Short Polyglutamine Tracts in the Androgen Receptor Are Protective against Breast Cancer in the General Population

Yves Giguère, Eric Dewailly, Jacques Brisson, Pierre Ayotte, Nathalie Laflamme, Alain Demers, Véronique-Isabelle Forest, Sylvie Dodin, Jean Robert, and François Rousseau

Abstract

We studied the association of breast cancer with the polymorphic polyglutamine repeat of the androgen receptor (AR) in 255 incident cases of breast cancer and 461 matched controls from the Quebec City metropolitan area. Women for whom the sum of both of the AR (CAG)n-repeats alleles is less than 39 (short-alleles AR genotypes) have one-half the risk of breast cancer compared with women for whom the sum of AR (CAG)n-repeats is 40 or more (odds ratio (OR), 0.5; 95% confidence interval (CI), 0.3–0.83; P = 0.007). This association is stronger in postmenopausal women (180 cases, 297 controls; OR, 0.36; 95% CI, 0.19–0.7; P = 0.003).

We also observed an interaction between the type of menopause (natural versus surgical) and the AR genotype on breast cancer risk. Alternately, when subjects were grouped according to their (CAG)n-repeat genotype (homozygous for short alleles (CAG)n = 20; other genotypes (“long allele”), results were similar (OR, 0.5; 95% CI, 0.27–0.82; P = 0.007). Thus, women with short-alleles AR genotypes appear to be protected against breast cancer. Short-alleles AR genotypes were observed in 16% of the general population as represented by the control group. Short polyglutamine repeats in the AR protein have been reported to be associated with an increase in the capacity of the receptor to activate transcription of reporter genes in vitro. Furthermore, androgens have been previously shown to inhibit in vitro the growth of breast cancer cell lines. This suggests that differences in the number of polyglutamines in the AR protein may influence individual risk of breast cancer, especially in postmenopausal women, and that this apparent protection could be the consequence of an increased response/sensitivity to androgens.

Introduction

It has been recognized for several years that family history is a well-known risk factor for breast cancer, generating a relative risk of about 2 to 2.8 for sisters of women with breast cancer (1–3). Twin studies have shown that heritability of breast cancer ranges between 0.3 and 0.4 (4), and a recent survey of 9512 pairs of twins suggested a heritability of 0.27 (2). Segregation analyses in a large population-based series of patients by Newman et al. (5) suggested that between 4 and 10% of all breast cancer cases would be attributable to one or more highly penetrant susceptibility genes. Intense efforts to study families with a high incidence of breast and ovarian cancers led to the identification of two major genes involved in dominantly inherited breast cancer: BRCA1 (6, 7) and BRCA2 (8, 9), which are likely to be responsible for the majority (~70%) of inherited breast cancers. More than 75% of reported mutations in BRCA1 gene result in truncated proteins that are likely to be nonfunctional (OMIM 113705). It also seems unlikely that BRCA1 and BRCA2 genes play an important role in the development of breast cancer in the absence of a mutated germ-line allele (7). It is now considered that no more than 10% of all cases of breast cancers are attributable to an inherited susceptibility of a rare autosomal dominant mutated gene with high penetrance (10).

Because it is likely that most of the relatively rare mutated genes resulting in a high penetrance of breast cancer have been identified (BRCA1, BRCA2), various groups have been studying the potential role of common normal variants of genes already known to be involved in the etiology of breast cancer (11). Dunning et al. (12) tested the putative association between normal allelic variants of the BRCA1 gene with breast and ovarian cancer but concluded that the most common polymorphisms of this gene did not make a significant contribution to breast or ovarian cancer risk in the general population. Given that breast cancer is a hormone-dependent disease, genes encoding receptors for steroid hormones known to influence the natural history of the disease are also considered as good candidates for susceptibility loci. Studies of estrogen receptor polymorphisms in breast cancer have not shown a consistent contribution of genetic variation at this locus in the etiology of breast cancer (13, 14).

