Modification of BRCA1- and BRCA2-associated Breast Cancer Risk by AIB1

Genotype and Reproductive History


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ABSTRACT

Women who have inherited a germ-line mutation in the BRCA1 or BRCA2 (BRCA1/2) genes have a greatly increased risk of developing breast cancer compared with the general population. However, there is also substantial interindividual variability in the occurrence of breast cancer among BRCA1/2 mutation carriers. We hypothesize that genes involved in endocrine signaling may modify the BRCA1/2-associated age-specific breast cancer penetrance. We studied the effect of alleles at the AIB1 gene using a matched case-control sample of 448 women with germ-line BRCA1/2 mutations. We found that these women were at significantly higher breast cancer risk if they carried alleles with at least 28 or 29 polyglutamine repeats at AIB1, compared with women who carried alleles with fewer polyglutamine repeats [odds ratio (OR), 1.59; 95% confidence interval (CI), 1.03–2.47 and OR, 2.85; 95% CI, 1.64–4.96, respectively]. Late age at first live birth and nulliparity have been associated with increased breast cancer risk. We observed increases in BRCA1/2-associated breast cancer risk in women who were either nulliparous or had a late age at first live birth and had AIB1 alleles no shorter than 28 or 29 or more AIB1 polyglutamine repeats (OR, 4.62; 95% CI, 2.02–10.56 and OR, 6.97; 95% CI, 1.71–28.43, respectively) than women with none of these risk factors. Our results support the hypothesis that pathways involving endocrine signaling, as measured through AIB1 genotype and reproductive history, may have a substantial effect on BRCA1/2-associated breast cancer risk.

INTRODUCTION

Heritance of a germ-line mutation in the BRCA1/2 genes is associated with an increased risk of developing breast cancer. However, there is also substantial variability in the penetrance of breast cancer in BRCA2 mutation carriers (1–3). These observations imply that germ-line mutations in BRCA1/2 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 BRCA1/2 carriers may therefore depend on the knowledge of risk-modifying factors in addition to BRCA1/2 mutation status.

There is substantial evidence that BRCA1/2-associated breast carcinogenesis is affected by steroid hormones. Epidemiological studies have reported that the penetrance of BRCA1- and/or BRCA2-associated breast cancer risk is associated with hormone-related exposures, including reproductive history (2, 4). Ablation of ovarian hormone exposure after bilateral prophylactic oophorectomy significantly decreases BRCA1-associated breast cancer risk (5). Genotypes involved in steroid hormone metabolism pathways, including the CAG repeat polymorphism found in exon 1 of the AR gene (5) modifies BRCA1-associated breast cancer penetrance. BRCA1 has also been shown to be a coactivator of the AR (6), and this activation may be mediated through the effects of p160 coactivators including SRC-1a, GRIP1, and AIB1 (7). AIB1 Online Mendelian Inheritance in Man (OMIM) accession no. 601937 is a member of the p160 family of transcriptional coactivators that interacts with steroid hormone receptors to enhance ligand-dependent transcription and is required for female reproductive function and mammary gland development (8). AIB1 was identified in a search for genes that are amplified in breast tumors (9, 10). Anzick et al. (10) determined that AIB1 was amplified in 10% and overexpressed in 64% of a series of 105 breast tumors. Bautista et al. (11) subsequently reported that AIB1 was amplified in 4.8% of another set of breast tumors. Those authors also reported that AIB1 enhanced estrogen-dependent transcription, suggesting that altered expression of AIB1 may influence the progression of steroid hormone-dependent cancers.

A glutamine-rich region exists in AIB1 between residues 1053 and 1123 that is encoded by a CAG repeat polymorphism (12). The analogous region of SRC1 interacts directly with the AR and is required for enhancement of AR signaling (13). Therefore, the CAG repeat polymorphism in AIB1 is likely to have a functional effect on steroid hormone signaling pathways. In contrast to BRCA1/2-associated breast cancer risk, studies to date of non-BRCA1/2-associated breast cancer risk have not found a relationship between germ-line AR variants (14) or specific AIB1 alleles in postmenopausal women (15). However, the results of Park et al. (6) and Irvine et al. (7) suggest that AR and possibly AIB1 may not play a role in breast carcinogenesis in the presence of an intact and fully functional BRCA1 protein. To determine whether allelic variation in genes governing hormonal signaling may be involved in modification of BRCA1/2-associated cancer risk, we evaluated whether germ-line variation in AIB1 was associated with the penetrance of BRCA1/2-associated breast cancers. We report that the polyglutamine repeat polymorphism in AIB1 is significantly associated with breast cancer risk in women who carry a
disease-associated germ-line mutation in BRCA1/2, and that this risk modification is associated with variation in reproductive history.

