The joint effect of smoking and AIB1 on breast cancer risk in BRCA1 mutation carriers

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Women with BRCA1 mutations are at an elevated risk for breast cancer. AIB1 (NCOA3/SRC3) genotype and smoking may alter this risk. We examined the differences in breast cancer risk by AIB1 polyglutamine repeat polymorphism and pre-diagnosis smoking habits for BRCA1 mutation carriers to determine if there was an interaction between smoking and AIB1 genotype. Multivariate Cox proportional hazards regression was used with 316 female BRCA1 mutation carriers to model breast cancer risk. Ever having smoked was associated with a decreased breast cancer risk [Hazard Ratio (HR) = 0.63, 95% CI, 0.47–0.87]. A dose–response relationship between number of pack-years smoked and breast cancer risk was also found for women who smoked <20 pack years of cigarettes (HR = 0.72, 95% CI, 0.52–1.00) and for women who smoked ≥20 pack years (HR = 0.41, 95% CI, 0.23–0.71; P for trend = 0.0007). Women with a 28 repeat allele for AIB1 had a significantly reduced risk of breast cancer (HR = 0.72, 95% CI, 0.51–1.00). Women who smoked ≥20 pack-years with a 28 repeat allele had an even greater reduced risk of breast cancer (HR = 0.19, 95% CI, 0.07–0.54) compared to women who were never smokers with no 28 allele. Since AIB1 appears to modulate the effect of endogenous hormones via the estrogen receptor, and smoking affects circulating hormone levels, these results support evidence that steroid hormones play an important role in breast carcinogenesis in BRCA1 mutation carriers, and suggest mechanisms for developing novel cancer prevention strategies for BRCA1 mutation carriers.

Introduction

Women who have inherited a breast cancer susceptibility gene 1, BRCA1, mutation have a higher lifetime risk of developing breast or ovarian cancer than women without such a mutation (1–10). Breast cancer penetrance in women with a BRCA1 mutation is variable, however, and may in part be explained by other factors involved in breast carcinogenesis (6,11). Both environmental exposures and additional cancer susceptibility genes may alter the occurrence and timing of BRCA1-associated breast cancer.

Tobacco smoke is also a well-known carcinogen (12,13), but its relationship with breast cancer has been unclear. Studies have reported a higher prevalence of DNA adducts and p53 mutations in the breast tissue of smokers compared with non-smokers and these mutations are breast cancer risk factors (14–17). Cigarette smoking is also considered to have anti-estrogenic effects in women: early menopause, a decreased risk of endometrial cancer, and an increased risk of osteoporosis have all been reported at higher prevalences in smokers compared with non-smokers. (18–20) The direct relationship between cigarette smoking and breast cancer in epidemiologic studies, however, has been equivocal. For women in the general population, only smoking for long duration or prior to first term pregnancy may increase breast cancer risk (21,22). A recent prospective study reported that smoking was positively associated with estrogen receptor (ER)-positive breast cancer.(22)

Only a few studies have examined smoking as a risk factor for women with familial breast cancer (23–25). Brunet et al. (23) performed a matched case–control study of 186 BRCA1 and BRCA2 mutation carriers (including a subset of women in the present study), and reported a significant protective effect of smoking upon breast cancer risk. This study was expanded recently to >1000 matched case–control pairs but failed to replicate their earlier finding of a statistically significant protective effect of smoking on breast cancer risk in women with BRCA1/2 mutations (26).

A prospective study of women from high risk families, uncharacterized for BRCA1 or BRCA2 mutations, found smoking increased risk of breast cancer (24). Recently, Reynolds et al. (25) found active smoking increased breast cancer risk significantly in a cohort of California teachers, but smoking was not a significant risk factor for women who had a family

Abbreviations: BRCA1, breast cancer susceptibility gene 1; CI, confidence interval; ER, estrogen receptor; df, degrees of freedom; HR, hazard ratio; SNPs, single nucleotide polymorphisms.

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history of breast cancer. Given these discrepant results, it remains unclear if smoking significantly affects breast cancer risk, and if smoking may have a different effect in women who are inherently at a higher risk for breast cancer.

