Ataxia–telangiectasia gene (ATM) mutation heterozygosity in breast cancer: a narrative review

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ABSTRACT

Background Despite the fact that heterozygosity for a pathogenic ATM variant is present in 1%–2% of the adult population, clinical guidelines to inform physicians and genetic counsellors about optimal management in that population are lacking.

Methods In this narrative review, we describe the challenges and controversies in the management of women who are heterozygous for a pathogenic ATM variant with respect to screening for breast and other malignancies, to choices for systemic therapy, and to decisions about radiation therapy.

Results Given that the lifetime risk for breast cancer in women who are heterozygous for a pathogenic ATM variant is likely greater than 25%, those women should undergo annual mammographic screening starting at least by 40 years of age. For women in this group who have a strong family history of breast cancer, earlier screening with both magnetic resonance imaging and mammography should be considered. High-quality data to inform the management of established breast cancer in carriers of pathogenic ATM variants are lacking. Although deficiency in the ATM gene product might confer sensitivity to DNA-damaging pharmaceuticals such as inhibitors of poly (ADP-ribose) polymerase or platinum agents, prospective clinical trials have not been conducted in the relevant patient population. Furthermore, the evidence with respect to radiation therapy is mixed; some data suggest increased toxicity, and other data suggest improved clinical benefit from radiation in women who are carriers of a pathogenic ATM variant.

Conclusions As in the 2017 U.S. National Comprehensive Cancer Network guidelines, we recommend high-risk imaging for women in Ontario who are heterozygous for a pathogenic ATM variant. Currently, ATM carrier status should not influence decisions about systemic or radiation therapy in the setting of an established breast cancer diagnosis.

Key Words Genetic testing, ataxia–telangiectasia, breast cancer, gene panel assays

INTRODUCTION

Multigene panel testing for the stratification of breast cancer risk is a topic of great controversy in the fields of genetics and medical oncology. Commercially available gene panels are increasingly used to test for CHEK2, ATM, TP53, PALB2, and several other pathogenic gene variants in women in whom a hereditary predisposition to breast cancer is suspected; however, the clinical implications of some of those variants are unknown1,2.

In this narrative review, we outline the clinical implications of one particular gene that is tested in most gene panel assays—the ATM gene. Despite the fact that heterozygosity for a pathogenic ATM variant is present in 1%–2% of the adult population3–5, clinical guidelines to inform physicians and genetic counsellors about the optimal management of such individuals are lacking. Hence, we describe the challenges and controversies in the management of women who are heterozygous for a pathogenic ATM variant with respect to screening for breast cancer and other malignancies, to choices for systemic therapy, and to decisions about radiation therapy.

DISCUSSION

Pathophysiology and Clinical Presentation

Ataxia–telangiectasia (AT) is a rare neurodegenerative disease that results in cerebellar ataxia, oculomotor
abnormalities, telangiectasias, immune deficiency, sino-pulmonary infections, radiosensitivity, and an elevated risk of cancer\textsuperscript{4–12}. Individuals affected by AT are most prone to lymphoid malignancies in childhood, but they are also at risk for developing epithelial cancers later in life\textsuperscript{1}. Cancers of the breast, lung, gastrointestinal and genitourinary tracts, brain, and parotid have been described, but their incidences are poorly understood\textsuperscript{3,5,7,13–15}.

Given that AT\textsuperscript{M} is associated with an autosomal recessive pattern of inheritance, only individuals with 2 faulty copies are affected by this neurodegenerative disease. The incidence of the condition in the United States is approximately 1 per 88,000 live births\textsuperscript{2}. In contrast, heterozygosity for a pathogenic AT\textsuperscript{M} variant is present in 1\%–2\% of the adult population\textsuperscript{3–5}. Those individuals are phenotypically normal, but their risk for breast cancer is higher than that in the general population by a factor of approximately 2–3\textsuperscript{3,6–18}. Assuming a baseline risk of approximately 1 in 10 (10\%)\textsuperscript{21}, the risk increase translates into a 20\%–30\% lifetime risk of breast cancer among North American women. Hence, the penetrance of pathogenic AT\textsuperscript{M} variants, compared with pathogenic BRCA\textsuperscript{1} variants, which result in a 45\%–80\% lifetime risk of breast malignancy, is considered moderate\textsuperscript{22,23}.

