Variants in the ATM Gene Associated with a Reduced Risk of Contralateral Breast Cancer

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Abstract

Between 5% and 10% of women who survive a first primary breast cancer will subsequently develop a second primary cancer in the contralateral breast. The Women's Environment, Cancer, and Radiation Epidemiology Study was designed to identify genetic and environmental determinants of contralateral breast cancer (CBC). In this study, 708 women with asynchronous CBC served as cases and 1,397 women with unilateral breast cancer served as controls. ATM, a serine-threonine kinase, controls the cellular response to DNA double-strand breaks, and has been implicated in breast cancer risk. Complete mutation screening of the *ATM* gene in all 2,105 study participants identified 240 distinct sequence variants; only 15 were observed in >1% of subjects. Among the rare variants, deleterious alleles resulting in loss of ATM function were associated with a nonsignificant increase in risk of CBC. In contrast, carriers of common variants had a statistically significant reduction in risk of CBC. Four of these 15 variants were individually associated with a significantly decreased risk of second primary breast cancer [c.1899-55T>G, rate ratio (RR), 0.5; 95% confidence interval (CI), 0.3–0.8; c.3161C>G, RR, 0.5; 95% CI, 0.3–0.9; c.5558A>T, RR, 0.2; 95% CI, 0.1–0.6; c.6348-54T>C RR, 0.2; 95% CI, 0.1–0.8]. These data suggest that some alleles of ATM may exert an antineoplastic effect, perhaps by altering the activity of ATM as an initiator of DNA damage responses or a regulator of p53. [Cancer Res 2008;68(16):6486–91]

Introduction

ATM is a key regulator of cellular pathways protecting cells from malignant transformation that can result from exposure to genotoxic agents, such as ionizing radiation, which induce DNA double-strand breaks. Many of the proteins regulated either directly or indirectly by ATM phosphorylation such as BRCA1, CHEK2, FANCD2, or p53 have been implicated in the etiology of various cancers, including breast cancer, raising the possibility that genetic variation in *ATM* might modify the activities of these downstream substrates and affect cancer risk.

Rare, severely deleterious mutations in *ATM* are responsible for the autosomal recessive disorder, ataxia-telangiectasia (A-T; ref. 1). A-T is characterized by a progressive cerebellar ataxia, telangiectasias, oculomotor apraxia, immunodeficiency, hypersensitivity to ionizing radiation both *in vitro* and *in vivo*, and a significantly increased incidence of malignancies (2). Although A-T carriers are clinically asymptomatic for the disorder, an excess of breast cancer in mothers of A-T patients, who are obligate carriers, was first reported in the 1970s (3). Both retrospective and prospective studies of A-T families in the United States, as well as independent studies from the United Kingdom, France, and Scandinavia, also based on ascertainment for A-T, have provided confirmatory results (4–9). However, case-control studies of *ATM* mutations in patients ascertained for breast cancer have yielded less compelling findings. To date, none of these breast cancer studies that have performed generalized screening for *ATM* variation have been population-based and none have included a large series of patients with contralateral breast cancer (CBC). Studies that have been carried out in selected populations reveal a diverse array of *ATM* variants in human populations. The low frequency of individual *ATM* variants, and specifically, of the severely deleterious mutations observed in A-T families in which breast cancer co-occurs, has made it difficult to estimate the magnitude of the role of *ATM* in breast cancer risk in the population. Nevertheless, there is firm evidence that infrequent ATM truncating mutations (10) and certain missense mutations (11, 12) observed in A-T families and in families at high-risk for breast cancer, do impair ATM function and increase the risk for primary breast cancer.

The population-based Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study described here differs from previous studies of the role of *ATM* in breast cancer risk in that we restrict consideration to young women with a first primary breast cancer and then study the determinants for developing a second primary breast cancer in the contralateral breast (13). In

Note: A complete listing of the WECARE Study Collaborative Group appears at the end of this article.