Likewise, a woman’s breast cancer risk may be dictated by genes that modulate estrogen effects. For example, the number of polyglutamine (CAG) repeats in the steroid receptor co-activator gene \( AIB1 \) (\( NCOA3/SRC3/AIB1 \)) has been found to modulate the risk of breast cancer in women with a \( BRCA1 \) or \( BRCA2 \) mutation (27,28), although another study failed to find an association (29). The association between \( AIB1 \) polyglutamine repeat length genotype in two studies of familial non-\( BRCA \) mutation carriers also did not find an association with increased breast cancer risk (30,31), but a study examining single nucleotide polymorphisms (SNPs) within the \( AIB1 \) coding region did find a significant association between SNPs Q586H and T960T with breast cancer in a German and Polish population (32). Another study examining \( AIB1 \) polyglutamine repeat length and breast cancer risk in women with familial breast cancer failed to find an association (30). The variability of results may reflect an interaction between \( AIB1 \) genotype, environmental factors, in different \( BRCA \) mutation carrier populations and/or may also be reflective of the way \( AIB1 \) polyglutamine repeat length is coded and analyzed across the studies.

\( BRCA1 \)-associated breast cancers are hormone-sensitive, as evidenced by the dramatic reduction in breast cancer risk observed after prophylactic oophorectomy (33). Because \( AIB1 \) is a co-activator that affects estrogen levels, (34–38) and smoking is considered to have potential anti-estrogenic effects, we evaluated the joint effect of smoking history and \( AIB1 \) genotype on breast cancer risk in women with \( BRCA1 \) mutations only. In particular, we limited our analysis to women with \( BRCA1 \) mutations only to increase the underlying homogeneity of our sample set and to focus the biological hypotheses, and re-examined the coding of the \( AIB1 \) repeat polymorphism, to determine the true effect that \( AIB1 \) genotype may have on breast cancer risk in these women.

Materials and methods

Study population

Women who were either physicians or self-referred to risk evaluation clinics for genetic testing, generally because of a strong family history of breast and/or ovarian cancer, were ascertained at multiple sites in the USA and Canada (Creighton University, Omaha, NE; the Dana-Farber Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; the University of Pennsylvania, Philadelphia, PA; and the Women’s College Hospital, Toronto, Canada) (27). Women were eligible for entry into the study cohort if they tested positive for a known deleterious mutation in \( BRCA1/2 \) (27,28), while others have suggested that 

\( AIB1 \) genotype was examined in relation to breast cancer risk in several ways. Some reports have suggested that \( AIB1 \) polyglutamine polymorphisms \( \geq 29 \) repeats increase risk for breast cancer in \( BRCA1/2 \) carriers (27,28), while others have suggested that \( \leq 26 \) repeats was associated with higher breast density (42). Given the potential increased risk for breast cancer for either length, the shorter \( \leq 26 \) repeat allele or the longer \( \geq 29 \) repeat allele, we examined breast cancer risk by \( AIB1 \) genotype, using the most common middle length allele 28 as the referent group. Then, because some of the genotypes were rare, we collapsed the genotypes into groups of women who have at least one 28 repeat allele compared to women who did not have any 28 repeat allele because this was the most common low-risk allele, similar to a method used by Wilkening et al. (30). This categorization was chosen based on observations in previous reports that women with a 29 allele seem to be at greatest risk and women with a 28 allele are at lower risk for breast cancer (27,28), and represents a different approach from our previous report (27).

To test for an interaction under a multiplicative model between \( AIB1 \) and smoking history on breast cancer risk we used \( 2 \log \) likelihood tests between regression models comparing the significance of a multiplicative interaction term combining smoking (yes/no) and \( AIB1 \) allele (\( \geq 28 \) repeat allele/ \( < 28 \) allele) variables. This interaction tests for deviation from a multiplicative statistical model between these two variables. The joint effect of \( AIB1 \) and smoking was also estimated for women with ever smoking exposure or heavy smoking exposure only \( ( \geq 20 \) pack-years) with the \( AIB1 \) repeat allele, and compared with women who had never smoked and had a referent \( AIB1 \) allele (reference group).

Results

Year of birth, age at interview, oral contraceptive use and menopausal status varied significantly by smoking and breast cancer status for the \( BRCA1 \) women in our sample (Table I). The frequency of other reproductive variables such as age at menarche, age at first pregnancy and parity did not vary significantly across all four groups of women.
Ever smokers had a significantly decreased risk of breast cancer (HR = 0.63, 95% CI, 0.47–0.87) after adjusting for year of birth, parity, menopausal status, height, oral contraceptive use, and Jewish ancestry in the Cox regression models (Table II). In addition, there was a dose-response relationship between number of pack-years smoked and breast cancer risk (<20 pack-years HR = 0.72, 95% CI, 0.52–0.1.00; ≥20 pack-years HR = 0.41, 95% CI,0.23–0.71; P for trend = 0.007). We also examined smoking as a time-dependent covariate, but as the point estimates for smoking and breast cancer risk did not vary substantially from those obtained with the fixed smoking variables (data not shown), and there was a reduction in power when using the time-dependent covariates and drop; we did not use the time-dependent covariates in further analyses.