MATERIALS AND METHODS

Study Participants. A cohort of 656 women who inherited germ-line BRCA1/2 mutations was ascertained through families with a history of breast and/or ovarian cancer at Creighton University (Omaha, NE), the Dana-Farber Cancer Institute (Boston, MA), the University of Michigan (Ann Arbor, MI), Fox Chase Cancer Center (Philadelphia, PA), the University of Pennsylvania (Philadelphia, PA), the University of Utah (Salt Lake City, UT), or Women’s College Hospital (Toronto, Canada). These women were self- or physician-referred to risk evaluation clinics or hereditary breast cancer research studies because of a strong family history of breast and/or ovarian cancer and provided written informed consent for research under protocols approved by the institutional review boards at each institution. Of these women, 330 (50.3%) have been diagnosed with breast cancer.

To minimize the potential for biases using a retrospectively ascertained cohort, a nested case-control sample was generated using an incidence density sampling design. Women were included as breast cancer cases if they had developed an invasive breast cancer of any stage or grade. Women were excluded as cases if they had undergone prophylactic mastectomy or oophorectomy before the date of their breast cancer diagnosis. In addition, women were excluded as cases if they had a diagnosis of ovarian cancer before the date of their breast cancer diagnosis, because these women may have undergone treatments (e.g., oophorectomy) that may have changed their breast cancer risk. Control women were frequency-matched to cases on year of birth (±5 years), age, and mutation status (BRCA1 or BRCA2 mutation). Controls were excluded if they had ever undergone a prophylactic mastectomy or oophorectomy. The resulting case control sample of 448 women consisted of 278 breast cancer cases and 170 controls. The mean age of breast cancer diagnosis in cases was 39.7 years (range, 22–74 years) and the mean age of controls was 41.1 years (range, 19–71 years).

Genotype Analysis. Genotype analysis involved PCR amplification of a region of the AIB1 coding region beginning at residue 5390 and containing a track of 20–29 trinucleotide repeat alleles that encode polyglutamine residues. The repeat allele sequence studied was (CAG)6 CAA (CAG)9 (CAA CAG)4. The PCR amplification protocol consisted of 2.2 μl of 10× buffer (Qiagen), 4 μl of 10 mM deoxynucleotide triphosphates, (Pharmacia Biotech), 1.7 μl each of 10 μM primers (the forward primer labeled with HEX or FAM), 1 μl of Q solution (Qiagen), 0.3 μl of Taq polymerase, 2 μl of 20 ng/μl template DNA, and 9.0 μl of double-distilled water. The primers used for amplification were: forward, 5′-AGT CAC ATT AGG AGG TGG GC-3′; and reverse, 5′-TTC CGA CAA CAG AGG GTG G-3′. The amplified PCR products were analyzed on an ABI377 system using a 6% polyacrylamide gel. Alleles were sized by Genescan 3.0 software (Applied Biosystems). Several samples were sequenced to establish a key that converted PCR fragment length into polyglutamine repeat allele size.

Genotypes were categorized for analysis by allele size and frequency. As with other polyglutamine repeat length alleles (e.g., AR), the size of the repeat length may correspond with function (17, 18). Whereas the functional significance of alleles at AIB1 is not known, we hypothesize that repeat length may also have functional significance. To evaluate the effect of AIB1 polyglutamine repeat length on breast cancer risk, we divided the sample into two groups on the basis of the observed distribution of polyglutamine repeats in the sample. First, we compared women who had only alleles with 28 or more repeats compared with those who had one or more alleles of 27 repeats or fewer. Second, we compared women who had only alleles with 29 or more repeats with those who had one or more alleles of 28 repeats or fewer.

Statistical Methods. Unconditional logistic regression analysis was used to estimate the risk of breast cancer by AIB1 genotype and reproductive factors. Analyses were undertaken with adjustment for age, year of birth, and reproductive risk factors. These included age at menarche, total number of full term pregnancies (parity), age at first live birth. In addition, we considered a combined reproductive history class comparing women with an early age at first live birth versus women who were nulliparous or had a late age at first live birth to simultaneously consider the effects of parity and age at first live birth on breast cancer risk. Interactions between AIB1 genotype and other factors were modeled by stratifying across four categorical levels obtained from dichotomizing genotype (as defined above) and reproductive history (e.g., parous or nulliparous), using a single reference category as a baseline comparison group. Adjustment for age, year of birth, and reproductive history was also undertaken in the stratified and interaction analyses, although reproductive history variables involved in the stratification or interaction were not considered as a confounder in these analyses. Because we frequency-matched controls to cases on age, controls were nonsignificantly older than cases (41.1 versus 39.7 years; Kruskal-Wallis $\chi^2 = 1.9; df = 1; P = 0.168$). Although this insured that controls were at least as old as the diagnosis age of cases, all analyses were undertaken controlling for age to adjust for potential residual age effects. A score test for linear trend of the log odds (19) was used to evaluate whether there was a significant interaction trend of AIB1 and reproductive factors.