The AR protein comprises an important polyglutamine stretch within its large NH2-terminal modulating domain. This polyglutamine tract (close to the NH2-terminal end) is encoded by a trinucleotide repeat (CAG)n coding for 17–26 glutamines in the general population but showing an abnormal expansion of 40–52 glutamines in individuals affected with Kennedy’s disease and complete androgen insensitivity (15). This polymorphism has been reported to be associated with prostate cancer (16–18) and to affect in vitro transactivation activity of the AR (19, 20). In the reported association with prostate cancer, shorter (CAG)n alleles were associated with a relative risk of prostate cancer of ~2 as compared with larger alleles (16, 21). In in vitro studies, shorter AR polyglutamine tracts were associated with an increased transcriotional activity of the AR protein, suggesting that the AR receptor could be more “efficient” when harboring a short polyglutamine tract. Furthermore, rare point mutations at the AR locus have been associated with breast cancer in males (22).

The association of smaller AR alleles with increased prostate cancer risk is in agreement with the prediction that such AR products would show an increased “sensitivity” to similar androgens levels. Recently, polymorphism of the AR gene has been proposed to be a modulator of the penetrance of BRCA1 mutations in women (23), although it has not been associated directly with the occurrence of breast cancer in young women under 40 (24, 25). Also, Young et al. (26) recently reported an increased frequency of long AR (CAG)n alleles in males with breast cancer.

We hypothesized that the polyglutamine polymorphism of the AR gene could be associated with susceptibility to breast cancer in...
women. For this purpose, we recruited a study group of 255 incident breast cancer cases and 461 controls matched for age and area of residence (27) and genotyped them for the AR (CAG)n coding polymorphism.

MATERIALS AND METHODS

A study group of 255 incident cases of breast cancer from the Quebec City metropolitan area was recruited through breast cancer clinics in five hospitals as part of a study on environmental contaminants and breast cancer (27). In addition, 461 control women, matched for age and area of residency, were recruited during the study period and comprised 189 women hospitalized for conditions not related to breast disease and 272 women randomly selected from the general population files of the Régie de l’assurance maladie du Québec (RAMQ). The project was approved by the appropriate ethics committee of each participating institution, and each participant provided informed consent to participate in the study. Details about the recruitment strategy and general description of the sample are published elsewhere (27), and only women for which DNA was available were included in this study.

After DNA purification using a high-throughput salting-out minipreparation method (28), the AR (CAG)n trinucleotide repeats were analyzed by PCR amplification using radiolabeled oligonucleotides followed by migration in high-resolution gel electrophoresis in a 6% denaturing polyacrylamide gel. Genotyping of the (CAG)n repeats was performed according to Tilley et al. (29). Three homozygous women were sequenced to determine the exact number of CAG repeats; they had, respectively, 19, 22, and 25 CAG repeats. Autoradiograms were interpreted independently by three readers (Y.G., V-I. F., F. R.) who were blinded to the status (case versus control) of the samples studied. Agreement between readers was calculated at 95%. To insure that there was no gel-to-gel drift in genotyping from one series to another, a control sample was included in triplicate in each series of analyses and was used to calibrate the readings from each gel/autoradiogram to the others. Also, random samples from each series of analyses were independently reanalyzed to validate the allocation of genotypes.

In this sample, as expected, certain known risk factors were associated with an increased susceptibility to the disease. These included a positive family history of breast cancer in at least one first-degree relative (OR, 2.0; 95% CI, 1.3–3.0; P = 0.0009), a positive history for breast benign disease (OR, 2.5; 95% CI, 1.8–3.5; P = 0.0001); a natural menopause (OR, 1.7; 95% CI, 1.2–2.5; P = 0.006); postmenopausal hormone replacement therapy (OR, 1.6; 95% CI, 1.1–2.1; P = 0.006). However, smoking, BMI, breastfeeding, the number of deliveries, and the presence of menopause were not associated with an increased risk of the disease.

There was no difference (χ² test, P = 0.43) in the AR polymorphisms distribution between hospital and population controls. In addition, all of the analyses on AR polymorphisms and breast cancer

![Table 1 Characteristics of cases and controls](image-url)

Detailed characteristics of cases and each category of controls are presented. Values are expressed as mean ± SD for continuous variables and as a percentage for nominal variables.