Consistent with our previous report (27), the frequency of women with either BRCA1 or BRCA2 mutations and with 29 polyglutamine repeats for AIB1, differed significantly between those who had breast cancer and those who did not (x² = 8.59, 1 df, P = 0.0034) after adjustment for covariates. Also, consistent with our previous analysis with AIB1, BRCA1 mutation carriers with at least one 28 repeat allele had a reduced risk of breast cancer (HR = 0.72, 95% CI, 0.51–1.00) (Table III), after adjustment for year of birth, parity, height, menopausal status, oral contraceptive use and Jewish ethnicity. A further decrease in breast cancer risk was found in women having at least one AIB1 28 repeat allele and a positive smoking history (Table IV). Among the never smokers, women with at least one 28 repeat allele had a significantly
lower breast cancer risk than women with no 28 repeat allele (HR = 0.63, 95% CI, 0.40–1.00). Among women with no 28 repeat allele, those who had ever smoked had a statistically significant lower risk of breast cancer than women who had never smoked (HR = 0.57, 95% CI, 0.35–0.92). Ever smokers with at least one 28 repeat allele were at a significantly lower risk for breast cancer than never smokers with no 28 repeat allele (HR = 0.35, 95% CI, 0.21–0.58; P < 0.0001 for joint effect).

Women who were heavy smokers and had at least one 28 repeat allele had an even greater reduction in breast cancer risk, showing a highly significant difference in breast cancer risk compared with women who had never smoked and did not have a 28 repeat allele (HR = 0.19, 95% CI, 0.07–0.54; joint effect P = 0.002). The interaction term for AIB1 allele and smoking in the regression analysis did not deviate significantly from expectations under a multiplicative model for either ever smoking and AIB1 genotype (P = 0.69), or heavy smoking and AIB1 genotype (P = 0.81) (Table IV). Therefore, we conclude there is a strong joint effect of AIB1 and smoking on breast cancer risk in BRCA1 mutation carriers, and this effect is consistent with expectations of a multiplicative interaction between these two factors.

### Discussion

As an extension to our previous analysis where we found AIB1 genotype modulated breast cancer risk in women with BRCA1/2 mutations (27), we report here that smoking is associated with a decrease in breast cancer risk in a dose-dependent manner in our cohort of women with BRCA1 mutations only, and find evidence for a statistically significant joint effect between smoking and AIB1 genotype on breast cancer risk in these women with BRCA1 mutations. While data linking smoking and breast cancer risk in the general population have been inconsistent, it appears that an increase in number of pack-years smoked may have a protective effect in BRCA1/2 mutation carriers. This report suggests that the modulation of the effect of smoking on breast cancer risk may be due to variation in genotypes in estrogen regulatory genes in BRCA1 mutation carriers. A previous study examining the effect of smoking on breast cancer risk in women with BRCA1/2 mutations (23) included a subset of women in this study, and also found a highly protective effect of smoking. Smoking four pack-years or more was associated with a 50% reduction of breast cancer risk. Recently, however, a larger sample of including some of the same matched case-control study of BRCA1/2 mutation carriers as in the first study, reported no significant association between smoking and breast cancer (26), although there was evidence of a small, non-significant protective effect on breast cancer in heavy smokers (OR = 0.81, 95% CI, 0.57–1.15 for BRCA1/2 carriers who smoked ≥20 pack-years). The larger study also used a matched case-control study design and a large proportion of cases (>400) were excluded because a suitable control could not be found in the study; it also included both carriers of BRCA1 or BRCA2 mutations, whereas the present analysis is limited to BRCA1 carriers only and was analyzed as a retrospective cohort. A retrospective cohort study design provides a different approach to analyze the data because of the ability to account for censoring events, such as prophylactic surgeries and ovarian cancer which are common events in BRCA1 carriers that may alter breast cancer risk, without excluding unmatched women in the study. In addition, by using a cohort analysis, we are able to consider smoking exposures that occur prior to breast cancer diagnosis, unlike the study by Ghadirian et al. (26), where smoking history information was obtained for some cases after their breast cancer diagnosis.

