University of Michigan Medical School, Ann Arbor, Michigan 48109-0946; and Department of Biomathematics, University of California–Los Angeles School of Medicine, Los Angeles, California 90095 [K. L.]

Abstract

Recent studies have provided epidemiological evidence in support of a possible prostate cancer susceptibility locus on the X chromosome. The androgen receptor (*AR*) gene, located at Xq11–12, has been implicated as a risk factor for the development of prostate cancer. To examine the potential role of the *AR* locus in prostate cancer susceptibility, the *AR* CAG repeat length was measured in 270 Caucasian men with prostate cancer from 133 unrelated families. Each of these families has two or more confirmed cases of prostate cancer occurring in first- and/or second-degree relatives. No evidence for linkage of the *AR* gene to prostate cancer was observed. We tested for the previously reported association of short CAG alleles with prostate cancer using *t* tests, Pearson's χ^2 tests, and logistic regression; analyses were subsequently repeated to incorporate only men with moderate- to high-grade prostate cancer. No association between *AR* CAG allele length and prostate cancer was detected when either a subset of unrelated patients or a subset of unrelated patients with moderate- to high-grade cancer was compared with a set of unrelated controls. We failed to detect an association between short *AR* CAG alleles and early age of prostate cancer diagnosis. Once specific hereditary prostate cancer genes have been identified, future studies can more carefully delineate the potential role of this *AR* polymorphism as a modifier locus in high-risk families.

Introduction

Several studies have suggested that there may be X-linked prostate cancer susceptibility genes (1–4). The *AR*[3] gene, located on chromosome Xq11–12, has been considered to be a candidate prostate cancer gene. The gene encodes a transcription factor that binds male sex steroid hormones. Variation of the CAG repeat in exon 1 of the *AR* gene has also been studied for its possible direct role in prostate cancer causation. Stanford *et al.* (5) suggested a 3% decrease in prostate cancer risk for each additional *AR* CAG repeat in a population-based case-control study of middle-aged Caucasian men. Similarly, Giovannucci *et al.* (6) reported an association between prostate cancer and *AR* alleles with fewer CAG repeats (relative risk, 1.52) using prostate cancer cases and age-matched controls selected from participants in the Physician's Health Study. In this latter study, short *AR* CAG repeat lengths predisposed to higher histological grade and more advanced stage prostate cancer. These associations between short *AR* CAG alleles and prostate cancer may be a consequence of enhanced transactivation function (7, 8) or increased mRNA levels (9) observed in *in vitro* experiments using *AR* genes with fewer CAG repeats.

In 1995, investigators at the University of Michigan initiated the Prostate Cancer Genetics Project with the goal of determining the molecular basis for the inherited predisposition to prostate cancer. We now report the analysis of *AR* CAG repeat length in 270 Caucasian prostate cancer patients who are participating in this study. We set out to determine whether prostate cancer was linked to the *AR* gene and whether we could measure an effect of short *AR* CAG alleles on the occurrence, age of diagnosis, and/or histological grade of prostate cancer in our families.

Materials and Methods

Study Population. The study population consists of 270 Caucasian patients with prostate cancer who are participating in the University of Michigan Prostate Cancer Genetics Project. From this data set, we selected men with prostate cancer from families with two or more confirmed cases of prostate cancer for this present analysis. Written consent was obtained from all participants, and research protocols were approved by the Institutional Review Board at the University of Michigan. The 270 Caucasian prostate cancer patients represent 133 unrelated families. The average age of diagnosis of the 270 men determined by date of prostate biopsy was 64.0 ± 9.5 yr (range, 39–90). The diagnosis of prostate cancer was confirmed in 266 of the 270 men by review of pathological records. In the four remaining cases, the diagnosis of prostate cancer was confirmed in a physician's note, and these cases were, therefore, included in all analyses.

