ATM rs189037 (G > A) polymorphism increased the risk of cancer: an updated meta-analysis

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Abstract

Background: Rs189037 (G > A) is a functional single nucleotide polymorphism (SNP) in the Ataxia-telangiectasia mutated (ATM) gene that may be associated with the risk of cancer. We performed a meta-analysis to determine whether rs189037 polymorphism influences the occurrence of cancer and examined the relationship between this SNP and the etiology of cancer.

Methods: Case-control studies were retrieved from literature databases in accordance with established inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between rs189037 and cancer. Subgroup analysis and sensitivity analysis also were performed.

Results: After inclusion criteria were met, fifteen studies—comprising 8660 patients with cancer (cases) and 9259 controls—were included in this meta-analysis. Summary results indicated that an association was found between rs189037 and cancer risk. In the dominant model, the pooled OR using a random effects model was 1.207 (95% CI, 1.090–1.337; P < 0.001). The A allele of rs189037 increased the risk of lung cancer, breast cancer, and oral cancer. Results of subgroup analysis by ethnicity indicated that the SNP was associated with the risk of cancer among East Asian and Latino, but not Caucasian.

Conclusions: Results of this meta-analysis suggest that rs189037 is associated with the occurrence of lung cancer, breast cancer, and oral cancer as the risk factor. These data provide possible avenues for future case-control studies related to cancer.

Keywords: ATM, Cancer, Meta-analysis, Gene polymorphism

Background

The occurrence of cancer is increasing because of the population aging, smoking, physical inactivity, et al [1]. It is a cellular abnormality, uncontrolled growth caused by numerous damages or mutations in the genetic material due to hereditary or environmental factors, which is immune to many signals that control cell growth and death [2]. The genetic factors take more proportion on the causation of cancer than the lifestyle or environmental factors [3]. Many candidate genes or variations have been identified to contribute to the susceptibility of the cancer.
in ATM gene were also associated with the prostate cancer predisposition [8]. The loss of ATM function can give rise to ataxia telangiectasia, a pleiotropic disease with whose hallmarks, such as neurodegeneration, cancer-proneness, premature aging, radio-sensitivity, et al [9]. It can control genome stability, modulate oxidative stress response, autophagy, and cancer stem cell survival as tumor suppressor gene [10].

The variation of ATM gene can affect the normal function of the protein and increase the risk of cancer. Rs189037 (G > A) is located at the 5′UTR of ATM gene and is one of the critical polymorphism that may be related to the occurrence of different cancers and tumor diffusing capacity [11–15]. However, no consistent conclusion has been determined, and there remains discord between the findings in the literature, which may be attributable to a number of factors varying between studies including the types of cancer, the sample sizes, the genetic backgrounds of study subjects, and the potential presence of confounding bias [16].

When there is considerable variation in the results of studies on medical topics that have been studied extensively, meta-analysis can be used as a method to identify a common effect [17]. Such an analysis was conducted by Kang et al. (2014) to assess whether the ATM rs189037 polymorphism was associated with the risk of papillary thyroid carcinoma [18]. But only one case-control study was focused on rs189037. Bhowmik et al. analyzed the association of rs189037 with the risk of lung cancer and head and neck cancer in 2015 [19]. A total of 9 case-control studies were considered for this quantitative analysis. The third 2017 meta-analysis including ten case-control studies (4731 cases and 5142 controls) also reported the association between rs189037 and lung cancer susceptibility [12]. It seems superfluous to perform the meta-analysis of rs189037 and its association with cancer risk, whereas that the two latest meta-analyses only focused on the lung cancer and there are additional studies reporting its role in the other cancer types, such as breast cancer, papillary thyroid carcinoma, leukemia [14, 15, 20]. Therefore, we have performed a new meta-analysis of the ATM rs189037 polymorphism and the risk of different cancer types that includes more recent research.

Methods
Identification of relevant studies
We performed a literature search of three online literature databases (PubMed, Web of Science and Embase) to screen and identify available studies to be included in the meta-analysis. The keywords that were used are as follows: ATM, ataxia-telangiectasia mutated, rs189037, and cancer. Additionally, other possible studies were screened from the reference lists of included studies and relevant reviews.

