Androgen Receptor Gene Polymorphism and Breast Cancer Susceptibility in the Philippines

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Abstract

Up to one-third of women with breast cancer have a family history of breast cancer, and ~5% of cases are attributed to mutations in high-risk breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*. It is believed that genes of lower penetrance, but of greater prevalence, may also modulate a woman's risk of breast cancer. We studied the association of breast cancer and the trinucleotide repeat polymorphism (CAG_n) in exon 1 of the androgen receptor gene (*AR*) in 299 cases of breast cancer and in 229 hospital-based controls from the Philippines. Women for whom the mean length of the CAG repeat allele was ≤25 units had approximately one-half of the risk of breast cancer compared with women with a mean repeat length of ≥26 [odds ratio (OR), 0.47; 95% confidence interval (CI), 0.28–0.8). The association with breast cancer risk was particularly strong among older women (≥50 years; OR, 0.2; 95% CI, 0.04–0.94). The association was also observed for the longer of the two *AR* alleles; there was a 5% increase in breast cancer risk for each unit increase in CAG repeat number. These findings support the theory that short trinucleotide repeat genotypes of the *AR* gene protect against breast cancer.

Introduction

Exposures to endogenous and exogenous hormones are known to influence breast cancer risk. Hormonal signals are manifest in the breast via hormone receptors. Through binding to their receptors, ovarian hormones stimulate breast cell proliferation, resulting in greater opportunity for the occurrence and clonal propagation of nucleotide sequence errors induced by carcinogens or by spontaneous errors in DNA replication. Established reproductive breast cancer risk factors, such as early age at menarche, oophorectomy, and late age at menopause, provide an indirect link between exposure to estrogens and progesterone, and breast cancer risk.

The AR[2] is involved in the differentiation, development, and regulation of breast cell growth (1, 2). The role of androgens in breast cancer development and carcinogenesis remains unclear (3, 4). Androgens may influence breast cancer risk indirectly through their conversion to estradiol or by competing for steroid binding proteins, or directly by binding to the AR and either promoting or opposing breast cell growth (5). Among postmenopausal women, circulating androgen levels appear to be positively associated with breast cancer risk (6), but it is not known whether these effects are mediated by the AR.

The AR is a ligand-dependent transcriptional activator, and the *AR* gene contains a highly polymorphic trinucleotide repeat (CAG_n) in the first exon, which encodes a glutamine tract. It is hypothesized that the shorter the length of this tract, the greater the affinity of androgens to the AR and the greater the androgenic effects (7, 8). The length of this tract varies between individuals but is typically in the range of 10–40 repeat units. The role of the CAG_n polymorphism of *AR* in cancer predisposition is supported by association studies of breast and prostate cancer risk. For breast cancer, a significantly decreased risk has been observed with smaller repeat lengths (9). Giguère *et al.* (9) reported an OR of 0.5 (95% CI, 0.3–0.83; $P = 0.007$) for women with small alleles (such as $CAG_n < 20$). In that study a particularly strong effect was seen among postmenopausal women (OR, 0.36; 95% CI, 0.19–0.7; $P = 0.003$). Suter *et al.* (10) found a modest increase in premenopausal breast cancer risk associated with a repeat length of >22 units (OR, 1.3; 95% CI, 1.0–1.7). Other studies found no associations between breast cancer risk and CAG repeat length (11–13). These studies included mainly younger women and used different cut-off points. We tested the hypothesis that the length of the polyglutamine polymorphism (CAG_n) in *AR* is positively associated with breast cancer susceptibility in a case-control study of women from the Philippines. We studied 299 women with incident invasive breast cancers, and 229 control subjects from the Philippine General Hospital in Manila.

Materials and Methods

Study Population. A hospital-based case-control study was carried out at the PGH in Manila, during the period August 1997 to June 2000 (active recruitment occurred during a 1-year period) as described previously (14). In total, blood specimens were collected from 299 incident breast cancer cases from PGH in Manila. All of the cases had a positive biopsy and histological confirmation of invasive breast carcinoma. These represent incident cases with the exception of 5 prevalent cases.

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[2] The abbreviations used are: AR, androgen receptor; OR, odds ratio; CI, confidence interval; PGH, Philippine General Hospital.

