HHS Public Access

Author manuscript

Int J Radiat Biol. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Int J Radiat Biol. 2017 October ; 93(10): 1121–1127. doi:10.1080/09553002.2017.1344363.

ATM, radiation, and the risk of second primary breast cancer

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Abstract

Purpose—It was first suggested more than 40 years ago that heterozygous carriers for the human autosomal recessive disorder Ataxia-Telangiectasia (A-T) might also be at increased risk for cancer. Subsequent studies have identified the responsible gene, Ataxia-Telangiectasia Mutated (*ATM*), characterized genetic variation at this locus in A-T and a variety of different cancers, and described the functions of the ATM protein with respect to cellular DNA damage responses. However, an overall model of how *ATM* contributes to cancer risk, and in particular, the role of DNA damage in this process, remains lacking. This review considers these questions in the context of contralateral breast cancer (CBC).

Conclusions—Heterozygous carriers of loss of function mutations in *ATM* that are A-T causing, are at increased risk of breast cancer. However, examination of a range of genetic variants, both rare and common, across multiple cancers, suggests that *ATM* may have additional effects on cancer risk that are allele dependent. In the case of CBC, selected common alleles at *ATM* are associated with a reduced incidence of CBC, while other rare and predicted deleterious variants may act jointly with radiation exposure to increase risk. Further studies that characterize germline and somatic *ATM* mutations in breast cancer and relate the detected genetic changes to functional outcomes, particularly with regard to radiation responses, are needed to gain a complete picture of the complex relationship between *ATM*, radiation and breast cancer.

Keywords

ATM; breast cancer; Ataxia-Telangiectasia; radiation therapy; allelic heterogeneity

Introduction

The Ataxia-Telangiectasia Mutated (*ATM*) gene, which is mutated in the autosomal recessive genetic disorder Ataxia-Telangiectasia (A-T) (Savitsky et al. 1995), encodes a master regulator of the cellular response to DNA double strand breaks, whether these result from endogenous agents such as reactive oxygen species or external agents such as ionizing

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

radiation. Involved in both the sensing and signaling of the presence of DNA double strand breaks, ATM mediates critical cellular decisions regarding the response to genotoxic insults, which may include activation of cell cycle checkpoint machinery, application of DNA repair, or initiation of apoptosis (Lavin 2008).

The ATM gene and protein

In humans, the *ATM* gene maps to chromosome 11q22.3 and includes 69 exons of which 65 are coding (Gatti et al. 1988, Uziel et al. 1996). The predominant *ATM* transcript is more than 13,000 nucleotides in length and encodes a 3056 amino acid protein of approximately 370 kD in size. ATM is a member of the phosphatidylinositol 3-kinase-related protein kinase (PIKK) family which includes other proteins, such as ATR and DNA-PK, that are also involved in DNA damage responses (Bakkenist and Kastan 2004). There are a limited number of conserved domains mapped in ATM of which the most important is the C-terminal serine/threonine kinase domain which mediates much of the signaling function of ATM. The kinase domain is flanked by FAT and FATC domains indicating sequence similarity with the related proteins FRAP and TRRAP (Bosotti et al. 2000). At the N terminal end of ATM is a TAN domain involved in telomere length maintenance (Seidel et al. 2008) and an array of repeated HEAT motifs (Andrade and Bork 1995) that may facilitate the formation of large protein complexes.