The inclusion criteria were as follows: [1] the study were designed as case-control; [2] the cases in the identified studies were cancer patients; and [3] the studies reported the frequencies of ATM alleles and/or genotypes. When authors published multiple articles using the same or overlapping datasets, we selected the most recent study for inclusion. Exclusion criteria included the omission of healthy controls or the duplication of earlier research. In the event that inclusion data – including allele frequency, genotype or another sample characteristic – were not present in a report, we contacted the authors by email for the relevant information.

Data extraction
Two investigators (Zhi-liang Zhao and Lu Xia) independently extracted the data from each eligible publication, including the last name of the first author, the year of publication, the geographic region, the genotyping method, the sample size, and the number of genotypes reported for both cases and controls. In addition, to determine the contributions of underlying characteristics on the findings of the included reports, we also extracted data regarding patient ethnicities, sources of controls, and types of cancer.

Quality assessment
The quality of the included studies was assessed by the Newcastle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/.default.asp). The scores of five or more (maximum of nine) were considered “high quality”, while the studies with the scores under five were regarded as “low quality”.

Statistical analysis
The Hardy-Weinberg equilibrium of control genotypes was calculated using a χ² test. The strength of the association of rs189037 and cancer was evaluated with ratios (ORs) and 95% confidence intervals (CIs). A random effects model to resolve inter-study heterogeneity was used to calculate pooled estimates of the ORs and 95% CIs among the included studies [21].

Three genetic models (allele contrast model, dominant model, and recessive model) were used to measure the overall pooled ORs. As described in the previous study, OR1 (GG vs. AA), OR2 (GG vs. GA), and OR3 (GA vs. AA) were compared, with the definition of A as the risk allele [17]. If OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was selected. If OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was selected. If OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete overdominant model was selected. If OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was selected [22, 23].
We evaluated the degree of inter-study heterogeneity using a Q statistic [24, 25], where $P > 0.05$ was defined as an absence of heterogeneity [26]. We performed subgroup analysis for ethnicity (i.e., Caucasian, East Asian, etc.) and source of controls (i.e., hospital- or population-based).

We evaluated whether a single study potentially influenced the pooled effect size by means of sensitivity analysis. Specifically, we omitted each study from the meta-analysis in turn and subsequently evaluated whether any significant alterations were made to the pooled effect size.

Publication bias was investigated by using funnel plots generated for each study in which the standard error of log(OR) was plotted against the log(OR). Possible publication bias was determined when the plot was asymmetric, in which case an Egger test was used to determine degree of asymmetry, with $P < 0.05$ indicating publication bias [27].

All the statistical calculations were performed by Stata version 10.0 (Stata Corp., College Station, TX).

**Results**

We searched the database and identified 219 articles. According to the established inclusion criteria, a total of 15 publications were finally screened and included in our meta-analysis [13–15, 20, 28–38]. We collected 15 case-control studies, which contained 8660 patients with cancer (i.e., cases) and 9259 unaffected participants (i.e., controls). The individuals with the different genetic backgrounds were included (e.g., East Asian, Latino, and Caucasian). The main characteristics of the included studies were summarized in Table 1. Based on the results of the NOS scale, 12 studies were regarded as high quality and 3 studies were regarded as low quality. The genotype and allele frequencies of rs189037 SNP and HWE in controls were presented in Table 2. Of the 15 studies, no study deviated significantly from HWE.

**Heterogeneity detection and pooled analysis**

The association between the rs189037 polymorphism and cancer risk was evaluated using pooled ORs (with 95% CIs) under dominant, recessive, homozygous codominant, heterozygous codominant and allele contrast genetic models (Fig. 1, Table 3). Finally, we selected the dominant model to perform the pooled analysis [22, 39]. The pooled results showed that rs189037 polymorphism was associated with cancer risk. In the dominant model, the summary OR generated by a random effects model was 1.207 (95% CI, 1.090–1.337; $P < 0.001$). The A allele of rs189037 increased the risk of cancer. Results of subgroup analysis by ethnicity indicated that the SNP was associated with the risk of cancer among East Asian and Latino, but not Caucasian (Table 4). Moreover, the association between rs189037 and cancer was observed in subgroup analysis according to the source of controls (hospital based and population-based). Additionally, we also performed the subgroup analysis by the type of cancer. The results showed that rs189037 increased the