Our control group comprised 229 women who attended the PGH breast clinic but who did not have breast cancer, 163 of whom had a negative biopsy and 66 for whom a breast biopsy was not believed to be indicated after clinical breast examination. Approximately 95% of subjects were of Malay ethnicity, including combinations of Malay with Chinese or Spanish. All of the women completed a risk factor questionnaire by interview with a research assistant. Questions asked about reproductive, hormonal, dietary, and adolescent exposures, among others.

Molecular Analysis. DNA was extracted from peripheral blood leukocytes using standard protocols. The *AR* exon 1 CAG trinucleotide repeat was amplified by a nested PCR protocol using outside primers (forward primer 5′-GTGGAAGAT-TCAGCCAAGCT-3′ and reverse primer 5′-TTGCTGTTCCT-CATCCAGGA-3′) and inside primers (forward primer 5′-CCCGGCGCCAGTTTGCTGCTG-3′ labeled with cyanine-5, reverse primer is the same with the first PCR). The final products were analyzed by electrophoresis on 6% denaturing polyacrylamide gels. After direct sequencing of PCR products, the CAG repeats were calculated from the size of the predominant PCR product in relation to a series of previously determined CAG size standards (15). Information on 16 carriers of mutations in genes *BRCA1* or *BRCA2* is described in detail elsewhere (14).

Statistical Methods. Allele lengths were compared between cases and controls. Comparisons were made for the mean allele length, and separately for the shorter and the longer alleles. Dichotomous categories for CAG repeats were generated at all of the possible cut-points. These categories were analyzed using χ^2 and Fisher's exact tests for comparisons. Student *t* test was performed for the comparison of continuous variables. Breast cancer risk was also assessed using multivariate unconditional logistic regression. All of the *P*s are two-tailed and set at 0.05 for significance. Analyses were performed using SPSS statistical package for Windows (Version 11).

Table 1 Characteristics of breast cancer cases and controls from breast clinic of PGH, Manila, Philippines

	No. (%) of	
	Cases	Controls
Total (*n*)	299	229
Ethnicity		
Malay	220 (74.0)	163 (71.1)
Malay-Other (e.g. Malay-Chinese)	61 (20.4)	43 (18.8)
Spanish	5 (1.7)	3 (1.3)
Chinese	4 (1.3)	3 (1.3)
Spanish-Chinese	2 (.7)	1 (.4)
Unknown	7 (2.3)	16 (7.0)
Age distribution (yrs)		
20–34	33 (11.0)	72 (31.4)
35–44	127 (42.5)	86 (37.6)
45–54	118 (39.5)	63 (27.5)
55–70	21 (7.0)	8 (3.5)
Tumor histology		
Infiltrating ductal	257 (86.0)	—
Infiltrating lobular	2 (.7)	
Papillary	7 (2.3)	
Medullary	2 (.7)	
Other	17 (5.7)	
Unknown	14 (4.7)	
Stage		
I	8 (2.7)	—
II	94 (31.4)	
III	153 (51.2)	
IV	30 (10.0)	
Unknown	14 (4.7)	
Estrogen receptor[a]		
Negative	52 (40.3)	—
Positive	77 (59.7)	

[a] Percentages were calculated from cases for whom this information was available.

Results

The 299 cases and 229 controls in this study originated from a single breast cancer clinic at the PGH in Manila. The characteristics of these women are shown in Table 1. For each study subject the size of the two *AR* alleles was determined. The mean AR allele size was 23.3 ± 2.3 units for cases and was 23.0 ± 2.2 units for controls ($P = 0.11$). On average, the number of CAG repeats of the longer of the two *AR* alleles (the "long" allele) was 25.0 ± 2.5 for cases and was 24.6 ± 2.6 for controls ($P = 0.055$). The mean length of the shorter of the two alleles (the "short" allele) was 21.6 ± 3.0 for cases and 21.4 ± 3.0 for controls ($P = 0.43$).

We estimated the ORs for breast cancer associated with each cutoff point of *AR* allele length from 19 to 27 repeat units (Table 2). These ORs compare the odds of breast cancer for women in the category below the cutoff point, compared with women in the category above the cutoff point. In general, an increased risk of breast cancer was found with increasing AR length, both for the longer allele and for the shorter allele. The risk of breast cancer appeared to be decreased for women with smaller AR repeats, regardless of the cutoff value used. Because of the distribution of allele sizes in this population, the greatest statistical significance was observed with a cutoff of ≥25 repeat units (OR, 0.47; *P*, 0.005).

