WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

20 YEARS AFTER THE FIRST REPORT OF THE NEED FOR LABORATORY CLINICAL TRACKING OF ATAXIA-TELANGIECTASIA MUTATED (ATM) AS A STRATEGY IN THERAPEUTIC MANAGEMENT, A LITERATURE REVIEW

André Luiz Freitas De Lima Filho[1], Carine AM Tasso[1], Lisiane Cervieri Mezzomo[1], Silvia Maria Spalding[2], Luciane Noal Calil[2], Renata Pereira Limberger[1,2] and Adelina Mezzari[2]*

[1]Programa De Pós-Graduação Em Ciências Farmacêuticas Da Faculdade De Farmácia Da Universidade Federal Do Rio Grande Do Sul.
[2]Docente Do Departamento De Análises Clínicas Da Faculdade De Farmácia Da Universidade Federal Do Rio Grande Do Sul.

*Corresponding Author: Adelina Mezzari

Docente Do Departamento De Análises Clínicas Da Faculdade De Farmácia Da Universidade Federal Do Rio Grande Do Sul.

ABSTRACT

Purpose: ATM gene polymorphisms are thought to influence the risk of cancer and radiation-induced tissue toxicity risk in cancer patients treated with radiotherapy. However, the results of previous studies are not clearly defined. This review aims to examine the association between ATM gene polymorfisms and tissue toxicity after radiotherapy. **Methods:** A compreensive literature search using keywords such as "ATM gene" and/or 'polymorfism' and/or 'radiotherapy' was done to identify all the relevant studies that investigated the association between the ATM polymorphisms and cancer induced toxicity after radiotherapy in AT syndrome patients. The search was done in the PubMed database, and was conducted until December 2018. After extracting relevant details, each selected literature was evaluated for quality. The allele/genotype frequencies were extracted from each study. **Results:** That review were conducted using 26 elegible studies. Our findings suggest that polimorphisms of ATM gene were (or not) associated with the predisposition of tissue toxicity, as erytema, fibrosys. **Conclusions:** The results indicate that the ATM gene polymorphism are risk factors for tissue toxicity after radiotherapy. Large-scale and well-designed international studies are needed to furter analyze this field.

KEYWORDS: Breast câncer; DNA damage; DNA repair.

INTRODUCTION

Ataxia-telangiectasia (A-T) It is a rare neurodegenerative manifestation present in childhood, affecting the cerebellum, stature, dementia, oculomotor, infections, mainly respiratory system, immunodeficiency, sensitivity to ionizing radiation, DNA synthesis, as well as cancer.[1-6]

Mutation of the ataxia-telangiectasia (*ATM*) gene induces the coding of a multifunctional kinase, which connects to cellular functions. Serine protein / threonine kinase is encoded as part of the phosphatidylinositol-3-kinase (PIKK) family. This gene is hereditary which has an autosomal recessive trait being located in the long arm (Q) of chromosome 11 between positions 22 and 23 (11q22-23).[2,6] Individuals with two mutated *ATM* alleles are affected by A-T syndrome and consequently have loss of function. In heterocyclic individuals in the A-T mutation and phenotypically normal, they are at higher risk of cancer and also sensitivity to radiotherapy and chemotherapy.[5]

Lymphomas and leukemias are the most frequent in young people, up to 20 years old and with classic A-T, in adults the most frequent occurs with lymphoid tumors and solids, including breast, gastric, esophageal and liver carcinomas.[7] The association between A-T and breast cancer was first reported by Swift et al.[6] even before *ATM* gene cloning, the authors identified an excess of breast cancer in relatives of individuals with A-T. In the general population, the *ATM* gene mutation represents 1.4% to 2.2%, whereas in individuals affected by A-T this rate increases to 12.5%.[10]

Research on pathogenic *ATM* variants is scarce. With the current possibility of genetic panel assays, it has been possible to obtain more data on the prevalence of these variants among women with hereditary predisposition to cancer and radiotherapy. However, the low frequency of *ATM* mutations has hampered real knowledge about the accuracy of cancer risks.[8,9] In this sense, this review aims to provide an overview of the results in order to delineate the current understanding of the predictive

potential of gene polymorphism for radiotherapy risk response and radiotherapy toxicity.

METHODS

This review was conducted by the following phases: (a) planning, where a methodology was constructed and the objectives of this review and formulation of the research question; (b) implementation, through the identification of studies defined by keywords and inclusion and exclusion criteria, and finally; (c) extraction, by means of the scrutiny of the retrieved articles, where the data obtained was analyzed.