RESULTS

General Results. Characteristics of the cases and controls are shown in Table 1. Although controls were matched with cases for age and region in the initial environmental contaminants and breast cancer study (25), women withdrawal from the genetic study may have resulted in some different proportion of individuals within a stratum of age or region. This possibility was investigated, and even if the mean age was similar between cases and controls, there were more breast cancer cases among older women (≥50 years) than among younger women (OR, 1.5; 95% CI, 1.1–2.1; P = 0.009). Thus, age was still considered as a potential confounder in our analysis.

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![Figure 1 Distribution of AR genotypes](image-url)

Table 1 Characteristics of cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 255)</th>
<th>All controls (n = 461)</th>
<th>Hospital controls (n = 189)</th>
<th>Population controls (n = 272)</th>
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<tr>
<td>Age, yr (mean ± SD)</td>
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<td>52 ± 10</td>
<td>51 ± 11</td>
<td>52 ± 9</td>
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<td>Age at menarche, yr (mean ± SD)</td>
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<td>Number of deliveries (mean ± SD)</td>
<td>2.1 ± 1.6</td>
<td>2.3 ± 1.8</td>
<td>2.4 ± 2</td>
<td>2.2 ± 1.6</td>
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<td>BMI (kg/m²) (mean ± SD)</td>
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<td>25 ± 5</td>
<td>26 ± 5</td>
<td>24 ± 4</td>
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<td>Breast-fed ever (%)</td>
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<td>64</td>
<td>65</td>
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<tr>
<td>Ever use hormone replacement (%)</td>
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<td>33</td>
<td>36</td>
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<tr>
<td>Previous breast benign disease (%)</td>
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<td>15</td>
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<tr>
<td>Ever smoking (%)</td>
<td>47</td>
<td>53</td>
<td>56</td>
<td>51</td>
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</table>
yielded similar results whether we used the population-based or the hospital controls. Therefore, we describe results of analyses performed only after combining population- and hospital-based controls together.

**AR-Polyglutamine Polymorphism Is Associated with Susceptibility to Breast Cancer.** As an initial analysis and to establish a categorization of AR genotypes, the ratio of cases:controls was compared for each AR genotype on a three-dimension graph comprising one AR allele (X axis), the second AR allele (Y axis), and the case:control ratio on the third axis (Z axis; Fig. 1a). To smooth out the surface representing the crude ratios, ratios of all cases:controls in a $3 \times 3$ matrix centered on a given allele 1 × allele 2 combination in the graph were used as the Z-axis value. The $3 \times 3$ matrices that included less than 5 individuals (cases plus controls) were removed. By using this plotted 3D graph, which produced a satisfactory smoothing of the surface representing the data, it appeared that women could be categorized into two different risk groups according to their AR genotype. Indeed, women with the smallest risk of breast cancer were those carrying two AR alleles with a small number of CAG repeats. Fig. 1 suggests that an increase in risk progressed with an increase in both of the allele sizes until it (the risk) reached a plateau at some point at which the sum of the sizes of each (CAG)n allele was 40 triplets. Thus, women for whom the sum of both CAG repeat alleles did not exceed 39 we called “small-allele AR genotypes,” and those women for whom this sum equaled 40 or greater we called “long-allele AR genotypes.” Alternatively, AR genotypes were grouped as homozygous for alleles of 20 CAG-repeats or less (short-allele genotypes) and those carrying two alleles smaller than 27 repeats, which suggests also a higher susceptibility to breast cancer in women bearing long AR alleles and a **BRCA1** mutation. More recently, Dunning et al. (30) reported that the AR CAG-repeat could provide a cause-and-effect relationship between **AR** genotypes and breast cancer, although not a significant association with a higher risk of developing the disease compared with those bearing long-allele **AR** genotypes (Table 2). Women with short-allele AR genotypes had an OR for breast cancer of 0.50 (95% CI, 0.30–0.83; $P = 0.007$) as compared with those with long-allele AR genotypes. Decreasing the cutoff between “small” alleles and “long” alleles resulted in similar ORs, whereas increasing the cutoff from 40 to 41 for the sum of both alleles decreased the ORs, although they remained statistically significant.