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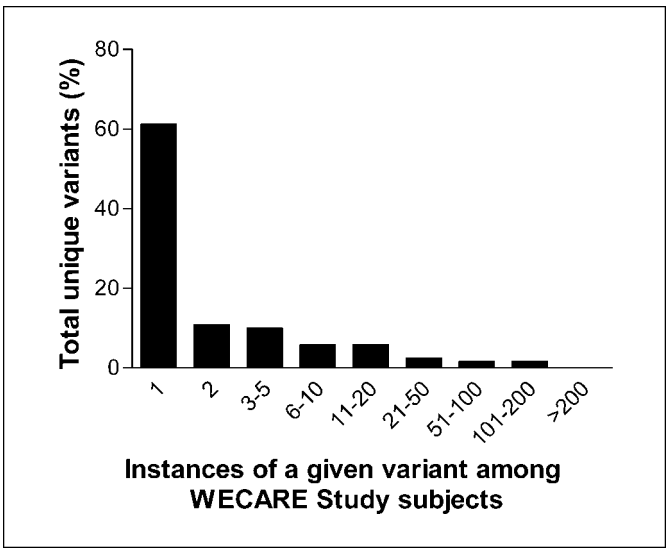

Figure 1. Distribution of ATM variants (n = 240) in the WECARE Study population.

this nested case-control study, cases were women with asynchronous CBC and controls were women diagnosed with unilateral breast cancer who were individually matched to cases by race, date of birth, registry, and date of diagnosis of first primary. Therefore, the control population represented the underlying population of breast cancer cases at risk for developing CBC, and the entire study population was enriched for genetic variants associated with breast cancer. We report here the results of screening all 2,105 participants in this study for variants in the *ATM* gene.

Materials and Methods

Study population. The WECARE Study is a multicenter, population-based, nested case-control study including 708 cases (women with asynchronous bilateral breast cancer) and 1,397 controls (women with unilateral breast cancer). All participants were identified, recruited, and interviewed through five population-based cancer registries, one registry covering all of Denmark and four in the United States covering, Iowa, three counties in Southern California (Los Angeles, Orange, and San Diego), and three counties in Washington State (King, Pierce, and Snohomish). Blood samples were obtained from all participants at interview. The study was reviewed and approved by local institutional review boards at each of these registry sites, and all biological samples and data were obtained under informed consent. The study design has been described in detail elsewhere (13).

Women with asynchronous bilateral breast cancer were eligible to be cases if they (*a*) were diagnosed between January 1, 1985 and December 31, 2000 with a primary invasive breast cancer that had not spread beyond the regional lymph nodes at diagnosis and a second primary *in situ* or invasive breast cancer diagnosed in the contralateral breast no earlier than 1 year after the first breast cancer diagnosis; (*b*) resided in the same study reporting area for both diagnoses; (*c*) had no previous or intervening cancer diagnosis; (*d*) were under 55 years of age at the time of diagnosis of the first primary breast cancer; and (*e*) were alive at the time of contact, able to provide informed consent, complete the interview, and provide a blood sample.

WECARE Study controls were individually matched to cases 2:1 on year of birth, year of diagnosis, registry region, and race. In addition, they met the following criteria: (*a*) diagnosed since January 1, 1985 with first primary invasive breast cancer while residing in one of the study reporting areas; (*b*) residing in the same study reporting area at the time of interview as when they were diagnosed with their breast cancer; (*c*) alive at the time of contact; (*d*) never diagnosed with a second primary breast cancer or any other cancer; (*e*) without prophylactic mastectomy of the contralateral breast. In addition, controls were countermatched to cases 2:1 on whether they had received radiation therapy (13).

The analyses reported here included 693 completed triplet sets consisting of two unilateral controls matched to a single asynchronous bilateral case, 11 matched case-control pairs, and 4 case-only sets. The frequency distribution of cases and controls was similar for age at reference date, race, registry, and duration of the at-risk period. Fifty-three percent of the WECARE Study population was recruited from the registries in Los Angeles and in Denmark, and the population was predominantly Caucasian.

