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

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ABSTRACT

Purpose: We conducted two meta-analyses of ATM genetic polymorphisms and cancer risk in individuals with or without radiation exposure to determine whether there was a joint effect between the ATM gene and radiation exposure in carcinogenesis.

Results: rs1801516, which was the only ATM polymorphism investigated by more than 3 studies of radiation exposure, was eligible for the present study. The meta-analysis of 23333 individuals without radiation exposure from 24 studies showed no association between the rs1801516 polymorphism and cancer risk, without heterogeneity across studies. The meta-analysis of 3787 individuals with radiation exposure from 6 studies showed a significant association between the rs1801516 polymorphism and a decreased cancer risk, with heterogeneity across studies. There was a borderline-significant difference between the ORs of the two meta-analyses ($P = 0.066$), and the difference was significant when only Caucasians were included ($P = 0.011$).

Materials and methods: Publications were identified by searching PubMed, EMBASE, Web of Science, and CNKI databases. Odds ratios (ORs) were calculated to estimate the association between ATM genetic polymorphisms and cancer risk. Tests of interaction were used to compare differences between the ORs of the two meta-analyses.

Conclusions: Our meta-analyses confirmed the presence of a gene-environment interaction between the rs1801516 polymorphism and radiation exposure in carcinogenesis, whereas no association was found between the rs1801516 polymorphism and cancer risk for individuals without radiation exposure. The heterogeneity observed in the meta-analysis of individuals with radiation exposure might be due to gene-ethnicity or gene-gene interactions. Further studies are needed to elucidate sources of the heterogeneity.

INTRODUCTION

The International Agency for Research on Cancer has confirmed that ionizing radiation is associated with an increased risk for a wide range of cancers, including breast cancer, thyroid cancer, and leukemia [1]. The risk for carcinogenesis associated with radiation exposure is influenced by genetic background [2, 3]. Understanding gene–environment interactions in carcinogenesis has been a stated priority for the National Cancer Institute [4].

The ataxia telangiectasia-mutated (ATM) protein plays a central role in mediating the cellular response to radiation-induced DNA damage [5]. Germ-line inactivating mutations in the ATM gene cause ataxia-
telangiectasia, a recessive genetic disorder with a high incidence of cancer [6]. Ataxia-telangiectasia heterozygotes appear to have a greater risk of developing cancer than the wild-type homozygotes, leading to the estimation that polymorphisms in the ATm gene may alter the risk of carcinogenesis [7]. In the past two decades, about 100 studies have been published to evaluate the associations of ATm genetic polymorphisms with cancer risk. Some of the polymorphisms have been reported by more than 10 studies, such as rs1801516, IVS10-6T > G, rs1800057, rs1800054, rs1800056, rs1800058, and rs4986761. Although most of the findings on these polymorphisms were inconsistent, a meta-analysis of 11120 participants showed a significant association between the rs1800057 polymorphism and breast cancer risk [8]. Recently, two meta-analyses demonstrated evidence for gene-environment interactions between the ATm gene and radiation exposure in the development of radiotherapy-induced adverse events [9, 10]. Taken together, these suggest a possible role of ATm genetic polymorphisms in carcinogenesis through gene–radiation interactions.

A number of studies have investigated the joint effect between the ATm gene and radiation exposure on cancer risk. The first study published in 2002 showed that polymorphisms in the ATm gene were not associated with an increased breast cancer risk in patients with Hodgkin’s disease after radiotherapy [11]. Subsequently, 5 studies have been conducted on this issue, with inconsistent results [12–16]. Given the uncertainty and the lack of a meta-analysis on this topic, we conducted two meta-analyses of ATm genetic polymorphisms and cancer risk in individuals in the presence or absence of radiation exposure to determine whether there was a joint effect between the ATm gene and radiation exposure in carcinogenesis.

RESULTS

Assessing quality of included studies

rs1801516 was the only ATm genetic polymorphism investigated by more than 3 studies of radiation exposure, and was eligible for the present study. A total of 29 studies were identified for the meta-analysis of individuals without radiation exposure [12, 17–44], and 6 studies for the meta-analysis of individuals with radiation exposure [11–16] (Figure 1). The ATm rs1801516 genotype distribution in controls was not in Hardy–Weinberg equilibrium (HWE) in 5 studies [12, 18–21], could not be assessed in 4 studies [11, 13, 25, 26], and was in HWE for the other studies [17, 22–24, 27–44]. As a result, 5 studies were identified with methodological errors and were excluded from a meta-analysis [12, 18–21]. The quality assessments according to Newcastle–Ottawa scale (NOS) [45] were described in Supplementary Table S1. The included studies had a relatively high quality with a median score of 7, ranging from 5 to 9. The quality was high for 22 studies (≥ 6) [11–16, 25, 26, 28–30, 32–40, 42, 43] and low for 8 studies (≤ 5) [17, 22–24, 27, 31, 41, 44].