Histological Grade of Prostate Cancer. The pathology records documenting 266 cases of prostate cancer were reviewed without knowledge of the *AR* CAG repeat length, and 264 cases were categorized into one of three groups: histological grade 1 (G1) with a Gleason sum ≤6 or well-differentiated prostate cancer; histological grade 2 (G2) with a Gleason sum 7 or moderately differentiated prostate cancer; and histological grade 3 (G3) with Gleason sum ≥8 or poorly differentiated prostate cancer. Insufficient information was available in the pathology reports of the remaining two cases to determine

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[2] To whom requests for reprints should be addressed, at 7310 CCGC, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0946. Phone: (734) 764-2248; Fax: (734) 647-9480; E-mail: kcooney@umich.edu.
[3] The abbreviations used are: AR, androgen receptor; OR, odds ratio; CI, confidence interval; HPC, hereditary prostate cancer; NPL, nonparametric linkage.

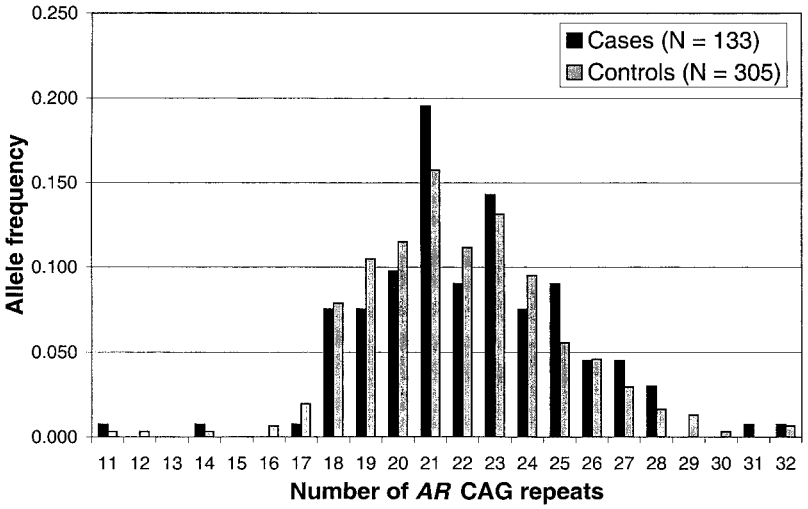

Fig. 1. The allele frequencies of the *AR* CAG polymorphism derived from the 133 Caucasian probands from families with two or more living men affected with prostate cancer are indicated by *black bars*. The allele frequencies derived from a pooled control population of men without prostate cancer ($n = 305$ alleles) are indicated by *gray bars*.

grade. These two cases, along with the four cases without pathological records, were excluded from analyses that included histological grade. In situations where multiple pathology reports were received, priority was given to the grade assigned to the largest volume of resected tumor (*e.g.*, prostatectomy *versus* biopsy), to the primary diagnosis (instead of recurrence or metastasis), and to the grade assigned by the most experienced genitourinary pathologist in the case of second opinions.

Determination of AR Exon 1 CAG Trinucleotide Repeat Length. Genomic DNA was extracted from whole blood using a commercially available kit (Puregene DNA extraction kit; Gentra Systems, Inc., Research Triangle Park, NC). DNA (100 ng) was amplified by two rounds of PCR using nested primers flanking the CAG repeat in exon 1 of the *AR* gene, with modifications of the protocol of Irvine *et al.* (10). The CAG repeat lengths were calibrated by comparing PCR product size to the PCR product of a CAG allele, the repeat length of which was determined by direct sequencing.

CAG Repeat Lengths from a General Caucasian Population. The allele frequencies of the *AR* CAG repeat sequence in the general Caucasian population were derived from the studies of Irvine *et al.* (10) and Stanford *et al.* (5). The first study reported the *AR* CAG repeat length from 39 apparently healthy men over the age of 35 yr from Los Angeles, California (10). The second study described similar data from 266 men residing in King County, Washington, who were between the ages of 40–64 yr and had no history of prostate cancer (5). Combining these studies provided *AR* CAG repeat data from 305 apparently healthy Caucasian men residing in the United States who were over 35 yr of age.

Linkage Analyses. To assess the degree of allele sharing among affected relatives at the *AR* CAG locus and, hence, linkage of prostate cancer to the *AR* gene, we performed nonparametric linkage analysis using GENEHUNTER version 1.3 (11, 12).

Other Statistical Analyses. Previous studies have suggested an inverse relationship between *AR* CAG allele size and prostate cancer occurrence. Hence, both one-sided and two-sided statistical tests were computed. Permutation tests (13) using the standard *t*-statistic were implemented. Because the permutation *t* test makes no distributional assumptions, derived *P*s are more accurate than the *P*s of the parametric *t* test. Empirical *P*s cited are based on 1000 or more random permutations of these data.