Mutation screening. DNA for screening was prepared from blood samples by red cell lysis and phenol/chloroform extraction. All coding exons (exons 4–65) of the *ATM* gene along with flanking intronic sequences ranging from 50 to 100 nucleotides were screened for variation using denaturing high-performance liquid chromatography (DHPLC; ref. 14). Amplicons yielding variant results upon DHPLC analysis were evaluated by direct nucleotide sequencing. Two independent observers separately evaluated all output traces from both DHPLC and nucleotide sequencing. Discrepant readings were identified at data entry and re-tested until final resolution was obtained. Final database entries were further checked for internal consistency and cross-checked with prior reported mutations catalogued in the ATM mutation database.[12]

Screening was performed at four separate sites using a standard protocol and similarly configured DHPLC devices (Transgenomic, Inc.). Most matched case-control triplets were screened on the same 96-well plate in order to minimize the effects of any variation in screening efficiency or accuracy over the course of the study. Matched samples were always screened in the same laboratory, although the laboratories were blind as to the identities of samples and any matching information. Quality control was assessed by a blinded intralab re-screening of 10% of samples at each site and by a second blinded interlab re-screening of an additional 10% by a single reference site (14). Quality control samples were distributed throughout the course of the screening. Of the 25,854 re-screening assays performed, only 103 (0.39%) yielded discrepant results. All discrepancies were subsequently resolved by nucleotide sequencing.

Statistical analyses. To assess the association between carrier status and risk of developing second primary breast cancer, relative risks with corresponding 95% confidence intervals (CI), were estimated using conditional logistic regression. All models were adjusted for exact age and included a log-weight covariate in which the coefficient of this log-weight was fixed at one. These computed weights account for the sampling probability of countermatching (15), and are based on the number of radiation exposed and unexposed subjects within the sampled risk set. In each model, the relative risk was also adjusted for other remaining ATM variants so that the rate ratios were relative to wild-type. All analyses were conducted using SAS TPHREG.

A-T–causing mutations were classified as those variants meeting one or more of the following criteria: (*a*) changes predicted to result in truncation of the ATM protein whether by direct termination or frameshift, (*b*) changes affecting the two highly conserved nucleotides flanking exons that direct splicing, (*c*) changes predicted to result in amino acid substitutions for which there is documented evidence of both a deleterious effect on ATM function and identification in diagnosed A-T patients, or (*d*) changes documented as A-T–causing in the ATM Mutation Database.

SIFT (16) scores were calculated using a Clustal alignment of available vertebrate *ATM* sequences. Similar analyses were performed on the WECARE Study data set using PolyPhen (17). The scores generated by the two programs were highly correlated and there were no significant differences in the analyses performed using either system of variant classification. For SIFT analyses, carriers whose ATM sequence differed from wild-type at more than a single position were classified based on the highest scoring single variant position present.

[12] http://chromium.liacs.nl/LOVD2/home.php

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Table 1. Risk of developing second primary breast cancer associated with *ATM* gene carrier status

ATM variants classification	Cases (*n*)	Controls (*n*)	Rate ratio* (95% CI)
Overall			
Wild-type	271	480	1.0
Carrier of any ATM variant	437	917	0.8 (0.7–1.0)
Common †			
Wild-type	271	480	1.0
Carrier of any common ATM variant	355	778	0.8 (0.6–0.9)
Rare †			
Wild-type	271	480	1.0
Carrier of any rare ATM variant	148	264	1.0 (0.8–1.4)

*Adjusted for exact age at diagnosis of the first primary and countermatching weight. Common and rare models also adjusted for carriers of other remaining ATM variants.
† Common variants are defined as those carried by ≥1% of the WECARE Study participants. Rare variants are those carried by <1% of the participants.