Search strategy

The population used in the research protocol was patients with cancer of any location and carriers of *ATM*, with or post radiotherapy treatment, in order to verify the prognosis as a clinical outcome. The context of the search was to evaluate whether patients who have a mutation (SNP) in the A-T gene may predispose to radiological sensitivity causing obscure prognosis.

To obtain the most up-to-date information on the subject, we used the Pubmed database, with advanced search using its descriptors and Booleans, where the search filter made available for randomized clinical trials was used. The following keywords were used: "*ATM* gene" and/or 'polymorfism' and/or 'radiotherapy'.

Recombinant clinical studies were from 1980 to 2018, where randomized clinical trials are any trial including only cancer patients and *ATM* and any trial comparing the use of radiotherapy in patients with cancer and *ATM*. The studies should be in the English and Spanish languages, with a profile of male and female participants, without an age limit.

The types of interventions analyzed were from patients receiving radiotherapy, checking whether the prognosis after treatment, as risck of tissue tocicity.

Studies were excluded when: (1) they were systematic review, reviews, case reports, commentaries or editorial articles, (2) provided insufficient data, (3) were repeated studies, (4) studies retrieved in languages other than criteria of inclusion or established period of time and (5) without descriptors in the titles.

Selection of studies

The articles retrieved from the database searches were selected by the titles (first step), abstracts (second stage) and full article (third stage) to select the studies. Thus, after completing the adequacy analysis of the research question, articles suitable for full reading were related. Access to the selected articles was through subscription by the Federal University of Rio Grande do Sul library.

The studies identified by the search strategy were evaluated for eligibility and those that appeared unrelated to the objectives were excluded in the screening of the title. The remaining articles were submitted to abstract and full text screening, based on inclusion and exclusion criteria. These criteria aimed at including original studies. A manual cross-reference search was performed on reference lists of eligible articles to ensure that relevant related articles were included in this study. The researchers were not blinded to the journal, author or institutions.

Extraction and presentation of data

Data were collected independently by five authors. The extracted data were included in a table by an author. The details of each study, including: name of the first author, year of publication, country of origin, sample size, tumor type, study material, outcome definition, method of analysis, identified prognostic and/or gene signature and validation (polymorphisms) were listed in a table. If data from any of the above items were not reported in the study, the items were indicated as "unreported". The data entry was checked for each study after completing the data extraction. The authors were contacted for important information that was either missing or unclear in the protocol of study.

Ethics. Ethical approval was not necessary.

RESULTS

Selection of articles and study characteristics

The data surveyed in Pubmed dated until december, 2018 revealed studies closely related to the topic. Of these, studies were irrelevant by title or abstract reading. All references were evaluated for inclusion based on the title and/or abstract potentially relevant articles were thereby included in the next stage for full-text evaluation. After reading their titles and abstracts, we excluded reviews or meta-analyses that were not relevant to our study or not published in English. The selection of studies based on inclusion and exclusion criteria included only 26 independent studies for the final review. All eligible studies were published between 2001 and 2018. Data extracted from the studies are summarized in Table 1, whose outlines the stages of selection of the studies and the final number of those eligible for the review, as well as the reasons for exclusion.

The distribution of these studies in the past 20 years, the main characteristics of these selected studies, including the first author's name, original country and genotype distribution were summarized in Table 1.

Table 1: Characteristics of the 26 elegible studies.