| Author  | Year | Region | Ethnicity | Controls source | Type of cancer | Genotyping method | Case/control | Male(case/control) | NOS scores |
|---------|------|--------|-----------|-----------------|----------------|-------------------|---------------|-------------------|------------|
| Kim     | 2006 | Korea  | East Asian| hospital-based  | lung cancer     | SNaPShot assay    | 616/616       | 483/483          | 4          |
| Wang    | 2010 | Taiwan | East Asian| hospital-based  | breast cancer    | PCR-RFLP          | 1232/1232     | 0/0               | 5          |
| Bau     | 2010 | Taiwan | East Asian| hospital-based  | oral cancer      | PCR-RFLP          | 620/620       | 586/582          | 5          |
| Lo      | 2010 | Taiwan | East Asian| hospital-based  | lung cancer      | MassARRAY         | 730/730       | 384/384          | 5          |
| Wang    | 2011 | Taiwan | East Asian| hospital-based  | leukemia         | PCR-RFLP          | 266/266       | 148/148          | 5          |
| Xu      | 2012 | Brazil | Latino    | hospital-based  | differentiated thyroid cancer | TaqMan | 592/885 | 146/379 | 6          |
| Hsia    | 2013 | Taiwan | East Asian| hospital-based  | lung cancer      | PCR-RFLP          | 358/716       | 254/488          | 5          |
| Zhao    | 2013 | China  | East Asian| hospital-based  | glioma           | TaqMan            | 384/384       | 222/217          | 6          |
| Damiola | 2013 | Belarus| Caucasian | population-based | papillary thyroid carcinoma | Illumina GoldenGate Genotyping Assay | 83/324 | 35/127 | 7          |
| Gu      | 2014 | China  | East Asian| hospital-based  | papillary thyroid carcinoma | MALDI-TOF-MS | 358/360 | 109/115          | 4          |
| Liu     | 2014 | China  | East Asian| population-based | lung cancer      | TaqMan            | 852/852       | 485/490          | 5          |
| Shen    | 2014 | China  | East Asian| hospital-based  | lung cancer      | TaqMan            | 487/516       | 0/0              | 5          |
| Song    | 2014 | Korea  | East Asian| hospital-based  | papillary thyroid carcinoma | TaqMan | 437/184 | 93/51 | 6          |
| Yue     | 2018 | China  | East Asian| hospital-based  | breast cancer    | ligase detection reaction method | 524/518 | 0/0             | 4          |
| Wang    | 2018 | China  | East Asian| hospital-based  | colorectal cancer | TaqMan | 1121/1056 | 631/561           | 5          |
occurrence of lung cancer, breast cancer, and oral cancer, but not leukemia, thyroid carcinoma, glioma, and colorectal cancer (Table 4).

Sensitivity analysis
We next sought to determine the contribution of individual studies to the pooled results via sensitivity analysis. To do this, we removed each study from the analysis, in turn, and then determined pooled ORs. We detected no significant changes between each of these analyses and the overall results of the meta-analysis, indicating that none of the included studies significantly altered the overall results. Therefore, our meta-analysis results are stable and reliable.
Table 3: Summarized ORs with 95% CIs for the association of \textit{ATM} rs189037 polymorphism with cancer

| Polymorphism       | Genetic model | n  | Statistical model | OR     | 95% CI          | \( p_z \) | \( I^2(\%) \) | \( p_{h} \) | \( p_{e} \) |
|--------------------|---------------|----|-------------------|--------|-----------------|----------|-------------|----------|----------|
| Rs189037           |               |    |                    |        |                 |          |             |          |          |
| Allele contrast    | 14            | Random | 1.123  | 1.049–1.202 | 0.001 | 53.5 | 0.009 | 0.337 |
| Homozygous codominant | 14          | Random | 1.267  | 1.105–1.454 | 0.001 | 52.0 | 0.012 | 0.308 |
| Heterozygous codominant | 14          | Random | 1.159  | 1.049–1.281 | 0.004 | 23.5 | 0.200 | 0.624 |
| Dominant           | 15            | Random | 1.207  | 1.090–1.337 | <0.001 | 40.9 | 0.050 | 0.415 |
| Recessive          | 14            | Random | 1.151  | 1.061–1.247 | 0.001 | 27.5 | 0.160 | 0.272 |

\( n \), the number of studies; \( p_z \), \( p_{h} \), \( p_{e} \) value for association test; \( p_{h} \), \( p_{e} \) value for heterogeneity test; \( p_{e} \), \( p_{h} \) value for publication bias test

Publication bias
Publication bias was assessed by generating and analyzing a funnel plot (Fig. 2), and no significant effect of publication bias was detected (\( P_e = 0.415 \)) (Table 3).