Meta-analysis for individuals in the absence of radiation exposure

This meta-analysis included 24 studies with 9858 cases and 13475 controls [17, 22–44] (Table 1). When all cancer types were considered, there was no significant association of the rs1801516 polymorphism with cancer risk (homozygous model: odds ratio [OR] = 0.84, 95% confidence interval [CI]: 0.68, 1.03, P = 0.074; heterozygous model: OR = 0.99, 95%CI: 0.91, 1.07, P = 0.784; recessive model: OR = 0.87, 95%CI: 0.69, 1.10, P = 0.231; dominant model: OR = 0.97, 95%CI: 0.89, 1.06, P = 0.632). There was little evidence of heterogeneity across studies (I² ≤ 29.1%). Subgroup analyses were conducted in order to check whether the features of the included studies affected the results of this meta-analysis. For each genetic model, there was little variation in the effect sizes according to cancer site, ethnicity, study quality, and study size. Figures 2–3 showed the forest plot of the association under the homozygous and dominant models, and Tables 2–3 showed the subgroup analyses under the homozygous and dominant models. The results under the heterozygous and recessive models were similar to those under the dominant and homozygous models, and thus were not shown in figures and tables. For all the meta-analyses, sensitivity analyses did not identify any single study that markedly influenced the estimates, indicating that these results were reliable.

We examined if there was evidence of publication bias for each meta-analysis that included 10 or more studies. Asymmetry in the funnel plots was not observed under any comparisons, and significant asymmetry was not suggested by Egger’s linear regression test or Beggs’s rank correlation test (Supplementary Figure S1).

Meta-analysis for individuals in the presence of radiation exposure

There were 6 studies with 1459 cases and 2328 controls eligible for this meta-analysis [11–16]. The main characteristics of these studies were presented in Table 4. 2 out of 6 studies investigated the association between the rs1801516 polymorphism and contralateral breast cancer risk in breast cancer patients after radiotherapy [13, 14], 1 study investigated the association between the rs1801516 polymorphism and breast cancer risk in patients with Hodgkin’s disease after radiotherapy [11], and 3 studies investigated the association between the rs1801516 polymorphism and papillary thyroid carcinoma risk in individuals who lived in the areas contaminated
by radionuclides [12, 15, 16]. 5 out of 6 studies were conducted in Caucasians [11–15], and 1 in Polynesians [16]. All the included studies had used histologic analyses to confirm cancers.

To include all 6 studies for a summary OR estimate, the meta-analysis could only be conducted under the dominant model. The result showed a significant association between the rs1801516 polymorphism and a decreased risk of radiation-induced cancer (OR = 0.64, 95% CI: 0.41, 0.99; P = 0.044), with high between study heterogeneity (I² = 71.4%, P = 0.004) (Figure 4). Sensitivity analyses identified that the study by Maillard et al. was the outlier, and the association was more significant after this study was excluded (OR = 0.55, 95% CI: 0.36, 0.83; P = 0.005) [16]. However, the heterogeneity remained significant (I² = 66.9%, P = 0.017), indicating that other factors might contribute to the heterogeneity. Table 5 showed the results of the subgroup analyses. A significant association was shown among Caucasians (OR = 0.55, 95% CI: 0.36, 0.83; P = 0.005), whereas no association was shown among other subgroups. In addition, there was obvious evidence of heterogeneity in all subgroups (I² ranged 66.9% to 81.8%), suggesting that the examined factors had a minimal influence on the variation of the estimates.

Table 1: Characteristics of studies included in the meta-analysis of individuals in the absence of radiation exposure