We also estimated the ORs for each combination of *AR* genotype (short and long allele) (Fig. 1). Fig. 1 suggests that risk of breast cancer increases with the length of both the short and long allele. The results of multivariate logistic regression demonstrated that the effect of the long allele was independent of that of the short allele, with an adjusted OR of 0.95 (95% CI, 0.89–1.0; $P = 0.08$) for each unit decrease in repeat number. This is equivalent to an OR of 0.64 as the repeat length of the long allele decreased by eight units (e.g. from 29 to 21 repeats).

The inverse association of short AR alleles appeared to be greater for women diagnosed with breast cancer at age ≥50; however, this subgroup was relatively small (Table 3). Similarly, stratification by family history of breast or ovarian cancer in a first-degree relative revealed strong associations among women with no family history (Table 3), but the subgroup of familial breast cancer patients was small.

A multivariate analysis was performed to examine the association between AR length and breast cancer risk, adjusting for age, family history, reproductive factors, oral contraceptives, and smoking. After adjustment the results were essentially unchanged (Table 4).

Discussion

The Philippines has the highest reported incidence rate of breast cancer in Asia (16). The (world-standardized) rate of 47.7/100,000 exceeds the rate reported for several Western countries, including Spain, Italy, and most Eastern European countries. We have estimated that at least 5% of breast cancers in the Philippines may be attributed to mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* (14). It is postulated that other genes of lower penetrance, but perhaps of greater

Table 2 AR exon 1 CAG_n allele categories and breast cancer risk among 299 cases and 229 controls

CAG repeat cut-off	No. of cases	No. of controls	ORs	95% CI	*P*
AR long allele					
≤21	16	6	2.1	0.81–5.45	0.13
≤22	49	35	1.09	0.68–1.74	0.81
≤23	94	94	0.66	0.46–0.94	0.028
≤24	139	131	0.65	0.46–0.92	0.018
≤25	183	169	0.56	0.38–0.82	0.003
≤26	218	181	0.71	0.48–1.07	0.12
≤27	254	206	0.63	0.37–1.08	0.12
AR short allele					
≤19	46	40	0.86	0.54–1.37	0.55
≤20	69	54	0.90	0.65–1.46	0.92
≤21	110	81	1.06	0.74–1.52	0.78
≤22	178	152	0.74	0.52–1.07	0.12
≤23	239	194	0.72	0.46–1.14	0.17
≤24	267	215	0.60	0.28–1.04	0.09
≤25	284	223	0.51	0.19–1.33	0.18
AR mean of alleles					
≤20	28	22	0.97	0.54–1.75	1
≤21	54	40	1.0	0.66–1.64	0.91
≤22	91	75	0.90	0.62–1.30	0.57
≤23	139	129	0.67	0.48–0.95	0.028
≤24	200	176	0.61	0.41–0.90	0.015
≤25	242	206	0.47	0.28–0.80	0.005
≤26	275	220	0.47	0.21–1.03	0.07
≤27	288	225	0.46	0.15–1.48	0.7

The odds ratios presented are those for breast cancer risk for women falling in the category below the cutoff value, compared to women above the cutoff point.

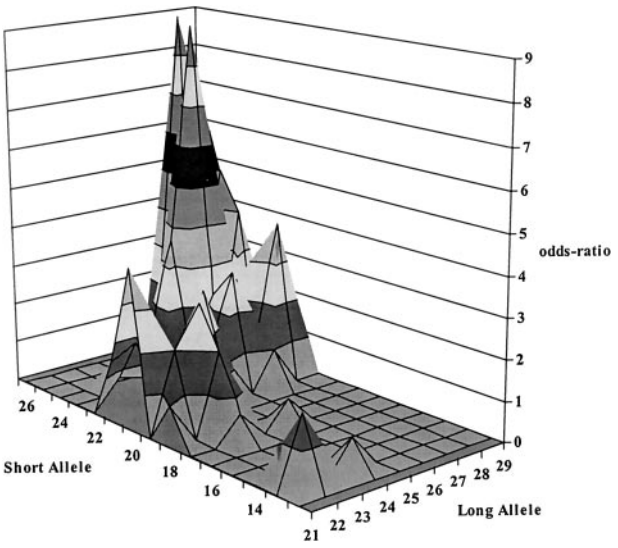

Fig. 1. Three-dimensional modeling of breast cancer risk estimates according to CAG repeat polymorphism of *AR*. "Short" and "long" allele are expressed in absolute number of CAG repeats, and estimated ORs have been calculated relative to women who have a median number of CAG_n on each of their alleles (22 and 24, respectively).