Differences in the reported risk for breast cancer among women who are heterozygous for a pathogenic AT\textsuperscript{M} variant can potentially be attributed to differing study designs and study populations and to the specific gene variants being assessed. As a result, three recent meta-analyses reported different pooled estimates of breast cancer risk in carriers of pathogenic AT\textsuperscript{M} variants\textsuperscript{18–20}. In a meta-analysis of the three largest published cohort studies, the relative risk of breast cancer in AT\textsuperscript{M} carriers was 2.8 (95\% confidence interval (ci): 2.2 to 3.7; \textit{p} = 4.7 \times 10^{-11})\textsuperscript{18}. All patients were relatives of individuals with the AT syndrome\textsuperscript{18}. In a second meta-analysis of four studies, all of which included only patients who belonged to an AT family, the relative risk of breast cancer was 3.04 (95\% ci: 2.06 to 4.48; \textit{p} < 0.000001)\textsuperscript{19}. Finally, a larger but more heterogeneous meta-analysis of nineteen studies suggested that, by age 80, the cumulative risk of breast cancer among carriers of pathogenic AT\textsuperscript{M} variants is 32.83\% (95\% credible interval: 24.55\% to 40.43\%)\textsuperscript{20}, approximately 3 times the baseline population risk. In that particular study, AT\textsuperscript{M} variants that were unlikely to be pathogenic were excluded, but a familial link to the AT syndrome was not required\textsuperscript{20}.

Historically, testing for pathogenic AT\textsuperscript{M} variants has been limited. However, with the current popularization of gene panel assays, more data about the prevalence of those variants among women with a suspected hereditary predisposition for breast cancer have become available. In a recent prospective study of 1046 patients who were BRCA1- or BRCA2-negative and at high risk for hereditary breast or ovarian cancer, 3.8\% (\textit{n} = 40) were found to harbour an alternative pathogenic gene variant\textsuperscript{24}. After CHEK2, AT\textsuperscript{M} was the second most frequent variant identified, and it accounted for more than 25\% (\textit{n} = 11) of identifications\textsuperscript{24}. In the largest gene panel study to date, the prevalence of pathogenic AT\textsuperscript{M} variants in 35,409 women with a first diagnosis of breast cancer was approximately 0.9\%\textsuperscript{25}.

Breast Cancer Risk—Does the Type of AT\textsuperscript{M} Variant Matter?

More than 300 different AT\textsuperscript{M} variants have been identified thus far, and hence, the clinical significance of any individual variant can be challenging to assess\textsuperscript{26}. Most variants that cause the AT syndrome result in truncation of its protein product\textsuperscript{27}, but at least 170 missense variants have been identified\textsuperscript{28}. In a meta-analysis, no difference in the pooled frequency of AT\textsuperscript{M} missense variants were evident in cases compared with controls\textsuperscript{28}, but the V2424G variant is still thought to be pathogenic\textsuperscript{29–32}. In fact, some literature suggests that the V2424G missense variant portends a particularly high risk of breast cancer, reaching a cumulative risk of 52\% (95\% ci: 28\% to 80\%) at 70 years of age\textsuperscript{31}. That estimate is based on 7 women with a V2424G missense variant in a study that enrolled a total of 3743 women with breast cancer\textsuperscript{31}. In another analysis of 15 families, the V2424G AT\textsuperscript{M} variant increased breast cancer risk by a factor of 8.0, but the confidence intervals were wide, and the risk was not significantly higher than that for families with other variants (\textit{p} = 0.053)\textsuperscript{32}. As in subgroup analyses of clinical trials, analyses of these “subsets” of patients with particular AT\textsuperscript{M} variations must be interpreted with caution; estimates of breast cancer risk are imprecise, and other risk factors (such as family history and modifying genetic variants) are often unaccounted for\textsuperscript{33–39}.