Results

All 2,105 WECARE Study participants were screened for variants occurring in any of the 62 coding exons and flanking intronic sequences of *ATM*. A total of 2,153 variant sequences were identified, corresponding to 240 unique variants. The distribution was strongly skewed towards rare variants; fewer than half of the variants had more than a single occurrence in the study population (Fig. 1).

Consideration of the reported associations of breast cancer with obligate carriers ascertained from A-T families suggests that *ATM* alleles that increase risk for breast cancer would likely be (*a*) rare in the population, given the low population incidence of A-T; and (*b*) highly deleterious, given the absence of detectable ATM function in most A-T cell lines. However, consideration of the role of ATM in regulating the products of other genes implicated in cancer risk such as BRCA1, CHEK2, FANCD2, or TP53 makes no prediction as to the frequency of alleles of interest or the direction of their effect. Therefore, in analyzing the data derived from ATM screening in WECARE Study subjects, the effects of common variants, i.e., those with minor allele frequencies >1%, and rare variants, were considered separately. Because of the large size of the WECARE Study population screened, in contrast to past studies, it was possible to compare the distribution of individual or groups of variants to that for the reference wild-type sequence, allowing for either positive or negative effects on risk to be discerned.

Overall, compared with controls, cases (CBC) were less likely to be carriers of an *ATM* variant, although this difference was not statistically significant (Table 1). The observed difference was largely attributable to the effects of the 15 common variants, for which, as a group, there were significantly fewer carriers among cases as compared with controls (rate ratios, 0.8; 95% CI, 0.6–0.9). The proportions of carriers of rare variants did not differ between case and control populations.

We further examined the rare variant category, which would be expected to include all of the A-T causative alleles in the WECARE Study population. Considering only confirmed A-T–causing mutations in this category resulted in a modest but nonsignificant increase in the rate of CBC in comparison to participants with wild-type alleles (Table 2). These known A-T–causing variants are primarily rare frameshift or nonsense variants, whereas missense variants constitute the largest propor-

Table 2. Risk of developing second primary breast cancer associated with rare ATM variants

ATM variant classification	Cases (*n*)	Controls (*n*)	Rate ratio* (95% CI)
A-T–causing mutations			
Wild-type	271	480	1.0
A-T–causing †	14	13	1.4 (0.6–3.4)
Variants of unknown effect classified by SIFT ‡			
Wild-type	271	480	1.0
Deleterious	39	56	1.3 (0.8–2.2)
Tolerated	36	72	0.9 (0.6–1.4)

* Adjusted for exact age at diagnosis of the first primary, countermatching weight and for carriers of the other remaining ATM variants.
† Meeting one or more of the following criteria: (*a*) changes predicted to result in truncation of the ATM protein whether by direct termination or frameshifting, (*b*) changes affecting the two highly conserved nucleotides flanking exons that direct splicing, (*c*) changes predicted to result in amino acid substitutions for which there is documented evidence of both a deleterious effect on ATM function and identification in diagnosed A-T patients, or (*d*) changes documented as A-T–causing in the ATM Mutation Database.
‡ Defined by SIFT. Variants with normalized probabilities <0.05 are predicted to be deleterious, whereas those ≥0.05 are predicted to be tolerated. Results for missense variants are adjusted for other variants.

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Table 3. Risk of developing second primary breast cancer associated with common ATM variants