ATM exists in cells as an inactive dimer. In the presence of DNA double-strand breaks, ATM transitions to an active monomeric form, a transition that is rapid, occurring in less than a minute from break induction, and coincident with a trans-autophosphorylation event on serine 1981 (S1981) (Bakkenist and Kastan 2003). While S1981 phosphorylation is often used as a marker of ATM activation, there are other non-canonical activation pathways for ATM, responding to stimuli such as chromatin relaxation (Bakkenist and Kastan 2003, Kanu and Behrens 2007), reactive oxygen species (Guo et al. 2010) or replication stress (Stiff et al. 2006, Yajima et al. 2009), which can result in the production of active ATM monomers without the characteristic phosphorylation on S1981, or active, but disulfide linked, ATM dimers. Site specific mutagenesis studies of serine 1987 in murine Atm, the analogous position to S1981 in humans, phosphorylation at this site is not essential for Atm activation (Pellegrini et al. 2006). ChIP studies in human cells suggest that the primary role of S1981 phosphorylation may be to promote retention of activated ATM monomers at the sites of DNA double strand breaks (Berkovich et al. 2008). Upon activation, ATM phosphorylates hundreds of substrates (Matsuoka et al. 2007), preferentially targeting serine and threonine residues when followed by a glutamine. These substrates include many of the key proteins involved in sensing, signaling and repairing DNA double-strand breaks as well as other proteins with roles in diverse cellular processes from metabolism to transcriptional regulation.

ATM mutations and disease

ATM was originally identified based upon its mutation in A-T, a disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasias, oculomotor apraxia, imunodeficiency, elevated serum alpha fetoprotein, hypersensitivity to ionizing radiation and a high incidence of cancer, primarily of lymphoid origin (Gatti et al. 1991). Cells from A-T

patients, upon exposure to ionizing radiation or radiomimetic chemicals, display increased numbers of DNA double strand breaks and impaired survival in clonogenic assays (Taylor et al. 1975). A-T results from bi-allelic deleterious mutations in *ATM* that, in most cases, result in the production of low or undetectable levels of ATM protein. Of the 1345 mutations reported from A-T patients listed in the *ATM* Mutation Database (www.lovd.nl/ATM) greater than 80% are predicted to truncate the protein with no obvious clustering in specific regions of the gene.

A-T patients have a high incidence of lymphoid cancers typically developing in the first two decades of life. Older patients have an elevated risk for solid tumors including breast and gastric cancers. It was first recognized 40 years ago that female first degree relatives of A-T patients had an elevated incidence of breast cancer (Swift et al. 1990, Swift et al. 1987, Swift et al. 1976). Subsequent studies of high risk breast cancer families have revealed statistically significant associations between heterozygosity for loss of function mutations in the *ATM* gene (i.e. mutations that are usually A-T causing) and breast cancer (Renwick et al. 2006). More recently, similar associations with germline *ATM* mutations have also been observed in familial gastric and pancreatic cancers (Helgason et al. 2015, Roberts et al. 2012). Given that the products of a number of genes already implicated in breast cancer risk such as *BRCA1*, *BRCA2*, *TP53*, *PALB2*, *CHEK2* and *NBN* are either directly phosphorylated by ATM, or are dependent on ATM function for their radiation-induced phosphorylation, a role for *ATM* mutations in breast cancer risk, particularly in radiation exposed individuals, is highly plausible.

Somatic mutations in the *ATM* gene also occur in cancer, and are particularly characteristic of certain lymphoid cancers such as mantle cell lymphoma and T pro-lymphocytic leukemia where bi-allelic *de novo ATM* mutations are observed (Schaffner et al. 2000, Stankovic et al. 2001, Stilgenbauer et al. 1997, Stoppa-Lyonnet et al. 2000, Stoppa-Lyonnet et al. 1998, Vorechovsky et al. 1997). The COSMIC database (http://cancer.sanger.ac.uk/cosmic) indicates that *ATM* is mutated in a wide array of cancers and tissues (Forbes et al. 2015). However, the distribution of mutations is strongly biased towards missense substitutions (approximately 67% of all mutations) and thus distinct from the distribution of germline mutations reported in A-T patients where truncating mutations predominate.

