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Modification of *BRCA1*-Associated Breast Cancer Risk by the Polymorphic Androgen-Receptor CAG Repeat

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Summary

Compared with the general population, women who have inherited a germline mutation in the *BRCA1* gene have a greatly increased risk of developing breast cancer. However, there is also substantial interindividual variability in the occurrence of breast cancer among *BRCA1* mutation carriers. We hypothesize that other genes, particularly those involved in endocrine signaling, may modify the *BRCA1*-associated age-specific breast cancer risk. We studied the effect of the CAG repeat-length polymorphism found in exon 1 of the androgen-receptor (AR) gene (*AR-CAG*). *AR* alleles containing longer CAG repeat lengths are associated with a decreased ability to activate androgen-responsive genes. Using a sample of women who inherited germline *BRCA1* mutations, we compared *AR-CAG* repeat length in 165 women with and 139 women without breast cancer. We found that women were at significantly increased risk of breast cancer if they carried at least one *AR* allele with ⩾28 CAG repeats. Women who carried an *AR-CAG* allele of ⩾28, ⩾29, or ⩾30 repeats were given a diagnosis 0.8, 1.8, or 6.3 years earlier than women who did not carry at least one such allele. All 11 women in our sample who carried at least one *AR-CAG* allele with ⩾29 repeats had breast cancer. Our results support the hypothesis that age at breast cancer diagnosis is earlier among *BRCA1* mutation carriers who carry very long *AR-CAG* repeats. These results suggest that pathways involving androgen signaling may affect the risk of *BRCA1*-associated breast cancer.

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Introduction

Inheritance of a germline mutation in the *BRCA1* gene (MIM 113705) is associated with an increased risk of developing breast cancer. However, there is also substantial variability in the ages at which breast cancers are diagnosed in *BRCA1* mutation carriers (Easton et al. 1995; Narod et al. 1995; Rebbeck 1999). These observations imply that germline mutations in *BRCA1* may be necessary to explain the Mendelian pattern of cancer in some families but may not be sufficient to completely describe the interindividual variability in the age-specific risk of cancer. The ability to effectively apply risk-prediction or cancer-prevention strategies in *BRCA1* carriers may therefore depend on knowledge of risk-modifying factors in addition to *BRCA1* mutation status.

Steroid hormone pathways regulate *BRCA1* expression (Gudas et al. 1995; Marks et al. 1997). Therefore, we hypothesize that allelic variation in genes governing hormonal signaling known to play a role in normal development and cancer risk may be involved in modification of *BRCA1*-associated cancer risk. For example, the androgen-receptor gene *AR* (MIM 313700), which functions as a ligand-dependent transcriptional activator in response to androgens, contains a highly polymorphic CAG trinucleotide repeat (*AR-CAG*) encoding glutamines in its first exon. The length of the *AR-CAG* polymorphism is inversely associated with the degree of transcriptional activation by the AR (Chamberlain et al. 1994; Kazemi-Esfarjani et al. 1995). Individuals with X-linked spinal and bulbar muscular atrophy (SBMA, Kennedy disease) have 40 or more *AR-CAG* repeats and manifest clinical androgen insensitivity (LaSpada et al. 1991). *AR* mediates breast tumor growth and progression (Zhu et al. 1997; Birrell et al. 1998). Increased *AR-CAG* repeat length has also been associated with decreased prostate cancer risk, presumably because of a decreased ability of androgens to stimulate transcription of genes involved in prostate growth (Hardy et al. 1996; Giovannucci et al. 1997; Ingles et al. 1997). However,

this result has not been replicated in all populations (Eeles et al. 1998). These findings suggest that *AR-CAG* repeat-length polymorphism may be involved in modifying the development of diseases caused by alterations in endocrine signaling.

Subjects and Methods

Subjects

A sample of 304 women who carry disease-associated germline *BRCA1* mutations was ascertained through families with a history of breast and/or ovarian cancer at Creighton University, the Dana Farber Cancer Institute, The University of Michigan, Fox Chase Cancer Center, The University of Pennsylvania, The University of Utah, and Women's College Hospital (Toronto) between 1978 and 1997. Women were self- or physician-referred because of a strong family history of breast and/or ovarian cancer. These women provided written informed consent for research under protocols approved by the institutional review boards at each institution. Of these 304 women, 165 (54%) were affected (mean age 40.5 years, range 21–73 years) and 139 (46%) were unaffected by breast cancer (mean age 44.5 years, range 19–89 years).