prevalence, may also modulate a woman's risk of breast cancer. The polymorphic polyglutamine repeat of exon 1 of the *AR* gene has been proposed to be a modifier of breast cancer risk (9). We found this polymorphism to be associated with breast cancer risk in the Philippines. Using a mean cutoff value of 25 repeat units we observed an OR of 0.47 (95% CI, 0.28–0.8).

Giguère *et al.* (9) examined the inverse association of CAG repeat length on breast cancer risk in Québec, but used different cutoff points for their classification of genotypes. They reported an OR of 0.5 (95% CI, 0.3–0.83) for women with mean allele sizes of 20 CAG repeats or less. Elhaji *et al.* (17) described a 2.4-fold increased risk of breast cancer associated with allele lengths of 26 CAG repeats or greater. In a study based on 368 breast cancer cases and 284 control subjects, Spurdle *et al.* (11) did not find any association between CAG repeats of 22 units or less and breast cancer in women <40 years of age. Dunning *et al.* (12) also did not find any association with breast cancer using a mean cutoff of 22 CAG repeats. In the Nurses' Health Study (13), several cut-points were examined, and no association was observed.

Our data indicate that there is no clear cut-point that can be used to dichotomize women into high- or low-risk groups (Table 1). There appears to be a continuous gradient of risk associated with alleles of different sizes. Although our *P* was most significant when a cut-point of 25 CAG units was used, this reflects the power of the study; *i.e.*, this cut-point divided the study sample into two groups of roughly equal size and, thereby, maximized study power. Similar effect sizes were seen for cutpoints of 23 and 24 repeat units (Tables 2 and 4).

By conducting our study in the Philippines, we were able to limit the effect of ethnic variation, a potential confounder in association studies of genetic polymorphisms. The Philippines represents an ethnically heterogeneous population of >70 million inhabitants, with >100 cultural and racial groups. The majority of the population is of Malay, Chinese, and Spanish ancestry. Malay refers to the original ancestors of Filipinos who were of Malay stock from the southeastern Asian mainland, as well as from what is now Indonesia. Our control subjects were comprised mainly of women under investigation for a breast complaint (63%). Women attending the breast clinic of the PGH in Manila were recruited before the determination of their case or control status. In this way, the cases and controls are well matched on demographic and other variables (18).

The *AR* may act in breast tumorigenesis by moderating androgen signaling acting at the level of the mammary epithelial cell. Because *AR* is located on the X chromosome (Xp11–12), breast epithelial cells in women express only one of the two *AR* alleles that a woman has inherited; the other is inactivated. Thus, each cell is under the influence of only a single "active" *AR* allele. Because breast cancers are clonal, each cancer should have a single allele consistently activated. Shan *et al.* (19) demonstrated the loss of the active *AR* allele in female breast cancers.

Our results suggest that breast cancer risk might be likely related to androgenic activity, and that shorter trinucleotide repeat length genotypes of *AR* (which have been associated with increased androgenic activity; Refs. 7, 8) are protective. This is consistent with experiments on breast cancer cell lines, which find that androgens decrease breast epithelial cell proliferation (20, 21). However, most epidemiologic studies find elevated circulating androgen levels to be a risk factor for breast cancer risk in postmenopausal women. The reason for this inconsistency is not known.

The AR polymorphism has also been related to the risk of prostate cancer. However, the proposed associations of risk for prostate cancer and breast cancer are in opposite directions, *i.e.*, longer CAG repeats are protective in prostate cancer (22–24). The contrasting associations for cancers of the prostate and breast might be the result of stimulation and inhibition of prostate and breast cell proliferation, respectively, with increased androgenic activity (20, 21, 25).