The discordance between the predominant loss of function mutations detected in A-T patients and A-T carriers who develop breast cancer and the predominantly missense somatic mutations observed in some cancers is noteworthy. Given that certain lymphoid cancers are associated with biallelic mutations in *ATM* yet A-T carriers are not at increased risk for these cancers (Stankovic, et al. 2001, Stoppa-Lyonnet, et al. 1998, Vorechovsky, et al. 1997), it seems likely that the mutations contributing to these disorders are functionally distinct from those that contribute to A-T. We have previously proposed a model for *ATM* action in cancer that assumed that truncating mutations in the *ATM* gene were functionally distinct from missense mutations (Gatti et al. 1999). Several newer studies provide suggestive support for such a model. A missense mutation, c.7271T>G, in *ATM* has been described that results in an atypically mild form of A-T but carries significant risk of breast cancer, comparable to that for BRCA2 (Bernstein et al. 2006, Stankovic et al. 1998). In the mouse, homozygous truncating mutations that mimic mutations observed in human A-T

patients are viable, but missense substitutions at critical residues for the kinase activity of Atm lead to genomic instability and embryonic lethality (Daniel et al. 2012, Yamamoto et al. 2012), demonstrating that at least selected missense substitutions can have distinct phenotypic effects from null mutations.

Contralateral breast cancer

Breast cancer patients are 2–5 times more likely to develop contralateral breast cancer (CBC) than are women without breast cancer to develop an initial breast cancer (Bernstein et al. 1992). Women at higher risk for CBC include those with a first primary at an early age (Chen et al. 1999, Li et al. 2003), lobular histology in a first primary (Bernstein, et al. 1992, Claus et al. 2003, Donovan 1990, Horn and Thompson 1988, Horn et al. 1987, Prior and Waterhouse 1978), and/or a family history of breast cancer (Bernstein, et al. 1992, Donovan 1990, Horn, et al. 1987, Kelsey et al. 1993, Peto and Mack 2000, Prior and Waterhouse 1978). The risk of developing CBC can be modified by therapies for the first primary. Women treated with radiation therapy have an increased risk of CBC: risk is proportional to increasing dose and inversely related to age at exposure. Multiple studies have demonstrated that *BRCA1* and *BRCA2* mutation carriers have substantially greater risk of CBC than non-carriers (Ansquer et al. 1998, Begg et al. 2008, Gershoni-Baruch et al. 2000, Malone et al. 2010, Pierce et al. 2000, Robson et al. 1998, Robson et al. 1999, Steinmann et al. 2001, Verhoog et al. 1999, Verhoog et al. 2000, Verhoog et al. 1998). However, the vast majority (90–95%) of all breast cancer cases are not carriers of *BRCA1* or *BRCA2* mutations (Campeau et al. 2008). Finally, other risk factors for UBC have also been shown to affect the risk of CBC, including reproductive factors (Largent et al. 2007), menarche age (Largent, et al. 2007), body size (Brooks et al. 2012, Li et al. 2009), alcohol consumption (Knight et al. 2009, Li, et al. 2009), and smoking (Knight, et al. 2009). In a recent study, reduction of mammographic density (MD), one of the strongest risk factors for UBC, was shown to relate to a significantly reduced risk of CBC (Li, et al. 2009). The context of CBC creates a unique opportunity to explore the role of *ATM* in breast cancer risk both because of the ability to incorporate well-defined information on radiation exposure from treatment and that any mutation that is associated with breast, cancer but rare in the general population, will be more prevalent in a sample of breast cancer patients.

The Women's Environmental, Cancer, and Radiation Epidemiology (WECARE) Study

The WECARE Study is an international, population-based, case-control study designed to identify the genetic and environmental factors contributing to asynchronous CBC. The study population consists of 708 case subjects, women with CBC, and 1399 control subjects, women with unilateral breast cancer (UBC). Two controls were individually matched to each case on age at diagnosis, length of follow up, registry reporting region, and race and/or ethnicity. For statistical efficiency, controls were further counter-matched on radiation exposure (Bernstein et al. 2004). All women in the WECARE Study were interviewed and complete medical treatment history information was collected. For all women who received radiation therapy for their first primary breast cancer, the radiation dose to the contralateral breast was reconstructed from treatment records and radiation measurements via simulations using patient-specific phantoms (Stovall et al. 2008). Blood samples were obtained from all women and the extracted DNA was used to complete full mutation screening of the *ATM*

(Bernstein et al. 2003), *BRCA1* and *BRCA2* genes (Borg et al. 2010, Malone, et al. 2010), partial screening for *PALB2* (Antoniou et al. 2014, Tischkowitz et al. 2012) and *CHEK2* (Mellemkjaer et al. 2008) and a genome-wide association study (manuscript in preparation).