N.	First author, year (Ref)	Country	Sample Size	Study Type	Cancer site
1	Angele, S et.al., 2001[11]	France	254/312	Case control	Breast cancer
2	Andreassen, Christian et.al., 2005[12]	USA	41	Coorte	Breast cancer
3	Li, Donghui et.al., 2006[13]	USA	92	Transversal	Pancreatic cancer
4	Ho, Alice Y et.al., 2007[14]	USA	131	Coorte	Breast cancer
5	Su, Dan et.al., 2007[15]	USA	230	Transversal	Non smal cell lung cancer
6	Okazaki, Taro et.al., 2008[16]	USA	119	Transversal	Pancreatic cancer
7	Pugh, Trevor J et.al., 2009[17]	USA	41	Transversal	Prostate brachiterapy patients
8	Zhang, Li et.al., 2010[18]	USA	253	Transversal	Lung cancer
9	Zschenker, Oliver et.al., 2010[19]	Germany	69	Coorte	Breast cancer
10	Yang M et.al., 2011[20]	USA	253	Coorte	Lung cancer
11	Ishikawa, Atsuko et.al., 2011[21]	USA	243	Transversal	Cervical cancer
12	Beranek, Martin et.al., 2011[22]	Czech Republic	20	Case-control	Cervical cancer
13	Tanteles, George A et.al., 2012[23]	United Kingdom	633	Transversal	Breast cancer
14	J. Brooks et.al., 2012[24]	USA	1399/708	Case control	Breast cancer
15	Beggs, Andrew D et.al., 2012[25]	USA	908	Transversal	Colorectal cancer
16	A. Raabe et.al., 2012[26]	Germany	83	Transversal	Breast cancer
17	Alsbeih, Ghazi et.al., 2013[27]	Arabia Saudita	155	Coorte	Nasofaringeal cancer
18	Cintra, Hellen Silva et.al.,2013[28]	Brazil	48	Transversal	Prostate cancer
19	H. Xiong et.al., 2013[29]	USA	362	Transversal	Non-small cell lung cancer
20	N. Usmani et.al., 2014[30]	Canadá	217	Coorte	Prostate implants
21	S. Paulikova et.al., 2014[31]	Czech Republic	55	Coorte	Cervical cancer
22	Kim, Seok-Hyun et.al., 2015[32]	USA	129	Transversal	Non Small cell lung cancer
23	Du, Zhongli et. al., 2015[33]	China	800	Case control	Esophageal and squamous carcinoma
24	S. Reuther et.al., 2015[34]	Germany	83	Transversal	Breast cancer
25	A. Prodosmo et.al., 2016[35]	Italy	496	Transversal	Breast and ovarian familial cases and diferent sporadic cancers
26	Agostini L. et.al., 2017[36]	Brazil	311	Transversal	Oral cavity/oropharyngeal carcinoma laryngeal tumors.

Among all eligible studies, the majority (n=9) disclosure about breast cancer.

The total number of subjects included in this study comprises 8.188. All studies were conducted in North America and Europe, and the country with the highest frequency of publications is United States (n=18). Al the research looked for studies that analyzed the relationship between gene/protein expression and polymorphisms the *ATM* gene, the design with the highest frequency found in our research was transversal (n=16).

DISCUSSION

In study reports, it has been found that individuals with heterozygous A-T have a higher risk of cancer than nonheterozygous individuals,[37] Swift et al., 1987,[6] reported that female relatives of patients with A-T have a higher risk of breast cancer. Subsequent studies have identified the responsible gene, ATM whose function compromises the response to DNA cell damage, and as a consequence other different cancers may manifest as lymphoid, gastric, pancreatic, among others.[38,39,40,41]

The *ATM* gene has the function of cell cycle regulation, apoptosis, DNA repair, cell cycle arrest, and DNA damage, among others.[3,42,43] Mutations or changes in this gene impair its function of controlling the cell cycle, repairing cell changes, as well as preventing the increase of malignancy.[44] It acts in the regulation and interaction with the different substrates of the cell cycle, which include the proteins that activate the G1, S or G2-M control points.[6]

The ATM Mutation Database (www.lovd.nl/ATM) reports 1.345 possible mutations in A-T patients. Of these more than 80% can truncate the action of protein in specific regions of the gene.

The *ATM* gene is one of the most frequently studied genes in cancer occurrence and progression. Chaudhary and Al-Baradie, 2014, described that ATM is involved in important life processes including DNA repair, cell cycle regulation, neuroprotection, immunity, metabolism, longevity and fertility.[45] In another study, he observed that *ATM* mutations induce autosomal recessive disorder in the individual, A-T, resulting in cellular radiosensitivity, chromosomal instability, immunodeficiency, and cancer predisposition.[46] In case-control studies, the authors evaluated the effects of polymorphisms on the risk of breast cancer, prostate cancer, rectal cancer, bladder cancer, lung cancer, pancreatic cancer, and thyroid cancer, but concluded that the results they are still inconsistent.[47,48]

Detection of *ATM* mutations has been obtained in samples of aspirate or fine needle biopsies in cancer tumor masses. As a result, it would be important to know which cancer with *ATM* mutation or deficiency is more sensitive to radiotherapy than wild type *ATM* cancers, and whether the use of radiotherapy at the disease site needs to know the molecular profile of the *ATM* tumor.[49]

For this review, a careful bibliographical research and quality assessment were directed to include all studies of moderate and high quality relevant for prognostic gene expression in recent years, but we must admit that there are some limitations in our review. Environmental factors and life style information were not available for all studies, thus these variables were not taken into consideration. Besides that, because of the difference in data presentation of age between studies (mean age, median age, and age group), we didn't assess the risk stratified by age. Lastly, a few types of cancer were included in our review due to the selected studies. However, only one or two studies were performed on the cancers except breast cancer, prostate, non small cells and cervical cancer, and this may potentially make the result biased.