Discussion
We explored the underlying relationship between rs189037 SNP of \textit{ATM} gene and the occurrence of cancer using a meta-analysis that included 15 case-control studies (8660 cases and 9259 controls). The pooled results indicated that there was an association, and subgroup analysis (8660 cases and 9259 controls). The pooled results indicated that there was an association, and subgroup analysis further investigated the distribution deviation between cases and controls.

Previously, three meta-analyses have reported the putative association between rs189037 and the occurrence of cancer [12, 18, 19]. Generally, our results were consistent with the previous studies. It seems that our meta-analysis is redundant, but there are some highlights compared with the previously published studies. Firstly, our analysis included the newly published studies since the previous meta-analyses were performed. A total of 15 studies were included, which could comprehensively represent rs189037 better compared with the previous meta-analyses. Additionally, the subgroup analyses were carried out by ethnicity, source of controls, and types of cancer to explore the potential origins of heterogeneity and to measure the study stability. Thus, to some degree, our meta-analysis could give a more accurate, comprehensive finding that there is an association between rs189037 SNP and lung cancer, breast cancer, and oral cancer, but not leukemia, thyroid carcinoma, glioma, and colorectal cancer.

However, the relatively small sample sizes of Latino and Caucasian populations limited our ability to isolate stable effects for these subgroups. Only one study reported the association of rs189037 with differentiated thyroid cancer in Latino including 592 cases and 885 controls [31]. For Caucasian, there is also just one study about the risk of papillary thyroid carcinoma including 83 cases and 324 controls [34]. Thus, we cannot obtain the comprehensive results of the association between rs189037 and cancer risk in Latino and Caucasian population because of the limited sample size.

Rs189037 is in the promoter region of \textit{ATM} gene and markedly changes the folding architectures. The secondary structure of rs189037 G/A alleles was significant changed using RNAfold prediction [38]. It has been confirmed to be associated with carcinogenesis [38, 40]. The G allele of rs189037 SNP is an independent risk factor for radiation-induced pneumonitis in Chinese thoracic cancer patients [41]. Moreover, rs189037 and other polymorphism in DNA repair genes can serve as candidate prognostic markers of the survival of non-small-cell lung cancer patients [42]. The combined analysis showed that this SNP was associated with the poor prognosis. In addition, Piaceri et al. reported that the rs189037 was associated with the longevity in Italian centenarians [43]. Taken into account that the A allele of rs89037 increased the risk of cancer in our meta-analysis, we need to do more efforts to explore its influence on the expression of \textit{ATM} protein.
However, there are some potential limitations in our current analysis. Firstly, the significant heterogeneity were detected in summary and subgroup analyses. Though the subgroup analysis was used to explore the possible origins of heterogeneity, no single factor could fully explain the heterogeneity. When the subgroup analysis was performed by the cancer types, the results showed that rs189037 increased the occurrence of lung cancer, breast cancer, and oral cancer, but not leukemia, thyroid carcinoma, glioma, and colorectal cancer. Clearly, the role of rs189037 polymorphism was influenced by cancer types. Thus, more cancer types need to be included and assessed in the future in order to comprehensively explore the effect of rs189037 in the cancer risk. Secondly, we did not analysis the gene-gene interactions and epigenetic, which were the influence factors of the cancer. Smoking, physical activity, and emotional state are also involved in the occurrence of cancer. Thirdly, just one SNP in ATM gene was analyzed and its information was limited. The occurrence of the cancer is usually thought to involve the multiple genes and their interactions.

**Conclusions**

Our study showed that there was an association between the rs189037 in ATM gene and lung cancer, breast cancer, and oral cancer. The studies containing different ethnicity populations need to validate the findings of this meta-analysis and to ascertain the epigenetic mechanisms and environmental influences that contribute to the risk of cancer.

**Acknowledgements**

This manuscript has been edited by native English-speaking experts of BioMed Proofreading.

**Funding**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

JY conceived and designed the study. ZLZ and LX were responsible for collection of data, performing statistical analyses, and manuscript preparation. CZ and ZLZ were responsible for reviewing the data. All authors contributed to drafting the manuscript, and all read and approved the final version.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Abbreviations**

ATM: Ataxia-telangiectasia mutated; CI: Confidence interval; HWE: Hardy-Weinberg equilibrium; OR: Odds ratios; SNP: Single nucleotide polymorphism
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