<table>
<thead>
<tr>
<th>First author, year [Ref.]</th>
<th>Ethnicity</th>
<th>Region/Country</th>
<th>Type of cancer</th>
<th>Family history of cancer</th>
<th>HWE in controls</th>
<th>Minor allele frequency</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maillet P, 2000, [44]</td>
<td>Swiss</td>
<td>Switzerland</td>
<td>Colorectal cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>0.14</td>
<td>46/163</td>
</tr>
<tr>
<td>Buchholz TA, 2004, [43]</td>
<td>Mixed</td>
<td>USA</td>
<td>Breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.14</td>
<td>58/528</td>
</tr>
<tr>
<td>Heikkinen K, 2005, [42]</td>
<td>Finnish</td>
<td>Finland</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>0.25</td>
<td>121/306</td>
</tr>
<tr>
<td>Gonzalez-Hormazabal P, 2008, [41]</td>
<td>Chilean</td>
<td>Chile</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>0.07</td>
<td>126/200</td>
</tr>
<tr>
<td>Angele S, 2003, [40]</td>
<td>NR</td>
<td>France</td>
<td>Breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>254/312</td>
</tr>
<tr>
<td>Renwick A, 2006, [39]</td>
<td>UK ethnic(whites)</td>
<td>UK</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>0.16</td>
<td>443/521</td>
</tr>
<tr>
<td>Angele S, 2004, [38]</td>
<td>Caucasian</td>
<td>UK</td>
<td>Prostate cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.17</td>
<td>628/445</td>
</tr>
<tr>
<td>Yang H, 2007, [37]</td>
<td>Caucasian</td>
<td>USA</td>
<td>Non-small cell lung cancer</td>
<td>No</td>
<td>Yes</td>
<td>&gt; 0.05</td>
<td>544/546</td>
</tr>
<tr>
<td>Tommiska J, 2006, [36]</td>
<td>Finnish</td>
<td>Finland</td>
<td>Breast cancer</td>
<td>Both</td>
<td>Yes</td>
<td>0.24</td>
<td>1581/702</td>
</tr>
<tr>
<td>Wu X, 2006, [35]</td>
<td>Whites (89.3%)</td>
<td>USA</td>
<td>Bladder cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.14</td>
<td>608/592</td>
</tr>
<tr>
<td>Sommer SS, 2002, [34]</td>
<td>Caucasian (≥ 80%)</td>
<td>USA</td>
<td>Breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>43/43</td>
</tr>
<tr>
<td>Xu L, 2012, [33]</td>
<td>REUS; mixed population</td>
<td>USA</td>
<td>Thyroid carcinoma</td>
<td>No</td>
<td>Yes</td>
<td>&gt; 0.10</td>
<td>592/885</td>
</tr>
<tr>
<td>Margulis V, 2008, [32]</td>
<td>NR</td>
<td>USA</td>
<td>Renal cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.14</td>
<td>323/337</td>
</tr>
<tr>
<td>Al-Hadyan KS, 2012, [31]</td>
<td>NR</td>
<td>Saudi Arabia</td>
<td>Head and neck cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.07</td>
<td>156/251</td>
</tr>
<tr>
<td>Schrauder M, 2008, [30]</td>
<td>NR</td>
<td>German</td>
<td>Breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.15</td>
<td>514/511</td>
</tr>
<tr>
<td>Dork T, 2001, [29]</td>
<td>Caucasian</td>
<td>Germany</td>
<td>Breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>1000/325</td>
</tr>
<tr>
<td>Wojcicka A, 2014, [28]</td>
<td>Caucasian</td>
<td>Poland</td>
<td>Thyroid cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.11</td>
<td>1603/1844</td>
</tr>
<tr>
<td>Kristensen AT, 2004, [27]</td>
<td>NR</td>
<td>Norway</td>
<td>Rectal cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.17</td>
<td>151/3526</td>
</tr>
<tr>
<td>Hirsch AE, 2008, [26]</td>
<td>African-American</td>
<td>USA</td>
<td>Breast cancer</td>
<td>No</td>
<td>NR</td>
<td>&gt; 0.05</td>
<td>37/95</td>
</tr>
<tr>
<td>Pereda CM, 2015, [24]</td>
<td>mixed</td>
<td>Cuban</td>
<td>Thyroid cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.11</td>
<td>197/206</td>
</tr>
<tr>
<td>Tecza K, 2015, [23]</td>
<td>Caucasian</td>
<td>Poland</td>
<td>Ovarian cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>223/335</td>
</tr>
<tr>
<td>Meier M, 2005, [22]</td>
<td>Caucasian</td>
<td>Germany</td>
<td>T cell acute lymphoblastic leukemia</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>103/96</td>
</tr>
<tr>
<td>Oliveira S, 2012, [17]</td>
<td>Portuguese</td>
<td>Portugal</td>
<td>Cervical cancer</td>
<td>No</td>
<td>Yes</td>
<td>0.17</td>
<td>79/280</td>
</tr>
</tbody>
</table>

Abbreviations: HWE, Hardy–Weinberg equilibrium.
Differences in the effect estimates between individuals in the presence or absence of radiation exposure

The effect estimates for individuals in the absence and presence of radiation exposure were compared to determine the relationship of the interaction (synergistic or antagonistic) between radiation exposure and the rs1801516 polymorphism in carcinogenesis. Figure 5 displayed the comparisons of the ORs between the main meta-analyses and between the subgroup analyses under the dominant model. The genetic effect for all participants in the presence of radiation exposure was borderline significantly larger than that for all participants in the absence of radiation exposure (radio of OR = 0.66, 95% CI: 0.42, 1.03; \( P = 0.066 \)). The difference was statistically significant when only Caucasians were included (radio of OR = 0.58, 95% CI: 0.38, 0.88; \( P = 0.011 \)).