Results from this study also suggest that different AIB1-CAG allele repeat lengths may have different effects upon BRCA1-associated breast cancer risk. Women with at least one 28 repeat allele appear to be at a lower risk for breast cancer in BRCA1 mutation carriers than women with longer repeat alleles (≥29 repeats) and possibly those with shorter repeat alleles (<26 repeats). AIB1 is thought to modulate the effect of endogenous hormones through ER activity (43–45). If AIB1 repeat length alters AIB1 protein function, AIB1 repeat length

### Table III. HRs for breast cancer in BRCA1 women by AIB1 genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Number of women with breast cancer (N = 176)</th>
<th>Number of women without breast cancer (N = 140)</th>
<th>Univariate HR (95% C.I.)</th>
<th>Multivariate HRs* (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/28</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>22/28</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>22/29</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>25/26</td>
<td>3</td>
<td>3</td>
<td>2.40 (0.62–9.37)</td>
<td>1.62 (0.37–6.54)</td>
</tr>
<tr>
<td>26/28</td>
<td>22</td>
<td>11</td>
<td>2.17 (1.14–2.42)</td>
<td>2.02 (1.03–3.95)</td>
</tr>
<tr>
<td>26/31</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>28/28</td>
<td>39</td>
<td>29</td>
<td>1.68 (1.02–2.78)</td>
<td>1.57 (0.91–2.70)</td>
</tr>
<tr>
<td>28/29</td>
<td>22</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29/30</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29/31</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No 28 allele</td>
<td>68</td>
<td>44</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>At least one 28 allele</td>
<td>109</td>
<td>96</td>
<td>0.69 (0.50–0.94)</td>
<td>0.72 (0.51–1.00)</td>
</tr>
</tbody>
</table>

* Cox proportional hazards models adjusted for year of birth, parity, height, menopausal status, oral contraceptive use and Jewish ancestry.

### Table IV. Multivariate HRs* of the joint effect between smoking and AIB1 repeat length alleles in women with a BRCA1 mutation

<table>
<thead>
<tr>
<th>Smoking exposure</th>
<th>N</th>
<th>No 28 allele N</th>
<th>At least one 28 allele N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>51</td>
<td>(1.0)b</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Ever Smokers</td>
<td>60</td>
<td>0.57</td>
<td>89</td>
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</tbody>
</table>

* Cox proportional hazards models adjusted for year of birth, parity, height, menopausal status, oral contraceptive use and Jewish ancestry.

Reference group.

Heavy smokers were women who reported ≥20 pack-years of smoking.

P

0.02

0.02

0.02
polymorphisms would affect ER transcriptional activity which could alter breast cancer susceptibility.

The association between AIB1 repeat allele length and breast cancer has been recently confirmed by another study examining the risk of breast cancer in BRCA1 mutation carriers (28). The authors examined the average length of AIB1 alleles in women with BRCA1 mutations and found that longer AIB1 alleles were estimated to be associated with a higher risk of breast cancer. This study also found a significantly increased risk of breast cancer in women who had two alleles with 29 or more repeats compared with women who had shorter repeat length alleles. Therefore, two studies suggest that BRCA1 mutation carriers with a 29 repeat allele have a higher risk of breast cancer than women with the common shorter 28 repeat allele. More research will be needed to determine if shorter repeat allele lengths for AIB1 affect breast cancer risk in BRCA1 mutation carriers as well.

We also found that women smokers with a BRCA1 mutation who had at least one 28 repeat allele in AIB1 genotype, were at significantly reduced risk for breast cancer. To extend this result, we also found that women with at least one 28 allele, who were heavy smokers (≥20 pack-years) had >5-fold reduction in breast cancer risk compared with non-smokers with no 28 allele. The joint effect between smoking and AIB1 was consistent with that of a multiplicative model. The joint effect between smoking and AIB1 accounts for a large part of the variability in breast cancer risk in women with BRCA1 mutations in this study.

How might smoking affect breast cancer risk in women with BRCA1 mutations? Recently, cigarette smoke condensates have been shown to induce the 2-hydroxylation pathway in estrogen metabolism, shunting a percentage of circulating estrogen away from the more potent 16α-hydroxylation pathway in mouse hepatoma cells (46). Thus, smoking may effectively decrease the circulating levels of the more carcinogenic estrogens. Their findings also suggested that cigarette-smoke condensates both bind to and activate the estrogen receptor and induce transcription, an effect that might increase breast cancer. It is unclear if these condensates could increase breast cancer risk with increased estrogen signaling or compete with estrogen for the ER. Given the multiple particulate substances in cigarette smoke, it is possible that cigarette smoke may have multiple effects on estrogen metabolism pathways.