Genotype Analysis

All study participants provided peripheral blood samples from which genomic DNA was extracted according to standard protocols. We used PCR to amplify the *AR-CAG* trinucleotide repeat found in exon 1 of *AR,* as described elsewhere (Giovannucci et al. 1997). The *AR-CAG* repeat-length polymorphism was modeled in three ways to reflect two alternative hypotheses about the activity of *AR* in breast carcinogenesis. The first two models reflect the activity of specific alleles acting at the level of the breast epithelial cell to modulate androgen signaling. First, the shorter of the two repeat-length alleles for each subject was considered in a survival analysis model. For example, if an individual inherited alleles with 22 and 25 *AR-CAG* repeats, we considered the effect of the 22-repeat allele on breast cancer penetrance. This allowed us to evaluate whether having at least one short-repeat allele affected breast cancer penetrance. Second, the longer of the two repeat-length alleles for each subject was considered in the survival model. As before, this allowed us to evaluate whether having at least one very long allele affected breast cancer penetrance. The third model reflects the effect of the combined *AR* genotype as having endocrine or paracrine activity on levels of steroid hormones in breast carcinogenesis. This hypothesis was modeled by consideration of the mean allele repeat length as a measure of jointly considering both alleles in each individual.

Statistical Methods

Cox proportional hazards models were used to evaluate the difference in breast cancer penetrance across *AR-CAG* repeat lengths. To correct for nonindependence of observations among participants drawn from the same families, the robust variance-covariance estimation approach of Lin and Wei (1989) was used, as implemented in STATA (StataCorp., release 5). Participants were followed up (retrospectively) from birth until one of several events occurred. The primary event of interest was the first diagnosis of a primary invasive breast cancer (n = 165 54%). Participants with no prior breast cancer diagnosis were censored when they developed ovarian cancer (n = 40; 13%), had a prophylactic mastectomy or oophorectomy (n = 46; 15%) or died (n = 15; 5%)—or when none of these events had occurred by the end of the observation period (n = 38; 13%). All Cox proportional hazards analyses were undertaken with and without adjustment for three hormone-related risk factors: age at menarche, age at first live birth, and total number of full-term pregnancies (parity). Parity and age at menarche are the only factors on this list that have been previously suggested as modifiers of breast cancer risk in *BRCA1* carriers (Narod et al. 1995).

AR-CAG repeat length is known to be correlated with endocrine signaling. However, the *AR-CAG* repeat is continuously distributed, and there is no a priori point at which cutoffs may be applied to identify allele-specific risk groups. Therefore, sensitivity analyses were undertaken to compare *AR-CAG* genotype classes by use of the log rank statistic estimated from Kaplan-Meier models. Risk (hazard) ratios were estimated by using Cox proportional hazards models. These analyses involved dichotomizing the total sample by using cutpoints along the *AR-CAG* repeat-length distribution to compare women whose *AR-CAG* repeat allele was less than, greater than, or equal to the specified number of repeats. Cutpoints were made within the range of observed *AR-CAG* repeat lengths. First, the effect of having at least one very short allele was evaluated by comparing groups divided at repeat lengths $<15/\geq 15$ through $<25/\geq 25$, where the repeat-length cutpoint was determined by the shorter of a woman's two *AR* alleles. Analyses were undertaken in this range because few alleles with <14 *AR-CAG* repeats were observed. The 25-repeat allele was used as the upper cutpoint bound, because few shorter alleles with >25 repeats were observed. Second, the effect of having at least one very long allele was evaluated by comparison of groups divided at allele lengths $<20/\geq 20$ through $<30/\geq 30$, where the repeat-length cutpoint was determined by the longer of a woman's two *AR* alleles. The 30-repeat *AR-CAG* allele was used as the upper bound, because few 31- or 32-repeat alleles were observed in this sample (fig. 1). This