DISCUSSION

This work represents the first comprehensive assessment of the literature on the gene-environment interaction for polymorphisms in the \( ATM \) gene and radiation exposure in carcinogenesis. rs1801516, which was the only \( ATM \) genetic polymorphism investigated by more than 3 studies, was eligible for the present study. Our meta-analyses showed that the rs1801516 polymorphism interacted with radiation exposure, resulting in a synergistic effect in carcinogenesis. In addition, we

Figure 1: Flow chart for inclusion and exclusion of studies. The search on Chinese National Knowledge Infrastructure (CNKI) database identified no study of the \( ATM \) rs1801516 polymorphism and cancer risk. 5 studies were identified with methodological errors and were excluded from the present meta-analysis in the subsequent quality assessment procedure [12, 18–21]. One article reported data for radiation exposed as well as unexposed populations, the results for each group were considered as a separate study [12].
Table 2: Subgroup analyses for the association between the ATM rs1801516 polymorphism and cancer risk in individuals in the absence of radiation exposure under the homozygous model

<table>
<thead>
<tr>
<th>Study selection</th>
<th>Studies (n)</th>
<th>Cases AA/GG</th>
<th>Controls AA/GG</th>
<th>Heterogeneity F(%)</th>
<th>P value</th>
<th>OR (95%CI)</th>
<th>Effect P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>12</td>
<td>174/5195</td>
<td>187/4683</td>
<td>0.0</td>
<td>0.858</td>
<td>0.81 (0.65–1.01)</td>
<td>0.060</td>
</tr>
<tr>
<td>≤ 5</td>
<td>8</td>
<td>11/804</td>
<td>122/3608</td>
<td>0.0</td>
<td>0.617</td>
<td>0.99 (0.53–1.83)</td>
<td>0.976</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large (&gt; 500)</td>
<td>12</td>
<td>173/5341</td>
<td>274/7144</td>
<td>0.0</td>
<td>0.675</td>
<td>0.82 (0.66–1.02)</td>
<td>0.081</td>
</tr>
<tr>
<td>Small (&lt; 500)</td>
<td>8</td>
<td>12/658</td>
<td>35/1147</td>
<td>0.0</td>
<td>0.909</td>
<td>0.98 (0.52–1.86)</td>
<td>0.962</td>
</tr>
<tr>
<td>Family history of casesb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic cancer</td>
<td>16</td>
<td>137/4989</td>
<td>264/7452</td>
<td>0.0</td>
<td>0.960</td>
<td>0.88 (0.70–1.11)</td>
<td>0.269</td>
</tr>
<tr>
<td>Family cancer</td>
<td>5</td>
<td>48/1010</td>
<td>83/1243</td>
<td>4.1</td>
<td>0.947</td>
<td>0.71 (0.49–1.03)</td>
<td>0.071</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>17</td>
<td>183/5615</td>
<td>307/7737</td>
<td>0.0</td>
<td>0.941</td>
<td>0.82 (0.67–1.02)</td>
<td>0.066</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>9</td>
<td>110/2889</td>
<td>119/2404</td>
<td>0.0</td>
<td>0.704</td>
<td>0.76 (0.57–1.01)</td>
<td>0.060</td>
</tr>
<tr>
<td>Sum</td>
<td>20</td>
<td>185/5999</td>
<td>309/8291</td>
<td>0.0</td>
<td>0.887</td>
<td>0.84 (0.68–1.03)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

AA represents the number of individuals who carry the AA alleles. GG represents the number of individuals who carry the GG alleles. Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio. *The genotype distribution in controls was in HWE in all the studies. bThe study by Tommiska et al. [36] reported the risks of both familial and sporadic cancer in comparison with the same controls, and the results for each were considered as a separate study.

Figure 2: Association between the ATM rs1801516 polymorphism and cancer risk in individuals in the absence of radiation exposure under the homozygous model. AA represents the number of individuals who carry the AA alleles. GG represents the number of individuals who carry the GG alleles. ORs for each study are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamond represents the estimated overall effect based on the meta-analysis. ORs and 95%CIs were computed by applying a continuity correction (addition of 0.5 in all the cells) in order to overcome problems resulted from cells containing zero values [69]. All statistical tests were two sided. Abbreviations: CI, confidence interval; OR, odds ratio.
showed convincing evidence of no association between the rs1801516 polymorphism and cancer risk for individuals in the absence of radiation exposure.

The present meta-analysis of 23333 participants in the absence of radiation exposure had a very large sample size, and was able to provide convincing evidence of no association between the rs1801516 polymorphism and cancer risk. Up to now, 5 meta-analyses have been performed for the role of the rs1801516 polymorphism on cancer risk: 4 on breast cancer [8, 46–48] and 1 on thyroid cancer [49]. One of the meta-analyses showed that homozygous carriers of the rs1801516 genotype had a lower breast cancer risk compared with carriers of the heterozygous and homozygous wild-type genotypes [48]. However, the other studies did not find a significant association between the rs1801516 polymorphism and cancer risk [8, 46, 47, 49]. Compared with the previous meta-analyses [8, 46–49], the present meta-analysis included more studies, and was able to employ rigorous methodology to estimate the genetic effect of the rs1801516 polymorphism on carcinogenesis. The overall meta-analyses of individuals in the absence of radiation exposure showed no association between the rs1801516 polymorphism and cancer risk under the four genetic models. We also conducted subgroup analyses based on cancer site, ethnicity, familial cancer history, study quality, and sample size. For each genetic model, we observed a small variability in the effect sizes between the subgroup analyses and the main meta-analysis. These suggested that the results of the main meta-analysis were independent on the features of the included studies. The extensive consistency provided optimal evidence of the credibility of no association between the rs1801516 polymorphism and cancer risk for individuals in the absence of radiation exposure.