Women with BRCA1 mutations tend to have estrogen receptor negative breast tumors (47,48); however, the diagnostic histopathology of a tumor may not be indicative of the effect of hormones on the etiology of a tumor. For example, prophyactic oophorectomy strongly reduces breast cancer risk in women with BRCA1 mutations (33). In addition, the regulation of BRCA1 in human breast cancer cells is hormonally dependent (49,50). BRCA1 has also been shown to inhibit the signaling of ligand-activated estrogen receptor in transfected cells, suggesting that mutations in BRCA1 disrupt the suppression of estrogen-dependent transcriptional pathways (51–53). Smoking has also been associated with the presence of ER negative tumors in both pre-menopausal and post-menopausal women (54,55). It is possible that in BRCA1 mutation carriers, heavy smoking exposure and AIB1 polymorphisms are jointly involved in common pathways involving ER activity and estrogen metabolism which may influence breast cancer risk.

Several factors in this study impact the generalizability of the results. The women in this study were ascertained from risk evaluation clinics and most likely presented because of a family history of breast and/or ovarian cancer, and thus the women who participated in this study may not be representative of all BRCA1 mutation carriers in the general population (56). However, these participants do represent the sample of women who are most likely to seek and receive genetic test results, and therefore the present results are relevant to the population of women most likely to have knowledge of their BRCA1 mutation status. There may also be a survival bias in this retrospective cohort, in that women who died quickly after developing breast cancer may not have been tested for BRCA1/2 mutations. If these women were disproportionately smokers, then the reduced risk of breast cancer measured in this study could be overestimated. However, large differences in breast cancer mortality due to smoking has not been reported (57,58), making it unlikely that such a survival bias would account for a large part of the risk reduction we have observed.

Birth cohort effects in smoking trends may influence the results if the heavy smokers were more likely to be older women. The regression models, however, adjust for birth year in a multivariate analysis to account for such trends. We also analyzed the data by birth cohort (<1940 and ≥1940) (59) and obtained similar results (data not shown). A possible limitation in this study is that we did not have information on the timing of exogeneous hormone replacement therapy use or about the specific preparations used by these women, and therefore we were unable to consider the effect of hormone replacement therapy prior to the development of breast cancer in these women.

The magnitude of the association, but not the direction, differs from our previous analysis of AIB1 repeat length and breast cancer risk in women with BRCA1 or BRCA2 mutations (27). A number of differences between the present study and our previous study could explain these differences. Given that the initiating events and risk may differ in women with mutations in BRCA1 and BRCA2 (10,60), in the present study we only evaluated the effect of smoking and AIB1 repeat length in women with mutations in BRCA1. Women with BRCA2 mutations were too small in number to analyze separately, and cancer risks and modifying effects of other factors may differ between BRCA1 and BRCA2 mutation carriers. In addition, the present study used Cox proportional hazards regression to estimate the time at risk for breast cancer, censoring events such as prophylactic removal of breasts or ovaries. Thus, we were able to avoid ‘matching’ cases to controls and thereby included a more complete cohort of women than was done in our case–control study of AIB1. These study design and analysis differences may explain why the magnitude of our association between AIB1 repeat allele length and breast cancer were attenuated. The main effects, however, remain the same; women with at least one 29 repeat allele have a higher breast cancer risk than women with a 28 repeat allele.

Even though smoking has been associated with a lower risk of some diseases, such as ulcerative colitis and endometrial cancer (18,61), the deleterious effects of cigarette smoking are well-documented. Lung, oral, esophageal and bladder cancer, not to mention non-cancerous diseases such as heart disease and cerebrovascular disease are strongly associated with cigarette smoking (62–65). Thus, our results should not be used to endorse the initiation of smoking for the prevention of breast cancer in BRCA1 mutation carriers. Rather, the results are useful in elucidating the mechanisms involved in breast cancer development. Determining the mechanisms by which smoking may exert an anti-estrogenic effect, its potential interaction...
with estrogen signaling pathways, and the potential for regulation of these effects by AIB1, should be a focus for future research. Understanding the pharmacogenetics of smoking and its relation to hormonal pathways may provide insights into new cancer prevention and control modalities in BRCA1 mutation carriers.

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