Radiation therapy and CBC risk in the WECARE Study

Results from the WECARE Study, as well as reports from others, indicate that women receiving radiation therapy for a first primary breast cancer have an increased risk of developing CBC (Bernstein, et al. 1992, Bertelsen et al. 2008, Boice et al. 1992, Gao et al. 2003, Hooning et al. 2008, Stovall, et al. 2008). Among WECARE CBC cases, the mean cumulative absorbed radiation dose to the quadrant of the contralateral breast where the second tumor developed was 1.1 Gy (range=0.02–6.2 Gy), corresponding to an average absorbed dose per fraction of 44 mGy. Women less than 40 years of age with a greater than 1.0 Gy absorbed dose to the tumor specific quadrant of the contralateral breast had a significantly increased risk of CBC relative to those unexposed, (RR = 2.5, 95% CI 1.4–4.5). This risk was inversely related to age at first exposure and dose dependent. Across all cases, the most common tumor site for second cancers was the upper outer quadrant of the breast. However in women receiving radiation therapy for a first cancer there was a significant increase in tumors occurring in the inner and central quadrants (P = 0.03). This shift in tumor location is consistent with the gradient of radiation exposure across the contralateral breast where absorbed doses decrease from the inner region (Mean = 1.9 Gy, range 0.2–7.7) to the central (Mean = 1.2 Gy, range 0.1–3.8) to the outer (Mean = 0.8 Gy, range 0.1–2.5) region (Stovall, et al. 2008).

ATM and the risk of CBC

The WECARE Study provides a unique opportunity to examine the main effects of genetic variation at *ATM* on risk for CBC as well as the joint effects of *ATM* and radiation therapy on risk. Mutation screening of the *ATM* gene in all 2105 WECARE Study participants by a tiered approach using denaturing high performance liquid chromatography followed by sequencing, identified 240 distinct sequence variants, most of which (225 of 240) were rare, occurring in less than 1% of subjects (Concannon et al. 2008). Among the rare variants, A-T causing variants, defined as those that either had been previously identified in A-T patients or were predicted to result in protein truncation, were associated with a non-significant increase in the risk of CBC (RR = 2.0, 95% CI = 0.7–5.9). Rare missense variants were associated with a modest, but non-significant increase in risk (RR = 1.2, 95% CI = 0.8–1.7). Using the bioinformatic tools SIFT (Kumar et al. 2009) or PolyPhen (Adzhubei et al. 2010) to classify these missense variants into those likely to be tolerated or deleterious did not reveal any statistically significant main effects on CBC risk for either group. In contrast to these results obtained for rare *ATM* variants, carriers of common variants, overall, had a statistically significant reduction in risk of CBC (RR = 0.8, 95% CI = 0.6–0.9). Four common variants were individually associated with a significantly decreased risk of second primary breast cancer (c.1899-55T>G, RR = 0.5, 95% 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).