Our meta-analysis of 3787 participants in the presence of radiation exposure provided evidence of an association between the rs1801516 polymorphism and decreased cancer risk for individuals who exposed to radiation. This meta-analysis included 6 studies across two ethnicities: 1 study in Polynesians and 5 studies in Caucasions. The nature of the two populations are different: the Polynesians are geographically isolated from the rest of the world, and have a significant variation in allele frequencies (minor allele frequency [MAF] in Polynesians = 0.02) as compared to the Caucasians (MAF in Caucasians = 0.19) [16]. The study in Polynesians showed that the minor allele carriers of the rs1801516

### Table 3: Subgroup analyses for the association between the ATM rs1801516 polymorphism and cancer risk in individuals in the absence of radiation exposure under the dominant model

<table>
<thead>
<tr>
<th>Study selection</th>
<th>Studies (n)</th>
<th>Cases AA + AG / GG</th>
<th>Controls AA + AG / GG</th>
<th>Heterogeneity I² (%)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>15</td>
<td>2145/6088</td>
<td>2035/5837</td>
<td>32.4</td>
<td>0.103</td>
<td>0.92 (0.85–1.00)</td>
<td>0.054</td>
</tr>
<tr>
<td>≤ 5</td>
<td>8</td>
<td>277/804</td>
<td>1452/3608</td>
<td>0.0</td>
<td>0.705</td>
<td>1.18 (1.00–1.41)</td>
<td>0.058</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large (&gt; 500)</td>
<td>14</td>
<td>2201/6205</td>
<td>3069/8220</td>
<td>0.052</td>
<td>41.5</td>
<td>0.95 (0.86–1.05)</td>
<td>0.325</td>
</tr>
<tr>
<td>Small (&lt; 500)</td>
<td>9</td>
<td>221/687</td>
<td>418/1225</td>
<td>0.573</td>
<td>0.0</td>
<td>1.06 (0.87–1.30)</td>
<td>0.536</td>
</tr>
<tr>
<td>Familial history of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial cancer</td>
<td>5</td>
<td>504/1010</td>
<td>649/1243</td>
<td>0.169</td>
<td>37.8</td>
<td>0.91 (0.79–1.06)</td>
<td>0.214</td>
</tr>
<tr>
<td>Sporadic cancer</td>
<td>19</td>
<td>1902/5665</td>
<td>3115/8428</td>
<td>0.170</td>
<td>23.6</td>
<td>0.97 (0.90–1.04)</td>
<td>0.352</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>19</td>
<td>2279/6068</td>
<td>3320/8345</td>
<td>0.126</td>
<td>27.9</td>
<td>0.95 (0.88–1.02)</td>
<td>0.114</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
<td>1306/3299</td>
<td>1107/2862</td>
<td>0.085</td>
<td>39.5</td>
<td>0.95 (0.81–1.10)</td>
<td>0.462</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>495/1897</td>
<td>621/2314</td>
<td>0.304</td>
<td>16.1</td>
<td>0.96 (0.84–1.10)</td>
<td>0.571</td>
</tr>
<tr>
<td>HWE in controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>2367/6482</td>
<td>3423/8988</td>
<td>0.073</td>
<td>32.9</td>
<td>0.96 (0.89–1.03)</td>
<td>0.640</td>
</tr>
<tr>
<td>Overall</td>
<td>23</td>
<td>2422/6892</td>
<td>3487/9445</td>
<td>0.114</td>
<td>27.1</td>
<td>0.97 (0.89–1.06)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

AA + AG represents the number of individuals who carry the AA or AG alleles. GG represents the number of individuals who carry the GG alleles. Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio. The study by Tommiska et al. [36] reported the risks of both familial and sporadic cancer in comparison with the same controls, and the results for each were considered as a separate study.
polymorphism were associated with an increased cancer risk compared with the main allele carriers in the presence of radiation exposure [16]. On the contrary, all the other studies (Caucasians) showed a consistently decreased cancer risk of the minor allele carriers compared with the main allele carriers in the presence of radiation exposure (2 of 5 comparisons were individually significant [13, 15]). In addition, the test of interaction showed a significant difference in the effect estimates between Caucasians in the presence and absence of radiation exposure. Furthermore, two meta-analyses demonstrated convincing evidence of an association between the rs1801516 polymorphism and radiotherapy-induced adverse events [9, 10]. Taken together, these suggested a gene-environment interaction between the rs1801516 polymorphism and radiation exposure in carcinogenesis, and the interaction might be modified by ethnicity. However, we could not rule out the possibility that the observed association between the rs1801516 polymorphism and cancer risk of Polynesians in the presence of radiation exposure was a chance finding. It should be noted that there was a high variability across studies included in this meta-analysis. Our subgroup analyses failed to explain the heterogeneity, indicating that the study-level factors examined had little influence on the variation of the estimates.