RESULTS

The AIB1 allele and genotype distributions are presented in Table 1. Because some individuals in this sample are related to one another, genotype frequencies should not be interpreted as reflecting population frequencies for this polymorphism. The most commonly observed alleles were the 26-, 28-, and 29-repeat alleles. Similarly, the 28/28, 28/29, and 29/29 genotypes were most commonly observed, with genotypes containing shorter (less than 26) or longer (more than 29) repeat lengths less common. The frequencies of the 26, 28, and 29 alleles in this sample were 14.0%, 38.2%, and 46.5%, respectively. The frequency of each of the other alleles was <1%.

AIB1 genotype was compared between 278 breast cancer cases and 170 matched controls. As presented in Table 2, women who carried at least one AIB1 allele of 28 or 29 or more repeats were significantly more likely to have breast cancer than women carrying shorter alleles (OR, 1.59; 95% CI, 1.03–2.47 and OR, 2.85; 95% CI, 1.64–4.96, respectively). Among cases, breast cancer was diagnosed at a mean age of 40.2 ± 9.0 years among carriers of at least one allele with 28 or more repeats and 38.4 ± 9.8 years among women with only shorter repeat alleles (Kruskal-Wallis $\chi^2 = 2.17; df = 1; P = 0.140$). Breast cancer was diagnosed at a mean age of 39.6 ± 8.2 years among carriers of at least one allele with 29 or more repeats and 39.8 ± 9.6

<table>
<thead>
<tr>
<th>Polypeptide repeat length</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
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<tbody>
<tr>
<td>20/28</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>22/28</td>
<td>2 (0.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>22/29</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>25/26</td>
<td>2 (0.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>26/26</td>
<td>6 (2.2%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>26/28</td>
<td>25 (9.0%)</td>
<td>20 (11.8%)</td>
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<tr>
<td>26/29</td>
<td>29 (10.4%)</td>
<td>29 (17.1%)</td>
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<tr>
<td>26/30</td>
<td>0 (0%)</td>
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<td>26/31</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>27/29</td>
<td>1 (0.4%)</td>
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| Cutpoint $<28^a$          |
|---------------------------|-----------|--------------|
| 28/28                     | 32 (11.5%)| 27 (15.9%)   |
| 28/29                     | 107 (38.5%)| 67 (39.4%)  |
| 28/30                     | 1 (0.4%)  | 0 (0%)       |
| 28/31                     | 0 (0%)    | 1 (0.6%)     |

| Cutpoint $<29^a$          |
|---------------------------|-----------|--------------|
| 29/29                     | 71 (25.5%)| 20 (11.8%)   |
| 29/30                     | 3 (1.4%)  | 0 (0%)       |

Total: 278, 170

* Denotes cutpoints used in the analyses presented in Tables 2 and 3.
years among women with only shorter repeat alleles (Kruskal-Wallis \[\chi^2 = 0.02; df = 1; P = 0.900\]).

To clarify further the relationship between repeat length and breast cancer risk, an analysis of trend was undertaken by defining three groups. These groups were defined by having a shorter AIB1 allele of <27 (i.e., “short” alleles), 27 or 28 (i.e., “medium” alleles), and ≥28 (i.e., “long” alleles). In this analysis, longer AIB1 repeat alleles were again associated with higher breast cancer risk. After adjusting for age at first live birth, parity, smoking status, and year of birth, we estimated this increased risk to be OR, 1.96 (95% CI, 1.25–3.08; P for trend = 0.0036). This corresponded to a 2-fold increase in breast cancer risk for each unit increase from the short to the medium to the long repeat-length groups.