To analyze the possibility of association between the CAG repeats in the *AR* gene and prostate cancer, we calculated Pearson's χ^2 tests for the relevant 2×2 contingency tables (SAS System software; SAS Institute, Inc., Cary, NC). All results are reported as ORs with two-sided 95% CIs. These calculations were conducted using an amended estimator for the OR incorporating a continuity correction as suggested by Gart and Zweifel (14) and Haldane (15). We also performed a logistic regression analysis to determine the OR for a decrease in allele size of one CAG repeat (3 bp). Genotype data were available from more than one affected male in 116 of 133 pedigrees (87%). Due to the potential correlation of affection status and *AR* CAG repeat length among affected family members, only one family member was included in the hypothesis tests for equal mean allele length and distributional homogeneity. Probands were selected for these analyses in 113 of 116 or 97.4% of families. In the remaining three families, the proband was unaffected; therefore, the first affected family member from which DNA was collected was used. Thus, the preceding hypotheses were tested using 133 unrelated prostate cancer patients and 305 healthy male controls.

Analyses were also performed to explore the relationship between short CAG alleles and high-grade prostate cancer. We used a strategy to select one prostate cancer case with the highest grade from each family that had one or more cases of G2 or G3 prostate cancer (defined as Gleason grade 7–10 or moderate to poorly differentiated cancer, $n = 93$ families). G3 cases were always selected over G2 cases. If a family had two or more cases of G2 or G3 prostate cancer, one case was randomly chosen for this analysis. Permutation *t* tests and association tests, as described previously, were implemented on this defined subset of study participants.

To investigate the potential relationship between age of prostate cancer diagnosis and length of the CAG repeat at the *AR* locus, we implemented the generalized estimation equations (GEE1) approach of Zeger and Liang (16); we assumed Gaussian observations and used the sandwich estimator of the variance to account for the correlation in age of diagnosis among related men. This approach allowed genotype data from all 270 affected men to be incorporated into the analysis. Hypothesis tests were also performed conditioning on histological grade.

Table 1 Comparison of number of CAG repeats between 289 patients and individual and pooled control populations

	n	Mean ± SD (median, 1st quartile, 1st decile)	One-sided *P*	Two-sided *P*
Prostate cancer patients	133	22.2 ± 3.1 (22.0, 20.0, 19.0)	0.86	0.28
Prostate cancer patients with moderate to high-grade (or G2 + G3) cancer	93	22.1 ± 2.8 (22.0, 21.0, 19.0)	0.79	0.45
Controls[a]	305	21.9 ± 3.0 (22.0, 20.0, 18.0)		

[a] The *AR* CAG repeat lengths in the control population were calculated using data from two studies of the *AR* CAG repeat; in both studies, the control populations were apparently healthy males (5, 10).

Table 2 ORs (95% CIs) for 2 × 2 dichotomous association tests

	AR CAG allele cut-off values used for association tests		
	≤17 *vs.* >17	≤21 *vs.* >21	≤18 *vs.* ≥26
Probands ($n = 133$)	0.69 (0.20–2.31)	0.90 (0.60–1.36)	0.73 (0.31–1.69)
Unrelated men with moderate- to high-grade prostate cancer ($n = 93$)	0.70 (0.17–2.80)	0.85 (0.53–1.35)	0.65 (0.20–2.09)

Results

NPL analysis using GENEHUNTER version 1.3 revealed a NPL Z-score of −0.73, with a corresponding one-sided *P* of 0.76. The 24 families with three or more affected men and no evidence of male-to-male disease transmission (4) also failed to show evidence of prostate cancer linkage to the *AR* gene (NPL Z-score, −0.64; corresponding one-sided $P = 0.74$).

The allele frequencies for the *AR* CAG repeat in the probands from our families with two or more cases of cancer (see "Materials and Methods") are compared graphically to allele frequencies from a control sample in Fig. 1. Permutation *t* tests were used to compare our population of prostate cancer patients to the control sample. We found no evidence that the mean allele length of the *AR* CAG fragments in the patient population is smaller than the mean allele length of the *AR* CAG fragments in the control population (one-sided $P = 0.86$ and two-sided $P = 0.28$; Table 1).