The ATM rs1801516 polymorphism is a polymorphic G-to-A transition at nucleotide 5557 of exon 39, resulting in a change from aspartic acid to asparagine at amino acid position 1853 of the protein [50]. In vitro data showed that human fibroblasts carrying the minor alleles of the rs1801516 polymorphism increased cellular radiosensitivity compared with those carrying the major alleles [51, 52]. Some variants of the ATM gene, including the rs1801516 polymorphism, were reported to be associated with a decreased ATM expression and a reduced capacity of DNA damage recognition [42, 53]. Based on these data, it was difficult to figure out how this single polymorphism might be associated with a decreased cancer risk for individuals who were exposed to radiation. Instead, a gene-gene interaction of the ATM gene with BRCA1 has been reported [28, 52]. Therefore, it could be expected that the polygenic action of unidentified variants of the ATM gene, including the rs1801516 polymorphism, might contribute to the observed association.

![Figure 3: Association between the ATM rs1801516 polymorphism and cancer risk in individuals in the absence of radiation exposure under the dominant model.](image-url)

- AA + AG represents the number of individuals who carry the AA or AG alleles. GG represents the number of individuals who carry the GG alleles. ORs for each study are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamond represents the estimated overall effect based on the meta-analysis. All statistical tests were two sided. Abbreviations: CI, confidence interval; OR, odds ratio.

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alleles or genes probably played a non-negligible role on the function of the rs1801516 polymorphism. The differences observed between Polynesians and Caucasians regarding the effect of the rs1801516 polymorphism on cancer risk following radiation exposure as well as the clinical heterogeneity were likely to be due to gene-gene interactions.

Our study has a number of possible limitations. 1) Due to fewer than 10 studies in the meta-analysis of individuals with radiation exposure, the publication bias was not tested by the funnel plot, for this method could not obtain enough power in the case [54]. However, based on the Venice criteria that assess cumulative evidence on genetic associations, an OR of > 0.85 or < 1.15 could be easily susceptible to biases, including phenotyping errors, genotyping errors, population stratification, and selective reporting biases [55–57]. This meta-analysis yielded an OR of 0.55, suggesting that this genetic effect was not so vulnerable to biases. 2) Except for the dominant model, other genetic models, such as recessive, heterozygous, and

Table 4: Characteristics of studies included in the meta-analysis of individuals in the presence of radiation exposure

