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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

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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 unknown[1,2].

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 population[3–5], 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

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abnormalities, telangiectasias, immune deficiency, sinopulmonary infections, radiosensitivity, and an elevated risk of cancer[6–12]. 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[7]. Cancers of the breast, lung, gastrointestinal and genitourinary tracts, brain, and parotid have been described, but their incidences are poorly understood[3,5,7,13–15].

Given that *ATM* 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[7]. In contrast, heterozygosity for a pathogenic *ATM* variant is present in 1%–2% of the adult population[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[8,16–20]. Assuming a baseline risk of approximately 1 in 10 (10%)[21], the risk increase translates into a 20%–30% lifetime risk of breast cancer among North American women. Hence, the penetrance of pathogenic *ATM* variants, compared with pathogenic *BRCA* variants, which result in a 45%–80% lifetime risk of breast malignancy, is considered moderate[22,23].

Differences in the reported risk for breast cancer among women who are heterozygous for a pathogenic *ATM* 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 *ATM* variants[18–20]. In a meta-analysis of the three largest published cohort studies, the relative risk of breast cancer in *ATM* carriers was 2.8 [95% confidence interval (CI): 2.2 to 3.7; $p = 4.7\times10^{-11}$][18]. All patients were relatives of individuals with the AT syndrome[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; $p < 0.000001$)[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 *ATM* variants is 32.83% (95% credible interval: 24.55% to 40.43%)[20], approximately 3 times the baseline population risk. In that particular study, *ATM* variants that were unlikely to be pathogenic were excluded, but a familial link to the AT syndrome was not required[20].

Historically, testing for pathogenic *ATM* 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% ($n = 40$) were found to harbour an alternative pathogenic gene variant[24]. After *CHEK2, ATM* was the second most frequent variant identified, and it accounted for more than 25% ($n = 11$) of identifications[24]. In the largest gene panel study to date, the prevalence of pathogenic *ATM* variants in 35,409 women with a first diagnosis of breast cancer was approximately 0.9%[25].

Breast Cancer Risk—Does the Type of *ATM* Variant Matter?

More than 300 different *ATM* variants have been identified thus far, and hence, the clinical significance of any individual variant can be challenging to assess[26]. Most variants that cause the AT syndrome result in truncation of its protein product[27], but at least 170 missense variants have been identified[28]. In a meta-analysis, no difference in the pooled frequency of *ATM* missense variants were evident in cases compared with controls[28], but the V2424G variant is still thought to be pathogenic[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[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[31]. In another analysis of 15 families, the V2424G *ATM* 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 ($p = 0.053$)[32]. As in subgroup analyses of clinical trials, analyses of these "subsets" of patients with particular *ATM* 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[33–39].

Given that the V2424G missense variant has been evaluated in a methodologically more rigorous case–control screening study, *ATM* c.7271T>6 (V2424G) was included in an unprecedented analysis of 10 rare genetic variants (in addition to 3 *PALB2* and 6 *CHEK* variants) by the Breast Cancer Association Consortium[40]. Among 42,671 patients with invasive breast cancer and 42,164 control subjects, the *ATM* V242G 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; $p = 0.0012$)[40]. Although the risk was statistically significant, the CI was wide, and the prevalence of this specific variant was very low (0.028%)[40].

ASSESSMENT AND DIAGNOSIS

Screening for Breast Cancer in Carriers of Pathogenic *ATM* 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 *ATM* variant[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%[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[42].

With the possible exception of the V2424G variant[31], which might be considered a high-risk gene variant, *ATM* is considered to afford a moderate lifetime risk of breast cancer for which management is unclear[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[39]. 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[41] and the recommendations published by Tung *et al.*[39]. 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[46,47]. 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 [0.80 (95% CI: 0.73 to 0.86)] compared with combined screening with mammography [0.94 (95% CI: 0.90 to 0.97)] must be considered in high-risk individuals[42,48].

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[3,5,7,13–15]. Easton[13] 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[3,5,14,15], 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)[7] and pancreatic cancer[49], a significant risk of cancer outside the breast has not been demonstrated[50–53]. 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[19,39]. Although screening tools for pancreatic cancer have not been validated, enrolment into trials evaluating potential screening strategies should be considered[39].

TREATMENT

Adjuvant Chemotherapy for Breast Cancer

ATM encodes a kinase that is involved in the repair of DNA double-strand breaks[54]. It signals the phosphorylation of DNA damage-response pathways, including *BRCA1* and *TP53*[55]; hence, deficiency in the *ATM* gene product might confer sensitivity to DNA-damaging pharmaceuticals such as inhibitors of poly (ADP–ribose) polymerase[56] 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[57]. Although data in mice and cell cultures suggest increased radiosensitivity in *ATM* mutation carriers[58–60], the risk of radiation toxicity is difficult to approximate in patients given the lack of high-quality randomized data[61–69]. Some studies suggest a particularly high risk of radiation-induced toxicity among individuals with 2 concurrent *ATM* variants[68], those with low *ATM* protein levels[69], and those with specific *ATM* polymorphisms[63]; 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[64]. 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%)[64]. 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[65]. However, only 7 of the variants were truncating in nature, and they were not confirmed to be pathogenic[65].