To further study the potential relationship between short *AR* CAG repeats and prostate cancer, we dichotomized the *AR* CAG repeat, consistent with previous studies that reported a positive association. We found no evidence for an association between prostate cancer and the presence of short alleles at the *AR* CAG locus using a cutoff of ≤17 *versus* >17 repeats (17), ≤21 *versus* >21 repeats (5, 10), or ≤18 *versus* ≥26 repeats (Ref. 6; Table 2). Results of the logistic regression analysis also revealed that CAG repeat length is not correlated with an increased risk for the development of prostate cancer (OR = 0.96; 95% CI = 0.90–1.03).

We identified 93 unrelated men with moderate-to-poorly differentiated cancer (66 G2 and 27 G3 cases; see "Materials and Methods"). In this group of men, the mean *AR* CAG allele length was also not significantly different from that of the control population (one-sided $P = 0.79$ and two-sided $P = 0.45$; Table 1). Similarly, no difference in CAG allele repeat lengths was detected when this group of men with moderate- to high-grade cancer was compared with controls using three different cutoff values (Table 2). Finally, CAG repeat length was not associated with risk for moderate- to high-grade prostate cancer using logistic regression (OR = 0.97; 95% CI = 0.90–1.05).

Allele length at the *AR* CAG polymorphism was found to have no significant effect on the age of diagnosis of prostate cancer (two-sided $P = 0.90$). The interaction between prostate cancer grade and allele size on age of diagnosis was not found to be significant (two-sided $P = 0.57$) using a model wherein G1 cases were compared with G2 and G3 cases. Furthermore, no difference in age of diagnosis was detected between the three different grades of prostate cancer after correcting for familial correlation (two-sided $P = 0.97$).

Discussion

Short repeat lengths of the CAG polymorphism in exon 1 of the *AR* gene have been hypothesized to predispose to prostate cancer (18). It is speculated that relatively small enhancements of *AR* activity mediated through increased transactivation and/or mRNA levels promote prostate carcinogenesis over time. However, we failed to detect an association between short *AR* CAG alleles and prostate cancer incidence when we compared our familial prostate cancer patients to a Caucasian control population. Furthermore, we observed no effect of short CAG alleles and the age of prostate cancer diagnosis nor on the development of high-grade cancer.

There are a number of possible factors that may have contributed to the lack of an observed association between short *AR* CAG alleles and prostate cancer in our study. The effect of short *AR* CAG alleles on prostate cancer risk, as determined in two case-control studies, is relatively small, if present at all (relative risk, ≤1.5; Refs. 5 and 6). Lack of a uniform model of analysis also makes these studies difficult to compare. Giovannucci *et al.* (6) examined CAG repeat length as a continuous variable and also compared men with ≤18 repeats with men with ≥26 repeats. Stanford *et al.* (5) and Irvine *et al.* (10) used the median number of 22 to divide their population for analysis. It is unclear whether these studies examined multiple cutoffs and were appropriately corrected for multiple testing. This point is particularly important given the rather weak evidence for association of short *AR* CAG alleles and prostate cancer incidence, as well as the variety of different models possible for viewing these data.

Population heterogeneity is a potential problem that may be encountered in case-control genetic epidemiology studies. If there are undetected racial/ethnic differences between the cases and unrelated controls, an apparent association between a particular allele and a disease may be confounded. This is a critical concern in studies of prostate cancer, where disease incidence varies dramatically with racial and ethnic background. Our study, as well as the previously reported *AR* CAG case-control studies, were all subject to the possible effects of genetic heterogeneity.

The patients described here are all participants in the University of Michigan Prostate Cancer Genetics Project; they were selected for this study because of early-onset and/or a

positive family history of prostate cancer. Indeed, 39 of our families (29% of the total of 133 families) fulfilled at least one or more of the proposed clinical criteria for HPC [these criteria are: (*a*) three or more affected individuals within one nuclear family; (*b*) affected individuals occurring in three successive generations (maternal or paternal lineage); or (*c*) a cluster of two or more relatives each affected before the age of 55 yr (19)]. The prostate cancer in these families may be attributable to one or more highly penetrant *HPC* genes that may mask the relatively modest potential effect of the *AR* CAG polymorphism. However, Rebbeck *et al.* (20) recently reported that *AR* alleles containing very long (≥29) CAG repeats may lead to an earlier age of breast cancer onset in women who also carry a *BRCA1* germline mutation. The role of the *AR* locus as a modifier of prostate cancer risk in these prostate families can be examined more thoroughly in the future as *HPC* genes are identified and characterized.