Table 3 Association of AR exon 1 CAG_n polymorphism with breast cancer

	Mean of alleles cut-off				Long allele cut-off			
	No. ≤25	No. >25	Crude ORs (95% CI)	Adjusted[a] ORs (95% CI)	No. ≤25	No. >25	Crude ORs (95% CI)	Adjusted[a] ORs (95% CI)
All women								
Cases	242	57	0.47 (0.28–0.8)	0.47 (0.24–0.94)	183	116	0.56 (0.39–0.81)	0.43 (0.26–0.71)
Controls	206	23			169	60		
Age group								
<50								
Cases	197	42	0.56 (0.32–0.98)	0.58 (0.27–1.23)	146	93	0.59 (0.40–0.89)	0.45 (0.26–0.76)
Controls	176	21			143	54		
50+								
Cases	45	15	0.2 (0.04–0.94)	0.2 (0.03–1.15)	37	23	0.37 (0.13–1.04)	0.35 (0.08–1.39)
Controls	30	2			26	6		
Menopause								
Premenopausal								
Cases	181	40	0.44 (0.23–0.82)	0.39 (0.17–0.91)	135	86	0.6 (0.39–0.92)	0.38 (0.21–0.68)
Controls	156	15			124	47		
Postmenopausal								
Cases	56	16	0.36 (0.11–1.16)	0.39 (0.08–1.75)	45	27	0.44 (0.18–1.06)	0.43 (0.12–1.56)
Controls	39	4			34	9		
Family history[b]								
Yes								
Cases	32	4	—	—	25	11	0.67 (0.2–2.27)	0.67 (0.14–3.08)
Controls	22	0			17	5		
No								
Cases	192	49	0.38 (0.2–0.7)	0.42 (0.2–0.89)	146	95	0.52 (0.34–0.8)	0.38 (0.22–0.66)
Controls	156	15			128	43		

[a] Adjusted for age at menarche, age at first birth, age at last birth, oral contraceptive use, and smoking.
[b] Family history of breast or ovarian cancer, includes only subjects for whom this information was available.

Table 4 Results of multivariate analyses of AR exon 1 CAG_n polymorphism and breast cancer

	ORs[a] (95% CI)	Adjusted[b] ORs (95% CI)
Total (*n*)		
AR long allele		
≤23	0.61 (0.42–0.9)	0.47 (0.28–0.77)
≤24	0.62 (0.42–0.9)	0.47 (0.29–0.76)
≤25	0.50 (0.33–0.76)	0.39 (0.23–0.67)
AR mean of alleles		
≤23	0.64 (0.44–0.93)	0.57 (0.35–0.91)
≤24	0.54 (0.35–0.83)	0.48 (0.28–0.84)
≤25	0.32 (0.17–0.61)	0.34 (0.16–0.74)

[a] Adjusted for age group, family history, acne, and menopausal status.
[b] Adjusted for age group, family history, acne, menopausal status, age at menarche, parity, age at first birth, age at last birth, oral contraceptive use, and smoking.

The AR CAG_n polymorphism has also been shown to modify the risk of breast cancer in *BRCA1* carriers. Rebbeck *et al.* (26) reported a relative risk of 1.81 (95% CI, 1.06–3.08) for breast cancer in *BRCA1* carriers who carried at least one CAG repeat allele of 28 or greater. Kadouri *et al.* (27) were not able to replicate this association.

It has been suggested that androgens may act independently, or may be mediated by estrogen metabolites (aromatization products) or by secondary effects of androgens on estrogen bioavailability and metabolism (sex hormone binding globulin effects). Testosterone may have an indirect effect on breast cancer risk because of its association with estrogen levels. Testosterone levels affect estrogen bioavailability, which may be of importance, because an increase in serum testosterone levels could lead to a decrease in the percentage of estradiol bound to sex hormone binding globulin.

In conclusion, trinucleotide repeat length genotypes of *AR* were associated positively with breast cancer risk in the Philippines. Our data support the previous observations by Giguère *et al.* (9), of a particularly strong effect among women ≥50 years. Additional work is necessary to elucidate the specific mechanisms by which androgens and the *AR*, which influence breast epithelial cell proliferation and carcinogenesis.

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