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[70], but those findings were not substantiated[71]. *ATM* status should therefore not be used to make treatment decisions with respect to radiotherapy[19].

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 40 years of age; 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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REFERENCES

1. Kurian AW, Hare EE, Mills MA, *et al.* Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014;32:2001–9.
2. Robson ME, Bradbury AR, Arun B, *et al.* American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol* 2015;33:3660–7.
3. Swift M, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia–telangiectasia. *N Engl J Med* 1987;316:1289–94.
4. Swift M, Morrell D, Cromartie E, Chamberlin AR, Skolnick MH, Bishop DT. The incidence and gene frequency of ataxia–telangiectasia in the United States. *Am J Hum Genet* 1986;39:573–83.
5. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia–telangiectasia. *N Engl J Med* 1991;325:1831–6.
6. Teive HA, Moro A, Moscovich M, *et al.* Ataxia–telangiectasia —a historical review and proposal for a new designation: ATM syndrome. *J Neurol Sci* 2015;35:3–6.
7. Thompson D, Duedal S, Kirner J, *et al.* Cancer risks and mortality in heterozygous *ATM* mutation carriers. *J Natl Cancer Inst* 2005;97:813–22.
8. Furtado S, Das S, Suchowersky O. A review of the inherited ataxias: recent advances in genetic, clinical and neuropathologic aspects. *Parkinsonism Relat Disord* 1998;4:161–9.
9. Morrell D, Cromartie E, Swift M. Mortality and cancer incidence in 263 patients with ataxia–telangiectasia. *J Natl Cancer Inst* 1986;77:89–92.
10. Levy A, Lang AE. Ataxia–telangiectasia: a review of movement disorders, clinical features, and genotype correlations. *Mov Disord* 2018;:[Epub ahead of print].
11. Su Y, Swift M. Mortality rates among carriers of ataxia–telangiectasia mutant alleles. *Ann Intern Med* 2000;133:770–8.
12. Dombernowsky SL, Weischer M, Allin KH, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. Risk of cancer by *ATM* missense mutations in the general population. *J Clin Oncol* 2008;26:3057–62.
13. Easton DF. Cancer risks in A–T heterozygotes. *Int J Radiat Biol* 1994;66(suppl 6):S177–82.
14. Pippard EC, Hall AJ, Barker DJP, Bridges BA. Cancer in homozygotes and heterozygotes of ataxia–telangiectasia and xeroderma pigmentosum in Britain. *Cancer Res* 1988;48:2929–32.
15. Borresen AL, Anderson TI, Treti S, Heiberg A, Moller P. Breast cancer and other cancers in Norwegian families with ataxia–telangiectasia. *Genes Chromosomes Cancer* 1990;2:339–40.
16. Chessa L, Lisa A, Fiorani O, Zei G. Ataxia–telangiectasia in Italy: genetic analysis. *Int J Radiat Biol* 1994;66(suppl):S31–3.
17. Renwick A, Thompson D, Seal S, *et al. ATM* mutations that cause ataxia–telangiectasia are breast cancer susceptibility alleles. *Nat Genet* 2006;38:873–5.
18. Easton DF, Pharoah PDP, Antoniou AC, *et al.* Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015;372:2243–57.
19. van Os NJ, Roeleveld N, Weemaes CM, *et al.* Health risks for ataxia–telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. *Clin Genet* 2016;90:105–17.
20. Marabelli M, Cheng SC, Parmigiani G. Penetrance of *ATM* gene mutations in breast cancer: a meta-analysis of different measures of risk. *Genet Epidemiol* 2016;40:425–31.
21. Lee AJ, Cunningham AP, Kuchenbaecker KB, Mavaddat N, Easton DF, Cantoniou CA on behalf of the Consortium of Investigators of Modifiers of *BRCA1*/*2* and the Breast Cancer Association Consortium. BOADICEA breast cancer risk prediction model: updates to cancer incidences, tumour pathology and Web interface. *Br J Cancer* 2014;110:535–45.
22. King MC, Marks JH, Mandell JB on behalf of the New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2. Science* 2003;302:643–6.
23. Antoniou A, Pharoah PD, Narod S, *et al.* Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117–30.
24. Desmond A, Kurian AW, Gabree M, *et al.* Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol* 2015;1:943–51.
25. Buys SS, Sandbach JF, Gammon A, *et al.* A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer* 2017;123:1721–30.
26. Ahmed M, Rahman N. *ATM* and breast cancer susceptibility. *Oncogene* 2006;25:5906–11.
27. Shiloh Y. *ATM* and related protein kinases: safeguarding genome integrity. *Nat Rev Cancer* 2003;3:155–68.
28. Tavtigian SV, Oefner PJ, Babikyan D, *et al.* Rare, evolutionarily unlikely missense substitutions in *ATM* confer increased risk of breast cancer. *Am J Human Genet* 2009;85:427–46.
29. Chenevix-Trench G, Spurdle AB, Gatei M, *et al.* Dominant negative *ATM* mutations in breast cancer families. *J Natl Cancer Inst* 2002;94:205–15.
30. Waddell N, Jonnalagadda J, Marsh A, et al. Characterization of the breast cancer associated ATM 7271T>G (V2424G) mutation by gene expression profiling. Genes Chromosomes Cancer 2006;45:1169–81.
31. Bernstein JL, Teraoka S, Southey MC, *et al.* Population-based estimates of breast cancer risks associated with *ATM* gene variants c.7271T>G and c.1066–6T>G (IVS10–6T>G) from the Breast Cancer Family Registry. *Hum Mutat* 2006:27:1122–8.
32. Goldgar DE, Healey S, Dowty JG, *et al.* Rare variants in the *ATM* gene and risk of breast cancer. *Breast Cancer Res* 2011;13:R73.
33. Taylor AM, Lam Z, Last Jl, Byrd PJ. Ataxia telangiectasia: more variation at clinical and cellular levels. *Clin Genet* 2015;87:199–208.
34. Broeks A, Urbanus JHM, Floore AN, *et al. ATM*-heterozygous germline mutations contribute to breast cancer susceptibility. *Am J Hum Genet* 2000;66:494–500.
35. Brunet J, Gutierrez-Enriquez S, Torres A, *et al. ATM* germline mutations in Spanish early-onset breast cancer patients negative for *BRCA1*/*BRCA2* mutations. *Clin Genet* 2008;73:465–73.
36. Chen J, Birkholtz GG, Lindblom P, Rubio C, Lindlom A. The role of ataxia–telangiectasia heterozygotes in familial breast cancer. *Cancer Res* 1998;58:1376–9.
37. FitzGerald MG, Bean JM, Hegde SR, *et al.* Heterozygous *ATM* mutations do not contribute to early onset of breast cancer. *Nat Genet* 1997;15:307–10.