Given that the V2424G missense variant has been evaluated in a methodologically more rigorous case–control screening study, AT\textsuperscript{M} c.7271T\textgreater\textasciitilde6 (V2424G) was included in an unprecedented analysis of 10 rare genetic variants (in addition to 3 PALB2 and 6 CHEK2 variants) by the Breast Cancer Association Consortium\textsuperscript{40}. Among 42,671 patients with invasive breast cancer and 42,164 control subjects, the AT\textsuperscript{M}V2424G variant was found in 12 patients and 1 control subject, resulting in an odds ratio risk estimate of 11.0 (95\% ci: 1.42 to 85.7; \textit{p} = 0.0012)\textsuperscript{40}. Although the risk was statistically significant, the ci was wide, and the prevalence of this specific variant was very low (0.028\%)\textsuperscript{40}.

ASSESSMENT AND DIAGNOSIS

Screening for Breast Cancer in Carriers of Pathogenic AT\textsuperscript{M} Variants

Apart from guidelines published by the U.S. National Comprehensive Cancer Network, which suggest high-risk breast cancer screening for women with a pathogenic AT\textsuperscript{M} variant\textsuperscript{41}, most clinical practice guidelines lack recommendations specific to this population. Further, the cut-offs for high-risk breast cancer screening vary around the world, ranging from 20\% to 30\%\textsuperscript{41–45}. In Ontario, for example, a high-risk screening program includes women with highly penetrant pathogenic gene variants (for example, BRCA1 and BRCA2) and those who are at 25\% or greater lifetime risk of developing breast cancer\textsuperscript{42}.

With the possible exception of the V2424G variant\textsuperscript{31}, which might be considered a high-risk gene variant, AT\textsuperscript{M} is considered to afford a moderate lifetime risk of breast cancer for which management is unclear\textsuperscript{39}. A recent counselling framework in the United States suggests annual mammography or magnetic resonance imaging (MRI), or both, in addition to routine breast examination, for women...
who are heterozygous for a pathogenic ATM variant “in the presence of a clear family history” of breast cancer. However, guidelines in other countries can differ based on locally accepted thresholds for high-risk screening.

In Ontario, we recommend an adapted approach to high-risk screening for carriers of a pathogenic ATM variant, similar to that presented in the 2017 National Comprehensive Cancer Network guideline and the recommendations published by Tung et al. Women who are heterozygous for a pathogenic ATM variant should undergo yearly mammographic screening starting by at least 40 years of age because their lifetime risk of breast cancer is likely greater than 25%; for women who also have a strong family history of breast cancer, earlier initiation of high-risk screening with both MRI and mammography should be considered.

In light of our recommendations, we acknowledge that the method of breast cancer screening for carriers of a pathogenic ATM variant has been debated. Although women with the at syndrome are known to be sensitive to ionizing radiation, and although in vitro studies suggest a similar effect in women with heterozygosity, the clinical relevance is unknown. Hence, carriers of a pathogenic ATM variant who qualify for high-risk screening based on a 25% or higher lifetime risk of breast cancer still qualify for annual MRI and mammography. Although avoidance of radiation by eliminating annual mammography might theoretically be safer, the reduced sensitivity of single-modality MRI examination was compared with combined screening with mammography and must be considered in high-risk individuals.

Given that the interpretation of ATM heterozygosity can be challenging, with more than 170 potential missense variants and numerous protein-truncating mutations, a genetics consultation for women with a pathogenic ATM variant is recommended to inform management.

Screening for Other Malignancies

The AT syndrome has been linked to several other malignancies, including colon cancer, pancreatic cancer, and lung cancer. Easton identified a higher risk of other (non-breast) cancers with a relative risk of 1.9 (95% CI: 1.5 to 2.5) when pooling the results of four studies, but inconsistent estimates and significant heterogeneity were limiting factors. Apart from some evidence of an increased risk of colorectal cancer (relative risk: 2.54; 95% CI: 1.06 to 6.09) and pancreatic cancer, a significant risk of cancer outside the breast has not been demonstrated. The evidence to support colorectal cancer-specific screening in the setting of ATM heterozygosity is insufficient, and hence, management should be tailored according to personal risk factors and family history.