Previous studies have suggested that short *AR* CAG alleles may predispose to more aggressive forms of prostate cancer, as indicated by high Gleason score tumors and/or advanced stage at diagnosis (6, 17, 21). In our analyses, which incorporated grade, we chose to group all cases up to and including Gleason sum 6, rather than Gleason sum 4, as "well-differentiated" or G1 cases. There is increasing evidence that prostate cancer progression may be more closely correlated with the percentage of Gleason grades 4 and/or 5 cancer (which correlates with a Gleason sum of 7 or higher; Ref. 22). Thus, we chose to divide our cases to emphasize the contribution of Gleason grades 4 and/or 5 cancer. Notably, the percentage of cancers that were scored as Gleason sum ≥7 is greater in the families presented here compared with the prostate cancer families described by Gronberg *et al.* (Ref. 23; 53% *versus* 33%).

In conclusion, linkage of prostate cancer to the *AR* gene was not observed. Taken together with the report by Sun *et al.* (24), the *AR* gene does not seem to significantly contribute to the observed clustering of prostate cancer in families. Furthermore, we found no evidence for an association between short *AR* CAG repeat lengths and the occurrence of prostate cancer when comparing representative subsets of unrelated men drawn from 270 familial prostate cancer patients to a pooled control sample. There was also no detectable effect of short CAG alleles on the age of prostate cancer diagnosis or on the development of high-grade cancer in this data set. This is the first comprehensive study of the *AR* CAG polymorphism in men with early-onset and/or a family history of prostate cancer. Because we could not detect an effect of this polymorphism in our patients, we suggest that the *AR* gene may play a minor role in the heritable form of this disease. However, as *HPC* genes are identified, future studies may further delineate the potential role of the *AR* gene as a modifier locus in prostate cancer families.

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References

1. Narod, S. A., Dupont, A., Cusan, L., Diamond, P., Gomez, J-L., Suburu, R., and Labrie, F. The impact of family history on early detection of prostate cancer. Nat. Med., *1:* 99–101, 1995.

2. Monroe, K. R., Yu, M. C., Kolonel, L. N., Coetzee, G. A., Wilkens, L. R., Ross, R. K., and Henderson, B. E. Evidence of an x-linked or recessive genetic component to prostate cancer risk. Nat. Med., *1:* 827–829, 1995.

3. Xu, J., Meyers, D. A., Freije, D., Isaacs, S. D., Wiley, K., Nusskern, D., Ewing, C. M., Wilkens, E., Bujnovszky, P., Bova, G-S., Walsh, P., Isaacs, W. B., Schleutler, J., Matikainen, M., Tammela, T., Visakorpi, T., Kallioniemi, O-P., Berry, R., Schaid, D., French, A., McDonnell, S., Schroeder, J., Blute, M., Thibodeau, S., Gronberg, H., Emanuelsson, M., Damber, J-E., Bergh, A., Jons-son, A., Smith, J., Bailey-Wilson, J. E., Carpten, J. D., Stephan, D., Gillanders, E., Admudson, I., Kainu, T., Freas-Lutz, D., Baffoe-Bonnie, A., Van Aucken, A., Sood, R., Collins, F., Brownstein, M. J., and Trent, J. Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat. Genet., *20:* 175–179, 1998.

4. Lange, E. M., Chen, H., Brierley, K., Perrone, E., Bock, C. H., Gillanders, E., Ray, M. E., and Cooney, K. A. Linkage analysis of 153 prostate cancer families over a 30 cM region containing the putative susceptibility locus HPCX. Clin. Cancer Res., *5:* 4013–4020, 1999.

5. Stanford, J. L., Just, J. J., Neal, C. L., Blumenstein, B. A., and Ostrander, E. A. Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. Cancer Res., *57:* 1194–1198, 1997.