Variant*	Effect	dbSNP †	Cases, *n* (%)	Controls, *n* (%)	Rate ratio ‡ (95% CI)
c.378T>A	p.Asp126Glu	rs2234997	8 (1.1)	17 (1.1)	0.7 (0.2–2.0)
c.735C>T	Silent	rs3218674	21 (3.0)	40 (2.8)	1.0 (0.6–1.9)
c.1899-55T>G	Silent	rs4987943	34 (4.8)	121 (9.5)	0.5 (0.3–0.8)
c.2119T>C	p.Ser707Pro	rs4986761	20 (2.8)	30 (3.0)	1.0 (0.5–1.9)
c.2572T>C	p.Phe858Leu	rs1800056	14 (2.0)	42 (2.7)	0.5 (0.2–1.0)
c.3161C>G	p.Pro1054Arg	rs1800057	23 (3.2)	64 (4.7)	0.5 (0.3–0.9)
c.3285-10delT	Silent		8 (1.1)	15 (1.1)	0.8 (0.3–2.0)
c.4258C>T	p.Leu1420Phe	rs1800058	24 (3.4)	47 (3.4)	0.8 (0.4–1.4)
c.4578C>T	Silent	rs1800889	52 (7.3)	121 (9.0)	0.7 (0.5–1.1)
c.5497-8T>C	Silent	rs3092829	37 (5.2)	69 (4.9)	0.9 (0.5–1.4)
c.5557G>A	p.Asp1853Gln	rs1801516	173 (24.4)	339 (24.5)	0.9 (0.7–1.1)
c.5558A>T	p.Asp1853Val	rs1801673	4 (0.6)	30 (2.6)	0.2 (0.1–0.6)
c.5762+27G>A	Silent	rs3218673	8 (1.1)	22 (1.5)	0.6 (0.2–1.6)
c.6348-54T>C	Silent		3 (0.4)	19 (1.5)	0.2 (0.1–0.8)
c.8786+8A>C	Silent		39 (5.5)	99 (6.3)	0.7 (0.4–1.1)

NOTE: Variants carried by >1% of the WECARE Study subjects.
*Variants indicated relative to the reference sequence for the ATM Mutation Database (http://chromium.liacs.nl/lovd/refseq/ATM_codingDNA.html). Nomenclature as recommended by the Human Variome Project.
† rs numbers are provided for those SNPs currently listed in dbSNP.
‡ Adjusted for exact age at diagnosis of the first primary, countermatching weight, and for carriers of the other remaining ATM variants so that the rate ratio is relative to those for wild-type for ATM variants.

tion of the rare variants identified in the WECARE Study. Because few *ATM* missense variants have been the subject of functional studies, it is reasonable to assume that additional A-T–causing missense mutations may exist. To address this possibility, we used the software program SIFT (16) to classify the rare *ATM* missense variants into those likely to be deleterious or tolerated. In this analysis, having a deleterious variant was nonsignificantly associated with an increased rate ratio (Table 2).

For the common ATM variants, there were sufficient observations in the WECARE Study population to allow their individual assessment for association with CBC (Table 3). Four of these individual variants were associated with a significantly decreased risk of CBC and none were associated with a significantly increased risk (Table 3). Two of these variants, c.3161C>G (p.Pro1054Arg) and c.5558A>T (p.Asp1853Val), predict amino acid substitutions that would have deleterious effects on protein structure based on either SIFT (score = 0.00 for each variant) or PolyPhen (PSIC = 2.025, "probably damaging" for each variant; refs. 16, 17). Several of the negatively associated alleles were in linkage disequilibrium, suggesting that they may not have independent effects but no common haplotype containing all of these alleles could be defined. These common variants displayed no significant interaction with other risk factors such as age at diagnosis, family history, or treatment modality although power to evaluate interaction effects was only modest given the frequencies of these variants.

Discussion

Our findings suggest a model in which genetic variation in *ATM* has a more complex relationship with breast cancer risk than previously anticipated, which might explain some of the persistent difficulties in defining its role. In our studies, ATM alleles known to cause A-T, as well as other predicted deleterious missense alleles, which may also be A-T–causative, were associated with a modestly increased risk of CBC. These classes of alleles have been previously shown to be highly penetrant for first primary breast cancer (10, 12). Their rarity, however, undermines the importance of their contribution to population risk. More important from a population perspective is the novel finding we report here, that some ATM alleles seem to confer a protective effect, at least against CBC.