38. Aloraifi F, McCartan D, McDevitt T, Green AJ, Bracken A, Geraghty J. Protein-truncating variants in moderate-risk breast cancer susceptibility genes: a meta-analysis of high-risk case–control screening studies. *Cancer Genet* 2015;208:455–63.
39. Tung N, Domcheck SM, Stadler Z, *et al.* Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016;13:581–8.
40. Southey MC, Goldgar DE, Winqvist R, *et al. PALB2, CHEK2* and *ATM* rare variants and cancer risk: data from COGS. *J Med Genet* 2016;53:800–1.
41. Daly MB, Pilarski R, Berry M, *et al.* NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian. Ver. 2.2017. *J Natl Compr Canc Netw* 2017;15:9–20.
42. Warner E, Messersmith H, Causer P, *et al. Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer.* Evidence-based guideline 15-11. Ver. 2. Toronto, ON: Cancer Care Ontario; 2012.
43. Oeffinger KC, Fontham ET, Etzioni R, *et al.* on behalf of the American Cancer Society. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA* 2015;314:1599–614.
44. U.K. National Institute for Health and Care Excellence (NICE). *Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People with a Family History of Breast Cancer.* London, U.K.: NICE; 2017. [Available online at: http://www.nice.org.uk/guidance/cg164; cited 4 December 2017]
45. Senkus E, Kyriakides S, Ohno S, *et al.* Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26(suppl 5):v8–30.
46. Speit G, Trenz K, Schultz P, Bendix R, Dork T. Mutagen sensitivity of human lymphoblastoid cells with a *BRCA1* mutation in comparison to ataxia telangiectasia heterozygote cells. *Cytogenet Cell Genet* 2000;91:261–6.
47. Neubauer S, Arutyunyan R, Stumm M, *et al.* Radiosensitivity of ataxia telangiectasia and Nijmegen breakage syndrome homozygotes and heterozygotes as determined by three-color FISH chromosome painting. *Radiat Res* 2002;157:312–21.
48. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med* 2008;148:671–9.
49. Grant RC, Selander I, Connor AA, *et al.* Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. *Gastroenterology* 2015;148:556–64.
50. Olsen JH, Hahnemann JM, Borresen-Dale AL, *et al.* Cancer in patients with ataxia–telangiectasia and in their relatives in the Nordic countries. *J Natl Cancer Inst* 2001;93:121–7.
51. Geoffroy-Perez B, Janin N, Ossian K, *et al.* Cancer risk in heterozygotes for ataxia–telangiectasia. *Int J Cancer* 2001;93:288–93.
52. Bernstein JL, Bernstein L, Thompson WD, *et al. ATM* variants 7271T>G and IVS10-6T>G among women with unilateral and bilateral breast cancer. *Br J Cancer* 2003;89:1513–16.
53. Spurdle AB, Hopper JL, Chen X, *et al.* No evidence for association of ataxia–telangiectasia mutated gene T2119C and C3161G amino acid substitution variants with risk of breast cancer. *Breast Cancer Res* 2002;4:R15.
54. Kitagawa R, Kastan MB. The ATM-dependent DNA damage signaling pathway. *Cold Spring Harb Symp Quant Biol* 2005;70:99–109.
55. Bartek J, Bartkova J, Lukas J. DNA damage signalling guards against activated oncogenes and tumour progression. *Oncogene* 2007;26:7773–9.
56. Gilardini Montani MS, Prodosmo A, Stagni V, *et al.* ATM-depletion in breast cancer cells confers sensitivity to PARP inhibition. *J Exp Clin Cancer Res* 2013;32:95.