Because AIB1 is thought to enhance hormone-dependent transcription, we also evaluated the effect of the AIB1 genotype across surrogate markers of endogenous hormone exposure as measured by reproductive history. As shown in Table 2, we observed no statistically significant effect of parity alone (nulliparous versus parous) or age at menarche (≥13 versus <13 years) on breast cancer risk in this sample. However, women who had a late age at first live birth (≥30 years) or were nulliparous were at significantly increased risk of breast cancer compared with women who had their first live birth before age 30 (OR, 3.06; 95% CI, 1.52–6.16). We also found significant differences in breast cancer risk across strata defined by AIB1 genotype and reproductive history (Table 3). An approximately additive interaction of age at first live birth and AIB1 genotype was observed, with effects as high as an OR of 4.62 or 6.97 in women who carried only long AIB1 repeat alleles (28 or 29 or more repeats, respectively) and who were nulliparous or had a late age at first live birth. These results were associated with significant tests for trend across levels of genotype and reproductive factors (\[\chi^2_{\text{TREND}} = 5.93; P = 0.015\) and \[\chi^2_{\text{TREND}} = 25.14; P < 0.001\) for menarche cutpoint made at polyglutamine repeat length longer than or equal to the indicated number, compared with genotypes containing only shorter number of repeats. AIB1 cutpoint made at polyglutamine repeat length longer than or equal to the indicated number, compared with genotypes containing only shorter number of repeats. AIB1 cutpoint made at polyglutamine repeat length longer than or equal to the indicated number, compared with genotypes containing only shorter number of repeats. AIB1 cutpoint made at polyglutamine repeat length longer than or equal to the indicated number, compared with genotypes containing only shorter number of repeats. AIB1 cutpoint made at polyglutamine repeat length longer than or equal to the indicated number, compared with genotypes containing only shorter number of repeats.

Our results implied that endocrine factors acting through reproductive hormone exposure and the AIB1 signaling pathway may be associated with increased breast cancer risk in women who have inherited germ-line mutations in BRCA1/2. Hormonal factors may modulate BRCA1-associated breast cancer risk by acting directly on the normal mammary epithelium to alter the initiation or progression of breast cancer. Alternatively, these factors may act through endocrine mechanisms to alter the levels of circulating hormones or via paracrine mechanisms involving effects mediated by hormonally responsive cells in the mammary epithelium or stroma.

It has been reported that AIB1 acts in concert with the ERs or ARs to mediate its endocrine effects. Anzick et al. (10) reported that AIB1 mediates the endocrine-signaling effects of estrogen exposure on breast epithelial or tumor cells. However, the majority of BRCA1-associated tumors are ER-negative (20). Therefore, our results suggest that if the effect of AIB1 in BRCA1 mutation carriers is mediated through ER, these effects must occur either when the premalignant breast cells express ER or alternatively through effects on AR or some other related hormone-signaling pathways. Bevan et al. (13) reported that the glutamine-rich region of the AIB1-related coactivator SRC1

"DISCUSSION"

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interacts directly with AR and is necessary and sufficient for enhancement of androgen-signaling capacity. Irvine et al. (7) reported that AR transactivation activity is dependent on AIB1 as a coactivator. We have reported previously that the CAG repeat polymorphism in exon 1 of AR modulates BRCA1-associated breast carcinogenesis (21), and suggests that androgen signaling may be involved in BRCA1-associated breast cancer risk. Both that study and the present report suggest that genes involved in endocrine signaling may modulate BRCA1/2-associated breast carcinogenesis. We are currently evaluating whether a combination of AIB1 and AR genotypes interact to modify BRCA1/2-associated breast cancer risk. However, more definitive information about the mechanisms underlying the association reported here must await the results of studies that define the relationship of the AIB1 polyglutamine polymorphism and AIB1 function.

We also report an effect of reproductive history on breast cancer risk in this sample. Breast cancer risk in the general population is affected by reproductive history (22). It is therefore plausible that these factors may also modify the occurrence of breast cancer in BRCA1/2 mutation carriers. Narod et al. (2) studied the effect of reproductive history in 333 women inferred from genetic linkage studies to be BRCA1 mutation carriers. They reported that breast cancer risk was modified only by low parity. Jernström et al. (4) reported a 70% increase in the risk of breast cancer among women diagnosed before age 40 who carried BRCA1/2 mutations. This result is in contrast to the statistically nonsignificant association we observed with parity alone in the present sample of breast cancer cases 22–74 years of age at the time of diagnosis. Using a small sample of putative BRCA1 mutation carriers, Chang-Claude et al. (23) did not identify any significant reproductive factors as breast cancer risk modifiers, although early age at menarche and late age at first live birth provided suggestive evidence for a modifying effect. In the present study, we infer that women who are either nulliparous or have had a late age at first live birth are at increased breast cancer risk, particularly if they carry an AIB1 genotype with 29 or more CAG repeats. These results suggest that endogenous exposure to hormones, as measured by reproductive history, affects BRCA1/2-associated breast cancer risk, and that the effects of age at first live birth and parity may be relevant when considering breast cancer risk in these women.