<table>
<thead>
<tr>
<th>First author, year [Ref.]</th>
<th>Ethnicity</th>
<th>Region/ Country</th>
<th>Investigation arm</th>
<th>Control arm</th>
<th>Family history of cases</th>
<th>HWE in controls</th>
<th>Minor allele frequency</th>
<th>Cases/ controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akulevich NM, 2009, [12]¹</td>
<td>Caucasian</td>
<td>European part of Russia</td>
<td>IR-induced thyroid cancer (Cases lived in the areas contaminated with radiocaclides from Chernobyl fallouts; the cases were younger than 15 years at the time of the Chernobyl accident; The median time to develop PTC was 14 years.)</td>
<td>IR-exposed controls (the controls were matched to the cases by age and geographic region.)</td>
<td>No</td>
<td>Yes</td>
<td>0.17</td>
<td>122/198</td>
</tr>
<tr>
<td>Damiola F, 2014, [15]¹</td>
<td>Caucasian</td>
<td>Belarus</td>
<td>IR-induced thyroid cancer (cases lived in the areas contaminated with radiocaclides from Chernobyl fallouts. At the time of the Chernobyl accident, the cases were younger than 18 years old; the cases were diagnosed within 6–12 years after the accident.)</td>
<td>IR-exposed controls (residents of the same settlements as the cases. Age of IR-exposed controls was set to be ± 3 years of the cases.)</td>
<td>No</td>
<td>Yes</td>
<td>0.16</td>
<td>70/250</td>
</tr>
<tr>
<td>Broeks A, 2008, [13]</td>
<td>Caucasian</td>
<td>Netherlands</td>
<td>Therapy-induced contralateral breast cancer (the first breast cancer was diagnosed before age 50. There is an interval of at least 1 year between the first and the second breast cancer.)</td>
<td>Unilateral breast cancer (the first breast cancer was diagnosed before age 50. The patients were disease-free of a second breast cancer for at least 5 years.)</td>
<td>No</td>
<td>NR</td>
<td>&gt; 0.10</td>
<td>247/190</td>
</tr>
<tr>
<td>Concannon P, 2008, [14]</td>
<td>Caucasian</td>
<td>USA</td>
<td>Therapy-induced contralateral breast cancer (the first breast cancer was diagnosed before age 55. There is an interval of at least 1 year between the first and the second breast cancer. Median interval between first diagnosis and reference date was 4.3 years.)</td>
<td>Unilateral breast cancer (the first breast cancer was diagnosed before age 55. The patients were disease-free of a second breast cancer for at least 1 year. Median interval between first diagnosis and reference date was 4.3 years.)</td>
<td>No</td>
<td>Yes</td>
<td>0.13</td>
<td>808/1397</td>
</tr>
<tr>
<td>Offit K, 2002, [11]</td>
<td>Caucasian</td>
<td>USA</td>
<td>Radiation-induced breast cancer after treatment for Hodgkin’s disease (The median time to develop breast cancer was 18 years.)</td>
<td>Patients with Hodgkin’s disease who did not develop breast cancer (The median follow-up was 17 years.)</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>37/23</td>
</tr>
<tr>
<td>Maillard S, 2015, [16]</td>
<td>Polynesian</td>
<td>France</td>
<td>IR-induced thyroid cancer (Cases lived in the areas where a total of 41 atmospheric nuclear weapons tests were carried out between 1966 and 1974 and where individuals were at an increased risk of developing thyroid cancer caused by radiocaclides [74]. All cases were under the age of 15 in 1974, and all were diagnosed for thyroid cancer between 1979 and 2004. Age distribution was ranged from 10 to 62.)</td>
<td>IR-exposed controls (the controls were matched to the cases by race, age and geographic region.)</td>
<td>No</td>
<td>Yes</td>
<td>0.02</td>
<td>175/270</td>
</tr>
</tbody>
</table>

Abbreviations: HWE, Hardy–Weinberg equilibrium; IR, ionizing radiation.
¹There is no overlap in the participants between the two studies [12, 15].
homozygous models, were not examined because of the limited information in the meta-analysis of individuals in the presence of radiation exposure. Therefore, the gene-environment interaction in other genetic models could not be determined. 3) Due to the lack of individual patient data, we were not able to conduct the present meta-analyses based on individual patient data, in which we can: (a) check each study to apply consistent conditions for inclusion and to standardize analysis techniques, and (b) adjust the analyses for covariates (radiation dose, gender, and age). It is especially so for the study by Broeks et al. that reported the significance of \( ATM \) \( rs1801516 \) variants on secondary breast cancer risk after treatment of primary breast cancer [13]. In this study, 32% patients included in the present meta-analysis did not receive radiotherapy [13]. Because the sensitivity analyses showed no difference in the effect estimates after exclusion of this study, we believed that the incomplete data might reduce the power of the analysis but did not bias it. Moreover, literature based meta-analyses were considered to be often consistent with those based on individual patient data [58], and should not be viewed as “inferior” [59].

In conclusion, the present study gave a clear picture of gene-environment interaction for the \( ATM \) \( rs1801516 \) genotype and radiation exposure in carcinogenesis: there was convincing evidence of no association between the \( rs1801516 \) polymorphism and cancer risk of individuals in the absence of radiation exposure; there was evidence of a gene-environment interaction between the \( rs1801516 \) polymorphism and radiation exposure in carcinogenesis, and the heterogeneity observed across studies might be due to gender-ethnicity or gene-gene interactions. Further studies are needed to elucidate sources of the heterogeneity.

**MATERIALS AND METHODS**

Our meta-analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [60].

**Selection criteria**

To be eligible for inclusion in our meta-analyses, a study had to meet all the following criteria: (1) it should be a case-control, cross-sectional, or cohort study in humans; (2) it can be published in any language, but it must be a full-text paper in an international peer-reviewed journal.

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**Table 5: Subgroup analyses for the association between the \( ATM \) \( rs1801516 \) polymorphism and cancer risk in individuals in the presence of radiation exposure under the dominant model**

<table>
<thead>
<tr>
<th>Study selection</th>
<th>Studies (n)</th>
<th>Cases</th>
<th>Controls</th>
<th>Heterogeneity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AA + AG/GG</td>
<td>AA + AG/GG</td>
<td>I² (%)</td>
<td>P value</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (&lt; 500)</td>
<td>4</td>
<td>86/565</td>
<td>198/733</td>
<td>68.1</td>
<td>0.014</td>
</tr>
<tr>
<td>HWE in controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>218/857</td>
<td>480/1635</td>
<td>75.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>5</td>
<td>248/1036</td>
<td>529/1529</td>
<td>66.9</td>
<td>0.017</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>214/878</td>
<td>396/1214</td>
<td>67.5</td>
<td>0.046</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>45/322</td>
<td>141/577</td>
<td>81.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Sum</td>
<td>6</td>
<td>259/1200</td>
<td>537/1791</td>
<td>71.4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

AA + AG represents the number of individuals who carry the AA or AG alleles. GG represents the number of individuals who carry the GG alleles.