Stratification of women according to their menopausal status revealed that the decreased risk associated with the short-allele AR genotypes was present mostly among menopausal women (OR, 0.36; 95% CI 0.19–0.70; $P = 0.003$) as compared with long **AR** allele genotypes (interaction test, $P = 0.08$). Noteworthy, when stratified according to the type of menopause (natural versus surgical), it appeared that, among postmenopausal women, the decrease in risk associated with small-allele **AR** genotypes was mainly present in women who had a surgical menopause (OR, 0.18; 95% CI 0.05–0.60; $P = 0.005$; interaction test, $P = 0.05$; Table 2). For all of the observed associations, adjustment for age (30–40, 40–50, 50–60, 60+), area of living (urban versus rural), family history of breast cancer, BMI, smoking, replacement hormonotherapy (hormone replacement therapy) or history of breast benign disease did not change significant ORs by more than 10%.

**DISCUSSION**

The present study suggests that the AR polyglutamine (CAG)n tract polymorphism within the population may be an important factor in the etiology of breast cancer. Although this exploratory study does not provide a cause-and-effect relationship between **AR** genetic variation and breast cancer, our findings nevertheless warrant additional investigations. This is especially relevant in the scope of the large body of evidence supporting a modulation of the risk of androgen-sensitive diseases, such as prostate cancer, by variations of the polyglutamine array at the AR locus. Furthermore, there is also in vitro evidence for a role of AR in breast cancer cell proliferation (see below).

Recent studies investigated the potential role of the (CAG)n **AR** polymorphism in breast cancer. Spurdle et al. (24) studied 368 cases and 284 controls and used a cutoff of 22 CAG repeats (average) to group **AR** genotypes. They did not find any association between **AR** (CAG)n genotype and breast cancer in women younger than 40 years of age. Rebbeck et al. (23) reported that the **AR** CAG-repeat could modulate **BRCA1**-associated breast cancer risk in a sample of 304 women who inherited germ-line **BRCA1** mutations. In their study, women with at least one CAG allele larger than 27, 28, or 29 repeats were diagnosed 0.8, 1.8, and 6.3 years, respectively, earlier than women carrying two alleles smaller than 27 repeats, which suggests also a higher susceptibility to breast cancer in women bearing long **AR** alleles and a **BRCA1** mutation. More recently, Dunning et al. (30) failed to observe a difference in susceptibility to breast cancer between women with 22 or less glutamine residues (i.e., ≤21 (CAG)n repeats) as compared with those with at least one allele with 23 glutamine residues or more (i.e., ≥22 (CAG)n repeats). When using a similar cutoff (i.e., ≤21 and ≥22 CAG repeats), we did not observe any association in the present sample (the ORs were not significantly different from 1.0, $P > 0.25$; even when comparing women with both alleles ≥22 CAG repeats with those with both alleles ≤21 repeats).

Interestingly, previous work on AR-associated risk of prostate disease also involved different **AR**-genotype categorization. Ingles et al. (17) reported an increased risk of prostate cancer in men carrying an allele with fewer than 20 CAG repeats compared with those

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**Fig. 1.** Three dimensional modeling of breast cancer risk estimates (OR) according to the AR (CAG)n repeat polymorphism. Allele 1 and allele 2 are expressed in absolute number of (CAG)n repeats, and estimated ORs have been calculated relative to women who have a median number of repetitions on each of their alleles (21 and 24 (CAG)n repeats for alleles 1 and 2, respectively). In a, ORs have been estimated using the matrix function approach (see “Results” section). In b, ORs have been estimated by use of a generalized additive model. The relation of the logit of the probability of breast cancer to the length of each allele and their interaction were fitted by smoothing (cubic) spline functions (45).
The results shown are ORs for women with short-allele AR genotypes (Short) using women with long allele genotypes (Long) as the reference group. Two methods for grouping AR genotypes were used, namely, the sum-of-alleles (short-allele genotypes having a sum of alleles of 39 or less and long-allele genotypes having 40 or more) and the absolute allele size (with short-allele genotypes having two alleles of 20 CAGs or less, and long-allele genotypes being all other genotypes); 95% CI for each OR is presented as well as the P of the relevant \( \chi^2 \) test when appropriate (\( \chi^2 \) inter.). Also shown are the absolute (\( n \)) and relative (%) number of participants in each category.