The treatment of cancer has radiotherapy as one of the important choices, but resistance to its use still remains an obstacle limiting its use. The use of radiation in the treatment of tumor cells initially needs to know and understand the signaling network that leads cancer cells to overcome cancer-induced cytotoxicity, resulting in their survival,[50] The cytotoxicity induced by ionizing radiation results in the breakdown of the double strand of DNA and consequently in the simultaneous signaling of the multiple protective pathways of cells for this purpose. HER, ERK1 / 2 and AKT receptors act on irradiated cells to prevent them from being apoptotic, while ATM, ATR and DNA-PK lead these cells to cyclic arrest by initiating DNA repair. Therefore, signaling pathways act together to rescue radiation-induced cell damage and at the same time promote their survival.[50]

Consequently, the *ATM* gene, like other proteins in the PIKK family, has multiple and complex functions, such as the phosphorylation of substrates involved in repairing DNA damage. DNA double strand breakage, induced by ionizing irradiation or replication error, results in rapid activation of ATM and ATR kinases which phosphorylate multiple targets, including damage recognition, repair protein recruitment, adhesion to spots of cell cycle control, transcriptional regulation and apoptosis. The proteins most involved in these activities are BRCA1 and RAD51 in damage repair, CHK1 and CHK2 in cell cycle control point arrest and p53 protein apoptosis.[2,50,51]

In addition, it is also important to emphasize that there is a relationship between this gene and the respiratory system, as it has action on cell proliferation and apoptosis in lung cancer via the AMP kinase (AMPK) pathway. Another relevant factor includes the genetic polymorphism in the TMJ reflecting the susceptibility to p53-induced radiation peneumonitis as well as to the various other types of lung carcinoma.[44]

CONCLUSION

In conclusion, our literature review has noted that despite the tremendous advances in interventional medical and surgical therapy over the past decades, many studies are still lacking to better understand the genotypes involved in ATM.

Further large-scale epidemiological investigations on this topic should be undertaken to confirm or refute our findings in this literature review study.

Well designed studies are needed to confirm genotype analysis in order to eventually be used in the clinic to better determine the treatment modalities of patients with positive ATM.

REFERENCES

1. Kastan MB, Zhan Q, el-Deiry WSet al. A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. Cell, 1992; 71: 587-597.
2. Ahmed M, Rahman N ATM and breast cancer susceptibility. Oncogene, 2006; 25: 5906-5911.
3. Bernstein JL, Haile RW, Stovall Met al. Radiation exposure, the ATM Gene, and contralateral breast cancer in the women's environmental cancer and radiation epidemiology study. Journal of the National Cancer Institute, 2010; 102: 475-483.
4. Brito JC, da Silva JA, da Nobrega PV [Ataxia-telangiectasia. Report of 4 cases]. Arquivos de neuro-psiquiatria, 1979; 37: 158-164.
5. Mangone FR, Miracca EC, Feilotter HE, Mulligan LM, Nagai MA ATM gene mutations in sporadic breast cancer patients from Brazil. SpringerPlus, 2015; 4: 23.
6. Swift M, Reitnauer PJ, Morrell D, Chase CL Breast and other cancers in families with ataxia-telangiectasia. The New England journal of medicine, 1987; 316: 1289-1294.
7. Suarez F, Mahlaoui N, Canioni Det al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2015; 33: 202-208.

8. Renwick A, Thompson D, Seal Set al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nature genetics, 2006; 38: 873-875.

9. Easton DF, Pharoah PD, Antoniou ACet al. Gene-panel sequencing and the prediction of breast-cancer risk. The New England journal of medicine, 2015; 372: 2243-2257.

10. Khalil HS, Tummala H, Hupp TR, Zhelev N Pharmacological inhibition of ATM by KU55933 stimulates ATM transcription. Experimental biology and medicine, 2012; 237: 622-634.

11. Angele S, Taniere P, Hall J [What do we know about ATM protein expression in breast tissue?]. Bulletin du cancer, 2001; 88: 671-675.