Despite the lack of evidence for colorectal cancer screening, there is evidence for pancreatic cancer screening. A study of 138 breast cancer patients treated with adjuvant radiation therapy after lumpectomy for T1 or T2 tumours did not reveal superior clinical outcomes in the 20 women with ATM sequence variations. However, only 7 of the variants were truncating in nature, and they were not confirmed to be pathogenic.

Thus, the evidence about radiation therapy in carriers of a pathogenic ATM variant is mixed: some data suggest increased toxicity, and other data suggest improved clinical benefit. One study suggested that the risk of contralateral breast cancer might be increased in carriers of ATM missense mutations who receive adjuvant radiotherapy compared with those who do not, but those findings were not substantiated. ATM status should therefore not be used to make treatment decisions with respect to radiotherapy.

TREATMENT

Adjuvant Chemotherapy for Breast Cancer

ATM encodes a kinase that is involved in the repair of DNA double-strand breaks. It signals the phosphorylation of DNA damage-response pathways, including BRCA1 and TP53; hence, deficiency in the ATM gene product might confer sensitivity to DNA-damaging pharmaceuticals such as inhibitors of poly (ADP-ribose) polymerase or platinum agents. The benefit of those agents has not been confirmed in clinical studies assessing carriers of a pathogenic ATM variant, and currently, standard-of-care treatment should be provided based on clinical and pathology variables.

Adjuvant Radiation Therapy for Breast Cancer

Patients with the at syndrome are sensitive to the effects of ionizing radiation. In fact, those treated with conventional doses of radiation therapy for lymphoid malignancies are at risk for severe radionecrosis. Although data in mice and cell cultures suggest increased radiosensitivity in ATM mutation carriers, the risk of radiation toxicity is difficult to approximate in patients given the lack of high-quality randomized data. Some studies suggest a particularly high risk of radiation-induced toxicity among individuals with 2 concurrent ATM variants, those with low ATM protein levels, and those with specific ATM polymorphisms; however, such data are exploratory in nature.

Opposing evidence suggests that radiation therapy might, in fact, be particularly effective in carriers of a pathogenic ATM variant because of their deficiency in DNA mismatch repair mechanisms. Among 43 patients with stage I or II breast cancer and a single ATM variant (known to be pathogenic because of a family history of the AT syndrome), 14 received adjuvant radiation therapy, and 29 did not. After a median 72-month follow-up period, recurrences were observed in 1 of the 14 of women treated with radiation (7%) and in 14 of the 29 women who were not so treated (48%). A study of 138 breast cancer patients treated with adjuvant radiation after lumpectomy for T1 or T2 tumours did not reveal superior clinical outcomes in the 20 women with ATM sequence variations. However, only 7 of the variants were truncating in nature, and they were not confirmed to be pathogenic.

Thus, the evidence about radiation therapy in carriers of a pathogenic ATM variant is mixed: some data suggest increased toxicity, and other data suggest improved clinical benefit. One study suggested that the risk of contralateral breast cancer might be increased in carriers of ATM missense mutations who receive adjuvant radiotherapy compared with those who do not, but those findings were not substantiated. ATM status should therefore not be used to make treatment decisions with respect to radiotherapy.

SUMMARY

Pathogenic ATM variants are found in 1%–2% of the population, doubling to tripling the risk of breast cancer in carriers. Given that the lifetime risk of breast cancer in those individuals is likely greater than 25%, women who are heterozygous for a pathogenic ATM mutation should start annual mammographic screening at least by age of 40 years; earlier onset of screening with both mammography and MRI should be considered if indicated based on family history. At this time, ATM mutation heterozygosity should not influence the choice of systemic therapy, nor a decision...
for or against therapeutic radiotherapy. Future prospective studies, international registries, and consortia such as the Evidence-Based Network for the Interpretation of Germline Mutant Alleles are required to better understand the risks and therapeutic implications of ATM heterozygosity in breast cancer screening and treatment.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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