Incorporating radiation dosimetry into the analyses of *ATM* genetic association with CBC in the WECARE Study revealed a more complex interaction. Women in the WECARE Study who carried any rare *ATM* missense variant predicted to be deleterious using either SIFT or PolyPhen, and who received radiation therapy for their first cancer, had a significantly elevated risk of CBC compared with unexposed women who carried the reference *ATM* sequence (< 1.0 Gy dose to the contralateral breast: RR = 2.8, 95% CI = 1.2 to 6.5; ≥1.0 Gy: RR = 3.3, 95% CI = 1.4 to 8.0) and, more importantly, compared with unexposed women who carried the same deleterious missense variant (< 1.0 Gy: RR = 5.3, 95% CI = 1.6 to 17.3; ≥1.0 Gy: RR = 5.8, 95% CI = 1.8 to 19.0). For this latter comparison, there was a statistically significant dose-response trend (excess relative risk (ERR)/Gy = 2.6, P_{trend} = .044). The interaction of radiation and deleterious *ATM* variants was further explored by considering age at, and time since, first diagnosis. Among women who carried *ATM* missense variants that were predicted to be deleterious, the rate ratio for treated versus not treated with radiation therapy was greater for women younger than 45 years at diagnosis (RR = 10.4, 95% CI = 2.3 to 47.2) than for older women (RR = 2.4, 95% CI = 0.6 to 9.5). Similarly, among women who carried predicted deleterious *ATM* missense variants, there was a steeper radiation dose slope for those with a longer latency (≥ 5 years) compared with those with a shorter latency (ERR/Gy: 4.3, 95% CI = 0.1 to 20.7 vs. 1.9, 95% CI = −0.1 to 9.1; respectively).

Discussion

How do the data derived from the WECARE Study inform the evolving understanding of the role of *ATM* in breast cancer and cancer risk in general? Unlike studies that compare affected cases to unaffected controls, WECARE explores factors that influence the risk of developing a second cancer in patients already treated for a first. This model may not be as generalizable as a classical population-based case-control design for identifying variants that increase risk for breast cancer as a main effect, but does allow for analyses of how genetic risk factors, both rare and common, may interact with treatment to modify risk. In analyzing the WECARE Study data, results were stratified into the broad mutation categories truncating, missense, splicing and silent, as prior studies, summarized in this review, had suggested that different classes of mutation might have different phenotypic consequences. Missense mutations were then further classified using bioinformatic predictors of effects on protein function. Given the low prevalence of A-T in the population and the association between A-T heterozygosity and breast cancer risk, common and rare variants in *ATM* were analyzed separately.

Three conclusions can be drawn from the findings regarding *ATM* and CBC from the WECARE Study : [1] selected common variants in *ATM* may exert a protective effect, reducing the risk of developing CBC, [2] rare *ATM* missense variants classified as likely deleterious to protein function increase risk for CBC in women treated with radiation therapy for a first cancer in a dose dependent manner, and [3] the joint effect of *ATM* mutations and radiation therapy on CBC risk suggests that ATM responds to the low doses of radiation scattering from individual fractionated treatments.

Protective effects with regards to breast cancer for variants in *ATM* have not been previously reported. One possible mechanism for such effects would be that these variants alter the threshold for ATM activation, destabilizing inactive ATM dimers and/or increasing the pool of activated ATM present at any given time in a cell. Indeed, preliminary studies carried out in B cell lines established from WECARE Study subjects suggests that the level of ATM phosphorylated on S1981 normalized to overall cellular ATM levels is increased in carriers of putative protective variants in *ATM* (Concannon et al., unpublished observations). This would be a main effect of these variants, protecting carriers from environmental sources of cellular stress, and more readily detectable in the WECARE Study where CBC cases and UBC controls differ in their exposure to either radiation therapy or systemic chemotherapy.

The observation that rare, deleterious missense variants in *ATM* act jointly with radiation to increase risk of CBC while A-T causing mutations do not, is consistent with prior suggestions of allelic heterogeneity at *ATM* with regard to breast cancer risk. However, caution is warranted in the interpretation of these findings. Carriers of A-T causing mutation are infrequent; numbers of such subjects may have been too small in the WECARE Study to observe a significant effect on CBC risk for this category. In addition, classification of missense variants in the WECARE Study is based only on bioinformatic predictors. There are no functional data indicating deleterious effects on *ATM*, nor is the possibility that these variants might, in fact, be A-T causing, ruled out. However, the low cumulative scatter doses to the contralateral breast estimated from simulations, particularly when averaged over the number of fractions, provides epidemiological evidence that genetic variation at *ATM* does affect the response to low individual radiation doses in the range of 50mGy. There are conflicting reports on whether ATM is activated by such doses (Bakkenist and Kastan 2003, Enns et al. 2015, Nakamura et al. 2006, Ojima et al. 2008).