57. Weissberg JB, Huang DD, Swift M. Radiosensitivity of normal tissues in ataxia–telangiectasia heterozygotes. *Int J Radiat Oncol Biol Phys* 1998;42:1133–6.
58. Barlow C, Eckhaus MA, Schaffer AA, Wynshaw-Boris A. *Atm* haploinsufficiency results in increased sensitivity to sublethal doses of ionizing radiation in mice. *Nat Genet* 1999;21:359–60.
59. Worgul BV, Smilenov L, Brenner DJ, Junk A, Zhou W, Hall EJ. *Atm* heterozygous mice are more sensitive to radiation-induced cataracts than are their wild-type counterparts. *Proc Natl Acad Sci U S A* 2002;99:9836–9.
60. Paterson MC, Anderson AK, Smith BP, Smith PJ. Enhanced radiosensitivity of cultured fibroblasts from ataxia telangiectasia heterozygotes manifested by defective colony-forming ability and reduced DNA repair replication after hypoxic gamma-irradiation. *Cancer Res* 1979;39:3725–34.
61. Ho AY, Fan G, Atencio DP, *et al.* Possession of *ATM* sequence variants as predictor for late normal tissue responses in breast cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;69:677–84.
62. Oppitz U, Bernthaler U, Schindler D, *et al.* Sequence analysis of the *ATM* gene in 20 patients with RTOG grade 3 or 4 acute and/or late tissue radiation side effects. *Int J Radiat Oncol Biol Phys* 1999;44:981–8.
63. Dong L, Cui J, Tang F, Cong X, Han F. Ataxia telangiectasia–mutated gene polymorphisms and acute normal tissue injuries in cancer patients after radiation therapy: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys* 2015;91:1090–8.
64. Su Y, Swift M. Outcomes of adjuvant radiation therapy for breast cancer in women with ataxia–telangiectasia mutations. *JAMA* 2001;286:2233–4.
65. Meyer A, John E, Dork T, Sohn C, Karstens JH, Bremer M. Breast cancer in female carriers of *ATM* gene alterations: outcome of adjuvant radiotherapy. *Radiother Oncol* 2004;72:319–23.
66. Bremer M, Klopper K, Yamini P, Bendix-Waltes R, Dork T, Karstens JH. Clinical radiosensitivity in breast cancer patients carrying pathogenic *ATM* gene mutations: no observation of increased radiation-induced acute or late effects. *Radiother Oncol* 2003:69:155–60.
67. Ramsay J, Birrell G, Lavin M. Breast cancer and radiotherapy in ataxia–telangiectasia heterozygote. *Lancet* 1996;347:1627.
68. Ianuzzi CM, Atencio DP, Green S, Stock RG, Rosenstein BS. *ATM* mutations in female breast cancer patients predict for an increase in radiation-induced late effects. *Int J Radiat Oncol Biol Phys* 2002;52:606–13.
69. Fang Z, Kozlov S, McKay MJ, *et al.* Low levels of ATM in breast cancer patients with clinical radiosensitivity. *Genome Integr* 2010;1:9.
70. Bernstein JL, Haile RW, Stovall M, *et al.* Radiation exposure, the *ATM* gene, and contralateral breast cancer in the Women's Environmental Cancer and Radiation Epidemiology study. *J Natl Cancer Inst* 2010;102:475–83.
71. Concannon P, Haile RW, Borresen-Dale AL, *et al.* on behalf of the Women's Environment, Cancer, and Radiation Epidemiology Study Collaborative Group. Variants in the *ATM* gene associated with a reduced risk of contralateral breast cancer. *Cancer Res* 2008;68:6486–91.