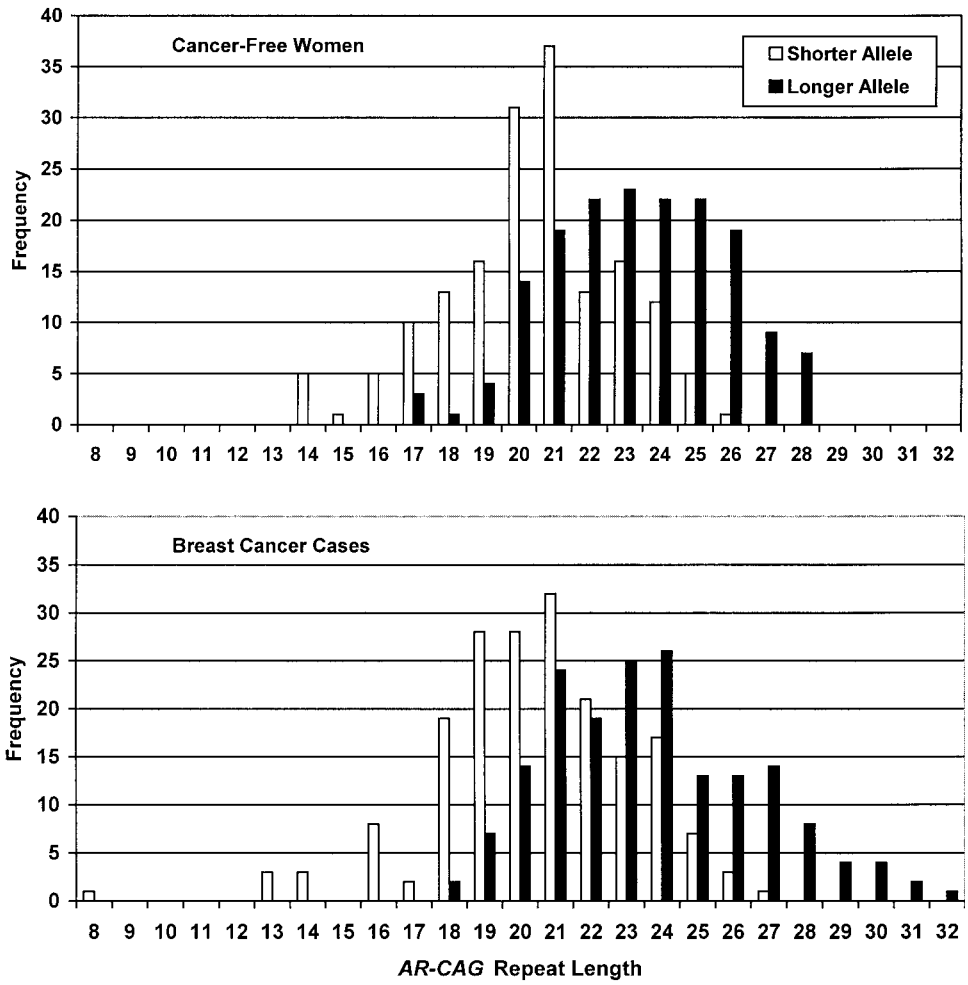

Figure 1 *AR-CAG* repeat-length distribution by breast cancer status

analysis allowed us to identify critical cutpoints along the continuous allele distribution for which breast cancer penetrance may be modified.

Results

We evaluated the effect of *AR-CAG* repeat length on breast-cancer penetrance in 304 women who carry germline mutations in the *BRCA1* gene. Mutations in *BRCA1* spanned the majority of the gene's coding region (ranging from Met1Ile to 5439delA). Mutations included 198 (65%) deletions (including large genomic deletions), 55 (18%) nonsense mutations, 31 (10%) insertions, and 20 (7%) disease-associated missense mutations. The three most commonly identified mutations were 185delAG (n = 49), Q1313ter (n = 33), and 5382insC (n = 26).

A frequency histogram depicting the observed distribution of *AR-CAG* repeat lengths is presented in figure 1. Although the distributions among cancer patients and cancer-free women are generally similar, we observed a skew in the distribution of breast cancer cases toward inheritance of at least one longer-repeat allele compared with cancer-free women. The median repeat length was 22 (range 8–32). The overall allele repeat distribution in our sample (including mean, median, and range) is similar to that of control populations reported elsewhere (Giovannucci et al. 1997; Hakimi et al. 1997). The median repeat length of the shorter allele carried by each individual was 21 (range 8–30). The median repeat length of the longer allele carried by each individual was 24 (range 17–32).