12. Andreassen CN Can risk of radiotherapy-induced normal tissue complications be predicted from genetic profiles? Acta oncologica, 2005; 44: 801-815.

13. Li D, Frazier M, Evans DBet al. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2006; 24: 1720-1728.

14. Ho AY, Fan G, Atencio DPet al. Possession of ATM sequence variants as predictor for late normal tissue responses in breast cancer patients treated with radiotherapy. International journal of radiation oncology, biology, physics, 2007; 69: 677-684.

15. Su D, Ma S, Liu Pet al. Genetic polymorphisms and treatment response in advanced non-small cell lung cancer. Lung cancer, 2007; 56: 281-288.

16. Okazaki T, Jiao L, Chang P, Evans DB, Abbruzzese JL, Li D Single-nucleotide polymorphisms of DNA damage response genes are associated with overall survival in patients with pancreatic cancer. Clinical cancer research : an official journal of the American Association for Cancer Research, 2008; 14: 2042-2048.

17. Pugh TJ, Keyes M, Barclay Let al. Sequence variant discovery in DNA repair genes from radiosensitive and radiotolerant prostate brachytherapy patients. Clinical cancer research : an official journal of the American Association for Cancer Research, 2009; 15: 5008-5016.

18. Zhang L, Yang M, Bi Net al. ATM polymorphisms are associated with risk of radiation-induced pneumonitis. International journal of radiation oncology, biology, physics, 2010; 77: 1360-1368.

19. Zschenker O, Raabe A, Boeckelmann IKet al. Association of single nucleotide polymorphisms in ATM, GSTP1, SOD2, TGFB1, XPD and XRCC1 with clinical and cellular radiosensitivity. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 2010; 97: 26-32.

20. Yang M, Zhang L, Bi Net al. Association of P53 and ATM polymorphisms with risk of radiation-induced pneumonitis in lung cancer patients treated with radiotherapy. International journal of radiation oncology, biology, physics, 2011; 79: 1402-1407.

21. Ishikawa A, Suga T, Shoji Yet al. Genetic variants of NPAT-ATM and AURKA are associated with an early adverse reaction in the gastrointestinal tract of patients with cervical cancer treated with pelvic radiation therapy. International journal of radiation oncology, biology, physics, 2011; 81: 1144-1152.

22. Beranek M, Drastikova M, Paulikova S, Sirak I, Vosmik M, Petera J Analysis of D1853N ATM polymorphism in radiosensitive patients with cervical carcinoma. Acta medica, 2011; 54: 111-116.

23. Tanteles GA, Murray RJ, Mills Jet al. Variation in telangiectasia predisposing genes is associated with overall radiation toxicity. International journal of radiation oncology, biology, physics, 2012; 84: 1031-1036.

24. Brooks JD, Teraoka SN, Reiner ASet al. Variants in activators and downstream targets of ATM, radiation exposure, and contralateral breast cancer risk in the WECARE study. Human mutation, 2012; 33: 158-164.

25. Beggs AD, Domingo E, McGregor Met al. Loss of expression of the double strand break repair protein ATM is associated with worse prognosis in colorectal cancer and loss of Ku70 expression is associated with CIN. Oncotarget, 2012; 3: 1348-1355.

26. Raabe A, Derda K, Reuther Set al. Association of single nucleotide polymorphisms in the genes ATM, GSTP1, SOD2, TGFB1, XPD and XRCC1 with risk of severe erythema after breast conserving radiotherapy. Radiation oncology, 2012; 7: 65.

27. Alsbeih G, El-Sebaie M, Al-Harbi N, Al-Hadyan K, Shoukri M, Al-Rajhi N SNPs in genes implicated in radiation response are associated with radiotoxicity and evoke roles as predictive and prognostic biomarkers. Radiation oncology, 2013; 8: 125.

28. Cintra HS, Pinezi JC, Machado GDet al. Investigation of genetic polymorphisms related to the outcome of radiotherapy for prostate cancer patients. Disease markers, 2013; 35: 701-710.

29. Xiong H, Liao Z, Liu Zet al. ATM polymorphisms predict severe radiation pneumonitis in patients with non-small cell lung cancer treated with definitive radiation therapy. International journal of radiation oncology, biology, physics, 2013; 85: 1066-1073.

30. Usmani N, Leong N, Martell Ket al. Single-nucleotide polymorphisms studied for associations with urinary toxicity from (125)I prostate brachytherapy implants. Brachytherapy, 2014; 13: 285-291.