Summary

The relationship between *ATM*, radiation and breast cancer remains complex. Genetic variants in *ATM* may have a range of effects on breast cancer risk from protective to high risk. Heterozygous carriers of germline *ATM* mutations that are A-T causing have an increased risk of developing breast cancer. Other rare missense variants, which may not be A-T causing, can, nevertheless, interact with radiation exposure, even at low doses, and increase risk for breast cancer. Studies that combine *ATM* mutation detection in both germline and tumor tissue with detailed functional characterization of variants will be necessary to resolve the role of *ATM* in breast cancer and enable reliable risk prediction.

Acknowledgments

The Women’s Environmental, Cancer and Epidemiology (WECARE) Study Collaborative Group includes Memorial Sloan Kettering Cancer Center (Coordinating Center) Investigators and Staff: Jonine L. Bernstein Ph.D. (WECARE Study P.I.); Marinela Capanu Ph.D.; Xiaolin Liang M.D.; Irene Orlow Ph.D.; Anne S. Reiner M.P.H.; Mark Robson, M.D.; Meghan Woods M.P.H. Collaborative Site Investigators: Leslie Bernstein Ph.D.; John D. Boice Jr. Sc.D.; Jennifer Brooks Ph.D.; Patrick Concannon Ph.D.; Dave V. Conti Ph.D.; David Duggan Ph.D.; Joanne W. Elena Ph.D., M.P.H.; Robert W. Haile Dr.P.H.; Esther M. John Ph.D.; Julia A. Knight Ph.D.; Charles F. Lynch M.D., Ph.D.; Kathleen E. Malone Ph.D.; Lene Mellemkjær Ph.D.; Jørgen H. Olsen M.D. DMSc.; Daniela Seminara Ph.D. M.P.H.; Roy E. Shore Ph.D., Dr.P.H.; Marilyn Stovall Ph.D.; Daniel O. Stram Ph.D.; Marc Tischkowitz M.D., Ph.D.; Duncan C. Thomas Ph.D. Collaborative Site Staff: Kristina Blackmore M.Sc.; Anh T.

Diep; Judy Goldstein; Irene Harris B.S., C.M.D.; Rikke Langballe M.P.H.; Cecilia O'Brien; Susan Smith M.P.H.; Rita Weathers M.S.; Michele West Ph.D.

Funding

Patrick Concannon was supported by grants from the NIEHS under Grant R01 ES027121 and the Defense Threat Reduction Agency under Grant 1-16-1-0048. This work was also supported by grants from the National Institutes of Health (U01 CA83178, R01 CA97397, R01 CA129639, R01 CA114236, and P30 CA008748)

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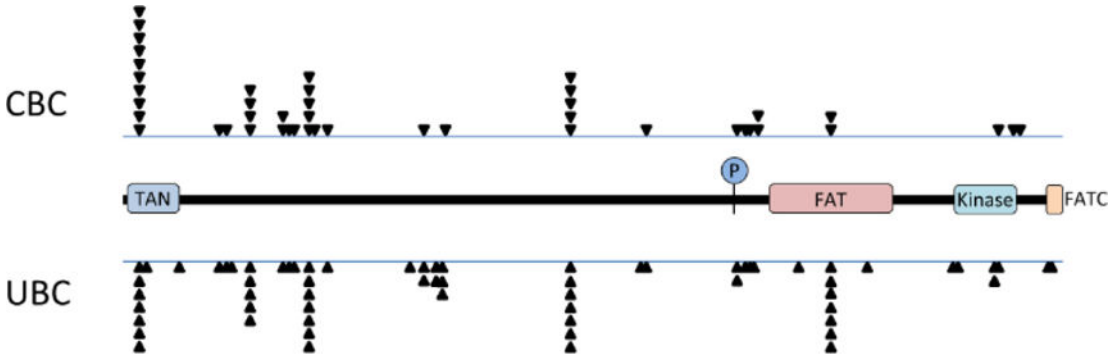

Figure 1.