The current study differs from past studies of CBC in its population-based design, which allowed us to ascertain large numbers of women with CBC and potentially extrapolate our findings to the general population. The WECARE Study is limited to women who survived their breast cancer; results may have differed if women who were deceased but otherwise eligible could have been included. However, the source population for the WECARE Study consists of women with early stage breast cancer. Because the preponderance of the women in this population are cured of their cancer, they would be less susceptible to biased sampling based on breast cancer survival. Further strengths of our study include the comprehensive nature of ATM screening and the size of the population screened. Although these features allowed us to detect the main effects of several putatively protective alleles at ATM, we had only limited power to evaluate their statistical interactions with other risk factors. In particular, we were unable to incorporate information on treatment into our evaluation of the effects of these alleles due to instability of the risk estimates resulting from small numbers of observations.

A significant protective effect for CBC associated with ATM variants has not been previously reported and there are no current studies with comparable designs to WECARE that would allow for immediate replication testing of our findings. However, we note that in several smaller previously published studies of *ATM* and breast cancer (18–20), a similar trend was present for at least one of these same variant alleles, although it was not remarked upon. For most of the variants, the minor allele is too

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infrequent to observe any significant effects, but for one of the more common of these variants, c.3161C>G, there are relevant data from several studies. Broeks and colleagues, in a study of unmatched CBC cases and unilateral breast cancer controls, reported a higher frequency of carriers among controls (odds ratio, 0.47; 95% CI, 0.19–1.2; ref. 21). Although not statistically significant, this finding is consistent with our observations in the WECARE Study population. Two other studies have examined the incidence of this variant in primary breast cancer cases as compared with unaffected controls. Bretsky and colleagues (18) observed an increased number of carriers among control individuals (odds ratio, 0.61; 95% CI, 0.25–1.5) whereas Angele and colleagues (19) observed no significant difference (odds ratio, 1.07; 95% CI, 0.57–2.00). Finally, Einarsdottir and colleagues reported a reduced hazard ratio for c.3161C>G carriers (hazard ratio, 0.62; 95% CI, 0.16–2.46; ref. 22). Although none of these published studies are large enough to draw statistically significant conclusions regarding the role of this variant in breast cancer risk, the trends are consistent with our findings in the WECARE Study and raise the possibility that the reduced risk associated with this variant may apply to primary breast cancers as well as to CBC.

Given the prominent role of ATM in the mammalian cellular response to DNA damage, its role as a regulator of the tumor suppressor p53 as well as other proteins specifically involved in breast cancer risk such as BRCA1 or CHEK2, and the large number of *ATM* variants present in human populations, the observation of a range of effects, both positive and negative, on breast cancer risk at this single locus should not be entirely unexpected. However, it raises the important question of how the presence of specific alleles at *ATM* might reduce the risk of second primary breast cancer.

The presence of DNA double-strand breaks activates ATM, a process characterized by rapid dissociation of inactive ATM dimers and phosphorylation of the resulting monomers in trans (23). Active ATM has a number of antineoplastic effects, including the stabilization and accumulation of p53 (24–27), activation of cell cycle checkpoints, and induction of apoptotic programs (28). ATM can also be activated in the absence of DNA damage by agents, such as chloroquine, that relax chromatin (23). In such cases, ATM phosphorylates and stabilizes p53, leading to its accumulation, without activating additional biochemical pathways that are dependent on the recruitment of ATM to sites of DNA damage. Mice carrying supernumerary copies of p53 have been shown to resist the chemical induction of tumors while aging normally (29), and pretreatment of mice with chloroquine, activating ATM, has been shown to protect against chemically induced mammary carcinomas (30). Thus, allelic products that display increased sensitivity to activation or a higher basal level of activated ATM could reduce the risk of malignant transformation or the subsequent proliferation of transformed cells by increasing the endogenous levels of the tumor suppressor p53. The alleles described here might achieve this effect by increasing the total cellular amount of ATM, lowering its threshold for activation or increasing its kinase activity. Functional studies of ATM activity in cells from carriers of these variant alleles should help to resolve their effects.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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