There were a number of limitations in the present analyses. First, the participants carried a variety of BRCA1/2 mutations, and we could not evaluate the effect of BRCA1/2 mutation type or location on the present results. However it is unlikely that the heterogeneous collection of BRCA1/2 mutations substantially influenced our inferences, and given the extreme heterogeneity of mutations in BRCA1/2, it is unlikely that a comprehensive analysis of the effect of mutation location or type could be carried out. Furthermore, by not limiting the analyses to a particular class of mutations, the present results may be applicable to the general population of BRCA1/2 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 distinguish whether this effect implicates AIB1 as an independent breast cancer risk factor or as a modifier of BRCA1/2-associated breast carcinogenesis.

Data are now becoming available about the function of specific AIB1 alleles that complement knowledge of the importance of this region in steroid hormone signaling (13). Patel et al. (24) found that the polyglutamine repeat length was associated with bone mineral density and that this association remained significant even when ER genotypes were considered. More recently, Jernström et al. (25) reported that AIB1 polyglutamine repeat length was associated with IGF-I levels among women who used oral contraceptives. Circulating IGF-I is strongly influenced by exogenous estrogen. This finding is consistent with that of Wang et al. (26), who demonstrated that AIB1-deficient mice had altered IGF-I expression. The finding that AIB1 polyglutamine repeat length may mediate the effect of exogenous estrogen to modulate IGF-I levels suggests that this polymorphism is functionally associated with estrogen signaling. Jernström et al. (25) concluded that the AIB1 polyglutamine repeat lengths reported here as being associated with breast cancer risk are more potent coactivators of estrogen signaling than others. These results support our inference that the length of the polyglutamine repeat is associated with BRCA1/2-associated breast cancer risk.

Analogous to studies of the CAG repeat polymorphism in AR (5), we created comparison groups based on the length of the polyglutamine repeats with the goal of studying genotype classes with longer or shorter repeat lengths. On the basis of the distribution of alleles presented in Table 1, it appeared that the primary source of the control differences is explained by the 29-repeat allele. In particular, the increased frequency of 29/29 genotype individuals was apparent in cases compared with controls, and there was a significant trend toward increasing risk with increasing repeat allele size (i.e., <27, 27 or 28, and >28). Because other alleles (i.e., those with <26, 27, or >29 polyglutamines) are rare, the creation of other genotype strata results in very small groups. Therefore, no statistically meaningful inferences could be made from an analysis of cutpoints other than those presented in Tables 2 and 3. As a result, it is also impossible to determine whether longer allele length is responsible for the reported effects, whether the effect is specific to the 29-repeat allele itself, or whether the 29-repeat allele is in linkage disequilibrium with some other relevant (but unmeasured) allele. Although a number of comparisons using other categorizations could have been considered, these analyses would be largely underpowered to detect relevant effects and would result in an increased number of hypothesis tests. Therefore, we have limited our analyses to the most prevalent and statistically meaningful genotype comparisons.

Finally, our primary analyses evaluated women with germ-line mutations in BRCA1 and BRCA2 together. However, it is apparent that these two genes confer different clinical and molecular phenotypes, and that comparisons should be made for each gene independently. Although our study design accounted for the potential of confounding by BRCA1 versus BRCA2 mutations by matching cases and controls by locus, analyses stratified on genotype were not possible as the majority of our sample (370 women, or 83%) consisted of BRCA1 mutation carriers. However, we undertook a subset analysis of BRCA1 mutation carriers only. In that subset, the OR effect of AIB1 genotypes with 29 or more repeats was 3.06 (95% CI, 1.54–6.08) in women who were nulliparous or who had an early age at first live birth and 9.25 (95% CI, 1.68–50.78) in women who had a late age at first live birth. These results suggest that the effect is consistent among the subset of BRCA1 mutation carriers in this sample. Additional evaluation should be undertaken to compare subsets of BRCA1 and BRCA2 mutation carriers separately and to explore why the effect of AIB1 on breast cancer risk may differ between BRCA1/2 mutation carriers and individuals in the general population (15).

We conclude that the length of the AIB1 repeat may affect breast cancer risk in women who have inherited a germ-line BRCA1/2 mutation, possibly through modulation of hormonal responses of the mammary epithelium. Our observations imply that germ-line mutations in BRCA1/2 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 BRCA1/2 carriers may therefore depend on knowledge of risk-modifying factors in addition to BRCA1/2 mutation...
status. However, additional research about AIB1 genotype will be required before it is possible to make clinical decisions about breast cancer risk, surveillance, or prevention among BRCA1/2 mutation carriers.

REFERENCES