6. Giovannucci, E., Stampfer, M. J., Krithivas, K., Brown, M., Brufsky, A., Talcott, J., Hennekens, C. H., and Kantoff, P. W. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc. Natl. Acad. Sci. USA, *94:* 3320–3323, 1997.

7. Chamberlain, N. L., Driver, E. D., and Miesfeld, R. L. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res., *22:* 3181–3186, 1994.

8. Kazemi-Esfarjani, P., Trifiro, M. A., and Pinsky, L. Evidence for a repressive function of the long polyglutamine tract in the human androgen receptor: possible pathogenetic relevance for the (CAG)n-expanded neuronopathies. Hum. Mol. Genet., *4:* 523–527, 1995.

9. Choong, C. S., Kemppainen, J. A., Zhou, Z., and Wilson, E. M. Reduced androgen receptor gene expression with first exon CAG repeat expansion. Mol. Endocrinol., *10:* 1527–1535, 1996.

10. Irvine, R. A., Yu, M. C., Ross, R. K., and Coetzee, G. A. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. Cancer Res., *55:* 1937–1940, 1995.

11. Kruglyak, L., and Lander, E. S. Faster multipoint linkage analysis using Fourier transforms. J. Comput. Biol., *5:* 1–7, 1998.

12. Kruglyak, L., Daly, M. J., Reeve-Daly, M. P., and Lander, E. S. Parametric and nonparametric linkage analysis: a unified multipoint approach. Am. J. Hum. Genet., *58:* 1347–1363, 1996.

13. Good, P. Permutation Tests: A Practical Guide to Resampling Methods for Testing Hypotheses. New York: Springer-Verlag, 1994.

14. Gart, J. J., and Zweifel, J. R. On the bias of various estimators of the logit and its variance with application to quantal bioassay. Biometrika, *54:* 181–187, 1967.

15. Haldane, J. B. S. The estimation and significance of the logarithm of a ratio of frequencies. Ann. Hum. Genet., *20:* 309–311, 1999.

16. Zeger, S. L., and Liang, K. Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics, *42:* 121–130, 1986.

17. Hakimi, J. M., Schoenberg, M. P., Rondinelli, R. H., Piantadosi, S., and Barrack, E. R. Androgen receptor variants with short glutamine or glycine repeats may identify unique subpopulations of men with prostate cancer. Clin. Cancer Res., *3:* 1599–1608, 1997.

18. Ross, R. K., Coetzee, G. A., Reichardt, J., Skinner, E., and Henderson, B. E. Does the racial-ethnic variation in prostate cancer risk have a hormonal basis? Cancer (Phila.), 75: 1778–1782, 1995.

19. Carter, B. S., Bova, G. S., Beaty, T. H., Steinberg, G. D., Childs, B., Isaacs, W. B., and Walsh, P. C. Hereditary prostate cancer: epidemiologic and clinical features. J. Urol., *150:* 797–802, 1993.

20. Rebbeck, T. R., Kantoff, P. W., Krithivas, K., Neuhausen, S., Blackwood, M. A., Godwin, A. K., Daly, M. B., Narod, S. A., Garber, J. E., Lynch, H. T., Weber, B. L., and Brown, M. Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. Am. J. Hum. Genet., *64:* 1371–1377, 1999.

21. Ingles, S. A., Ross, R. K., Yu, M. C., Irvine, R. A., La Pera, G., Haile, R. W., and Coetzee, G. A. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J. Natl. Cancer Inst., *89:* 166–170, 1997.

22. Stamey, T. A., McNeal, J. E., Yemoto, C. M., Sigal, B. M., and Johnstone, I. M. Biological determinants of cancer progression in men with prostate cancer. J. Am. Med. Assoc., *281:* 1395–1400, 1999.

23. Gronberg, H., Isaacs, S. D., Smith, J. R., Carpten, J. D., Bova, G. S., Freije, D., Xu, J., Meyers, D. A., Collins, F. S., Trent, J. M., Walsh, P. C., and Isaacs, W. B. Characteristics of prostate cancer in families potentially linked to the hereditary prostate cancer 1 (HPC1) locus. J. Am. Med. Assoc., *278:* 1251–1255, 1997.

24. Sun, S., Narod, S. A., Aprikian, A., Ghadirian, P., and Labrie, F. Androgen receptor and familial prostate cancer. Nat. Med., *1:* 848–849, 1995.