We found no simple association between breast cancer penetrance and continuous CAG repeat variables coded as mean repeat length (RR = 1.03, 95% CI 0.96–1.10), shorter repeat length (RR = 1.01, 95% CI 0.95–1.07), or longer repeat length (RR = 1.04, 95% CI 0.98–1.10). To identify points in the continuous *AR-CAG* repeat-length distribution associated with modified breast cancer penetrance, we performed sensitivity analyses using the shorter or longer of a woman's two alleles. No effect

of a woman's shorter *AR* allele was observed (fig. 2). In contrast, women who carried at least one long *AR-CAG* repeat allele (≥28 repeats) had a significantly earlier age at breast cancer diagnosis than women without one long-repeat allele (fig. 3). In the group of women who carried at least one allele with ≥28 repeats, we observed eight breast cancers (mean age at diagnosis 41.0 years) and four unaffected women (mean age at diagnosis 37.5 years) with 28-repeat alleles, four breast cancers (mean age at diagnosis 40.8 years) in women with 29-repeat alleles, and seven breast cancers (mean age at diagnosis 34.0 years) in women with ≥30-repeat alleles. There were no women in this study who carried two alleles with >28 repeats.

Estimates of hazard ratios (HRs) from Cox proportional hazards models indicated an increasing breast cancer penetrance as the repeat-length cutpoint increased (fig. 3). Women with ≥28 *AR-CAG* repeats ($n = 19$) developed breast cancer 0.8 years earlier than women who had only shorter alleles ($n = 146$; HR = 1.81, 95% CI 1.06–3.08). Similarly, women with ≥29 *AR-CAG* repeats ($n = 11$) developed breast cancer 1.8 years earlier than women who had only shorter alleles ($n = 154$; HR = 2.66, 95% CI 1.51–4.69), and women with ≥30 *AR-CAG* repeats ($n = 7$) developed breast cancer 6.3 years earlier than women who had only shorter alleles ($n = 158$; HR = 4.45, 95% CI 1.31–15.16). As indicated in figure 1, all women in our sample who carried at least one allele with ≥29 repeats were affected. All estimates presented here were made without adjustment for other potential confounding variables. However, inferences from survival analyses comparing *AR-CAG* repeats on breast cancer penetrance were identical in analyses that were unadjusted and adjusted for parity, age at menarche, age at first live birth, or ascertainment site. Note that the 24 individuals who carried at least one *AR-CAG* allele of ≥28 repeats included 20 unrelated women and two pairs of relatives (i.e., two relatives in each of two families, each pair carrying the same mutation). Five of the unrelated women in this group carried the same *BRCA1* mutation (185delAG).

It was not possible to conduct a complete evaluation of the effect of *BRCA1* mutation type given the extreme heterogeneity in the type and location of *BRCA1* mutations. However, we repeated our analyses including only women with at least one *AR-CAG* allele of ≥28 repeats by using a sample of women with unique *BRCA1* mutations. Our inferences were similar to those presented in figure 3: having at least one allele with 28 or more *AR-CAG* repeats (HR = 3.7, 95% CI: 1.6–8.4), 29 or more *AR-CAG* repeats (HR = 3.6, 95% CI: 1.3–9.8), or 30 or more *AR-CAG* repeats (HR = 4.5, 95% CI 1.1–18.1) remained significantly associated with breast cancer risk.

Discussion

We report that *AR-CAG* allele size is associated with breast cancer penetrance in *BRCA1* mutation carriers. Although the present association study is primarily hy-