### Table 2 Association of AR (CAG)n polymorphism with breast cancer

<table>
<thead>
<tr>
<th>Sum-of-alleles cutoff</th>
<th>Allele’s absolute size cutoff</th>
<th>( n (%) )</th>
<th>( n (%) )</th>
<th>OR</th>
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<th>( \chi^2 ) ( P )</th>
<th>( n (%) )</th>
<th>OR</th>
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<tr>
<td>Short (sum \leq 39)</td>
<td>22 (9)</td>
<td>233 (91)</td>
<td>0.45 0.25–0.79 0.006</td>
<td>17 (7)</td>
<td>238 (93)</td>
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<tr>
<td>Long (sum &gt;39)</td>
<td>33 (18)</td>
<td>156 (82)</td>
<td>0.55 0.32–0.95 0.03</td>
<td>25 (13)</td>
<td>164 (87)</td>
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<td>232 (85)</td>
<td>0.50 0.30–0.83 0.007</td>
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<td>67 (89)</td>
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\( a \) Hosp. Cont., hospital controls; Pop. Cont., population-based controls. See “Materials and Methods.”

Evidence linking the number of polyglutamine repeats to androgenic activity thus appears to be consistent for both prostate and mammary cells: short glutamine tracts in the AR increases activity, whereas long glutamine tracts decreases the activity. This could be indicative of an intrinsic functional difference between AR variants as suggested by Tut et al. (35) as opposed to a difference in tissue response.

Our results combined with the available experimental evidence on the functional effects of the polyglutamine sequence in the modulator domain of the AR gene bring us to propose that, although breast cancer may be partly attributable to an overstimulation of mammary tissue by pro-cancer factors such as estrogens, it may also be influenced by another important mechanism involving decreased androgenic activity. Shorter alleles of the AR gene would be associated with a better response to circulating androgens, possibly resulting in better “repression” of breast cancer development and/or progression. Our observation of a stronger effect of the AR genetic variation in menopausal women as opposed to premenopausal women is noteworthy. This could explain why Spurdle et al. (24) did not find any association in young women. However, the biological explanation for this observation is still uncertain. This observation could simply indicate that the decrease in risk associated with short-allele AR genotypes is specific to late-onset breast cancer cases (i.e., after menopause).

Also, we found a stronger association between AR polyglutamine tract variation and breast cancer in women who had a surgically induced menopause. However, the number of cases and controls was small in these strata, and we think that these results should be taken with caution.
with caution. If this association is confirmed, further investigation of this phenomenon will be required to identify its biological relevance.

It is unlikely that significant biases could have interfered with the results of this study. We cannot exclude the possibility that our results could be explained by a confounder that was not taken into account in patient evaluation. However, it appears that our observations are not attributable to covariates that were measured as part of the study. Also, only consecutive incident occurrences of the disease were used as cases, eliminating the possibility of an alteration in the genotype frequencies caused by disease aggressiveness. Also, controls were matched for age and area of living, which should compensate for putative effects of differences in genotype frequencies in the population age groups or from one area to the other (urban versus rural). Furthermore, because all cases and controls originated from the same urban area (population, ~800,000) that is >95% French-Canadian, we do not expect strong differences in allele frequencies from one region to another within this area. Thus, we do not believe that these results could be attributable to genetic stratification between cases and controls or within the various subsets of risk factors. However, we think that our findings should be replicated in other Caucasian populations, as well as in non-Caucasian populations. Interestingly, in this study population, AR genotype frequencies and modes were in agreement with published frequencies in other Caucasian populations (21, 44), which suggests that our findings should apply to other populations.

Although genetic variation at the AR locus may be a novel factor in individual susceptibility to develop breast cancer in women, other factors involved in the disease process such as somatic mutational events, as well as other physiological or environmental factors. Our findings, if they are confirmed, could justify AR genotyping as a significant factor to take into account in studies aiming at identifying risk factors for breast cancer. Also, interactions of AR genetic variations with other known risks factors for breast cancer may provide interesting new insights into the etiopathology of this disease.

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Short Polyglutamine Tracts in the Androgen Receptor Are Protective against Breast Cancer in the General Population

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