31. Paulikova S, Petera J, Sirak Iet al. ATM and TGFB1 genes polymorphisms in prediction of late complications of chemoradiotherapy in patients with locally advanced cervical cancer. Neoplasma, 2014; 61: 70-76.

32. Kim SH, Kim MJ, Cho YJet al. Clinical Significance of ABCG2 Haplotype-tagging Single

Nucleotide Polymorphisms in Patients With Unresectable Non-Small Cell Lung Cancer Treated With First-line Platinum-based Chemotherapy. American journal of clinical oncology, 2015; 38: 294-299.

33. Du Z, Zhang W, Zhou Yet al. Associations of ATM Polymorphisms With Survival in Advanced Esophageal Squamous Cell Carcinoma Patients Receiving Radiation Therapy. International journal of radiation oncology, biology, physics, 2015; 93: 181-189.

34. Reuther S, Szymczak S, Raabe Aet al. Association between SNPs in defined functional pathways and risk of early or late toxicity as well as individual radiosensitivity. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft ... [et al], 2015; 191: 59-66.

35. Prodosmo A, Buffone A, Mattioni Met al. Detection of ATM germline variants by the p53 mitotic centrosomal localization test in BRCA1/2-negative patients with early-onset breast cancer. Journal of experimental & clinical cancer research: CR, 2016; 35: 135.

36. Agostini LP, Stur E, Garcia FMet al. ATM, BCL2, and TGFbeta Gene Polymorphisms as Radiotherapy Outcome Biomarkers in Head and Neck Squamous Cell Carcinoma Patients. Genetic testing and molecular biomarkers, 2017; 21: 727-735.

37. Taylor AM, Harnden DG, Arlett CFet al. Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. Nature, 1975; 258: 427-429.

38. Swift M, Chase CL, Morrell D Cancer predisposition of ataxia-telangiectasia heterozygotes. Cancer genetics and cytogenetics, 1990; 46: 21-27.

39. Swift M Malignant disease in heterozygous carriers. Birth defects original article series, 1976; 12: 133-144.

40. Helgason H, Rafnar T, Olafsdottir HSet al. Loss-of-function variants in ATM confer risk of gastric cancer. Nature genetics, 2015; 47: 906-910.

41. Roberts NJ, Jiao Y, Yu Jet al. ATM mutations in patients with hereditary pancreatic cancer. Cancer discovery, 2012; 2: 41-46.

42. Zhou BB, Elledge SJ The DNA damage response: putting checkpoints in perspective. Nature, 2000; 408: 433-439.

43. Feng X, Li H, Dean Met al. Low ATM protein expression in malignant tumor as well as cancer-associated stroma are independent prognostic factors in a retrospective study of early-stage hormone-negative breast cancer. Breast cancer research: BCR, 2015; 17: 65.

44. Xu Y, Gao P, Lv X, Zhang L, Zhang J The role of the ataxia telangiectasia mutated gene in lung cancer: recent advances in research. Therapeutic advances in respiratory disease, 2017; 11: 375-380.

45. Chaudhary MW, Al-Baradie RS Ataxia-telangiectasia: future prospects. The application of clinical genetics, 2014; 7: 159-167.

46. Savitsky K, Bar-Shira A, Gilad Set al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science, 1995; 268: 1749-1753.

47. Zhao Y, Yang L, Wu Det al. Gene-environment interaction for polymorphisms in ataxia telangiectasia-mutated gene and radiation exposure in carcinogenesis: results from two literature-based meta-analyses of 27120 participants. Oncotarget, 2016; 7: 76867-76881.

48. Lu PH, Wei MX, Si SPet al. Association between polymorphisms of the ataxia telangiectasia mutated gene and breast cancer risk: evidence from the current studies. Breast cancer research and treatment, 2011; 126: 141-148.

49. DeWitt J, Cho CM, Lin Jet al. Comparison of EUS-guided tissue acquisition using two different 19-gauge core biopsy needles: a multicenter, prospective, randomized, and blinded study. Endoscopy international open, 2015; 3: E471-478.

50. Hein AL, Ouellette MM, Yan Y Radiation-induced signaling pathways that promote cancer cell survival (review). International journal of oncology, 2014; 45: 1813-1819.

51. Choi M, Kipps T, Kurzrock R ATM Mutations in Cancer: Therapeutic Implications. Molecular cancer therapeutics, 2016; 15: 1781-1791.