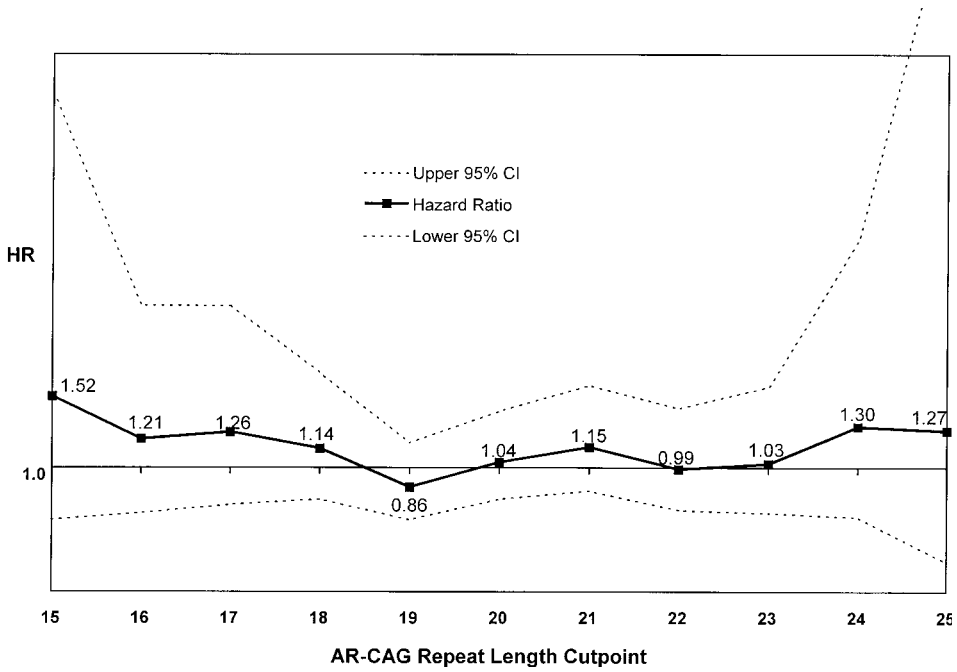

Figure 2 HRs associated with shorter *AR-CAG* repeat length among 304 *BRCA1* mutation carriers

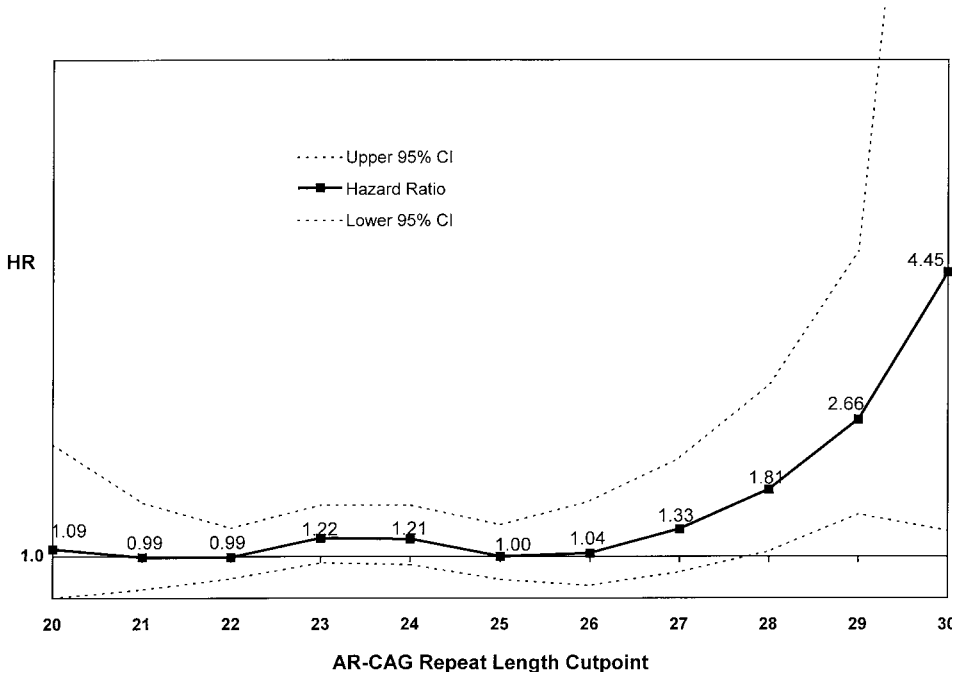

Figure 3 HRs associated with longer *AR-CAG* repeat length among 304 *BRCA1* mutation carriers

pothesis generating, there is a strong biological rationale for our findings. It is well known that *AR-CAG* repeat length modulates the transactivational activity of *AR* in vitro and is inversely associated with androgen sensitivity (LaSpada et al. 1991; Chamberlain et al. 1994; Kazemi-Esfarjani et al. 1995; Tut et al. 1997). The *AR* is expressed in normal breast epithelial cells and in some breast tumors, and it may be coexpressed with the estrogen and progesterone receptors in breast tumors (Hackenberg and Schulz 1996). Androgens are known to inhibit the growth of some breast cancer cell lines (Birrell et al. 1995). Ectopic *AR* expression leads to the inhibition of breast tumor–cell proliferation in response to androgens (Szelei et al. 1997). Although side effects have limited their use, androgens are effective in the treatment of women with metastatic breast cancer (Goldenberg et al. 1973). This information supports the hypothesis that decreased androgen activity associated with an increased number of *AR-CAG* repeats may result in increased breast cancer risk.

One means by which *AR* may act in breast tumorigenesis is by androgen signaling acting on the level of the mammary epithelial cell. Since *AR* maps to the X chromosome, breast epithelial cells in women express only one of the two *AR* alleles a woman has inherited. Thus, each cell is under the influence of only a single *AR* allele. Acting on knowledge of *AR* activity in breast cell proliferation, we hypothesize that decreased androgenic activity in breast cells expressing a very long *AR-CAG* repeat allele may result in increased breast epithelial cell proliferation. This increased proliferation may in turn affect the penetrance of breast cancer in *BRCA1* mutation carriers. In support of this hypothesis, Elhaji et al. (1997) have reported somatic mutations leading to a significant lengthening of the *AR-CAG* repeats in breast tumors from postmenopausal women. Thus, our finding of a relationship between the longer *AR-CAG* allele and breast cancer risk in *BRCA1* mutation carriers supports a model in which the effect is mediated at the level of the mammary epithelium in a cell-autonomous fashion.

An alternative to this hypothesis is an endocrine or paracrine mechanism for the action of *AR* in breast tumorigenesis. Androgens may modulate *BRCA1* risk via an endocrine mechanism by altering the levels of circulating hormones, such as estradiol, or via a paracrine mechanism involving effects mediated by the mammary stroma. For example, a recent epidemiologic study of the relationship between testosterone and breast cancer risk reported that decreased serum testosterone levels may have an indirect effect by influencing the bioavailability of estrogen (Zeleniuch-Jaquotte et al. 1997). Alternatively, androgens might act on the mammary stroma to indirectly affect the growth of the mammary epithelium. If either of these indirect mechanisms is mediating the effect of the *AR* polymorphism on *BRCA1* risk, the effect would be expected to be the result of the action of the *AR* in a number of cells, rather than in a cell-autonomous fashion, and thus would reflect the activity of both *AR* alleles. We modeled this effect of both

AR alleles as the average of the signal from the two alleles, and we found no support for this hypothesis. However, our ability to reject these hypotheses was limited, and we cannot rule out the possibility that endocrine or paracrine effects of androgens may affect breast cancer risk in *BRCA1* mutation carriers.

One limitation of the present study is that the participants carried a variety of *BRCA1* mutations, and we could not evaluate the effect of *BRCA1* mutation type or location on the present results. However, it is unlikely that the heterogeneity of *BRCA1* mutations affected the inferences of this study. Previous reports suggest that the location of the *BRCA1* mutation may, in part, determine breast versus ovarian cancer risk (Gayther et al. 1995). The data available from large consortia indicate that no differences exist in breast cancer risk by mutation location or type (D. Easton, personal communication). The common Ashkenazi Jewish mutations in *BRCA1* (i.e., 185delAG and 5382insC) confer approximately the same lifetime breast cancer risk (Struewing et al. 1997). In addition, the effect of *AR-CAG* repeat length among women who carried at least one longer allele of $\geqslant$28 repeats remained, even after limiting the sample to women who had unique *BRCA1* mutations. This suggests that *BRCA1* mutation type did not artificially induce the association of *AR-CAG* alleles and breast cancer risk. Given the extreme heterogeneity of mutations in *BRCA1*, it is unlikely that a comprehensive analysis of the effect of mutation location or type could be done. Furthermore, because the analyses were not limited to a particular class of mutations, the present results may be applicable to the general population of *BRCA1* mutation carriers from high-risk families. An additional limitation is that some individuals in the families studied here may have been excluded because they had died or were otherwise unable to participate in this research. As a result, the present results do not allow us to determine whether this effect implicates *AR* as an independent breast cancer risk factor or as a modifier of *BRCA1*-associated breast carcinogenesis.

Our results suggest that female *BRCA1* mutation carriers who have inherited at least one very long *AR-CAG* repeat may be diagnosed with breast cancer at a significantly earlier age than women who do not carry a very long *AR-CAG* repeat. Because the frequency of long *AR-CAG* repeats is rare, the *AR-CAG* repeat polymorphism may be relevant only to some *BRCA1* mutation carriers. However, the large magnitude of effect suggests that the personal impact on breast cancer risk to women who carry the very long repeats could be substantial. We conclude that the length of the *AR-CAG* repeat may affect the timing of breast cancer diagnosis in *BRCA1* mutation carriers, possibly through modulation of hormonal responses of individual mammary epithelial cells. However, these results are preliminary, and it is premature to consider knowledge about *AR-CAG* genotype in making clinical decisions about breast cancer risk, surveillance, or prevention among *BRCA1* mutation carriers.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Breast Cancer Information Core, http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/index.html (for *BRCA1*)
Genome Database, http://www.gdb.org/ (for *BRCA1* and *AR*)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *BRCA1* [MIM 113705] and *AR* [MIM 313700])

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