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

*All the studies included in these analyses were scored as high quality, and all the participants included were classified as sporadic groups.*
Figure 4: Association between the \( ATM \) rs1801516 polymorphism and cancer risk in individuals in the presence of radiation exposure under the dominant model. AA + AG represents the number of individuals who carry the AA or AG alleles. GG represents the number of individuals who carry the GG alleles. ORs for each study are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamond represents the estimated overall effect based on the meta-analysis. All statistical tests were two sided. Abbreviations: CI, confidence interval; OR, odds ratio.

Figure 5: Odds ratios from the meta-analyses of individuals in the presence of radiation exposure were compared with odds ratios from the meta-analyses of individuals in the absence of radiation exposure (dominant model). ORs for each group are represented by the squares, and the horizontal line crossing the square represents the 95% CI. All statistical tests were two sided. Abbreviations: CI, confidence interval; OR, odds ratio.
before December 31, 2015; (3) there was no restriction
on cancer type, but it must report adequate information on
genotype frequencies to estimate ORs for the cancer type. Case reports, editorials, meta-analyses, and review articles
were excluded.

A systematic literature search was conducted in Electronic databases, including PubMed, Web of
Science, EMBASE, and Chinese National Knowledge
Infrastructure (including China Doctoral/Master Dissertation Full-text Database, China Academic Journals
Full-text Database, Century Journals Project, and China
Proceedings of Conference Full-text Database), before
December 31, 2015. We used the keywords: “(atm OR
ataxia telangiectasia mutated) AND (polymorphism* OR
variant* OR mutant* OR genotype*)”, in the searching
process. This search yielded 3816 articles.

To achieve adequate statistical power for the meta-analysis on gene-environment interactions in
carcinogenesis, eligible polymorphisms were those
reported by more than three data sources of radiation
exposure. For this purpose, we employed a two-stage
screen strategy (Figure 1). First, we collected articles on
the association between ATM genetic polymorphisms
and cancer risk in individuals in the presence of
radiation exposure. After screened by title, abstract, or
full text if necessary, we identified 6 articles including
17 polymorphisms. References from the relevant articles
or reviews were also searched for additional studies. This
search yielded no extra articles. Finally, we found that/rs1801516 was the only ATM polymorphism investigated
by more than 3 articles. Second, we collected articles on
the association between the rs1801516 polymorphism and
cancer risk in individuals in the absence of radiation
exposure. We included all surrogates of the rs1801516
polymorphism, including rs52821794, rs60879649,
rs17503060 (http://www.ncbi.nlm.nih.gov/snp/), and
rs4988023 [61]. Our search on Chinese National
Knowledge Infrastructure database identified no article
on the rs1801516 polymorphism and cancer risk (possibly
due to a low MAF of < 0.05 in Asians [25, 62]. If different
articles reported on the same sample, only the most
complete information was included. If an article included
multiple sources or study populations, data were extracted
separately if possible. The article by Akulevich et al.
studied radiation exposed populations as well as unexposed
populations, the results for each group were considered
as a separate study [12]. Finally, 29 studies without radiation
exposure were identified to meet the inclusion criteria for
subsequent quality assessment (Figure 1).

Data collection

Two authors independently extracted data based on
a standardized form. The following information
was collected from each study: first author, year of
publication, country of origin, ethnicity, family history
of cases (familial cancer or sporadic cancer), MAF in
controls, controls in HWE, cancer site, and number of
genotyped cases and controls. Ethnicity was classified
as African-American, Amerindian, Asian, Caucasian, or
others based on the ethnicity of at least 80% of the study
population [63]. When a study did not state the included
ethnic groups, we considered the ethnicity of the source
population based on the country where the study was
performed [63]. When an article reported data for different
ethnic groups, the results for each group were considered
as a separate study. If it was impossible to separate
participants according to ethnicity, the participants were
considered as “others”. Study authors were contacted
when there was insufficient information. Disagreement
was resolved by discussion between authors.

Quality assessment

Two authors independently evaluated the quality of
each study, with discrepancies resolved during a consensus
meeting. We performed two types of quality assessments.
The first one was the assessment of methodological
errors. Deviation from HWE in controls is an indication
of a genotyping error or selection bias [64, 65], and was
considered as a methodological error. Because including
studies with methodological errors may lower the quality
of evidence in a meta-analysis [66], these studies were
excluded. However, it should be noted: (1) in case-only
studies, HWE deviations may reflect an association with
the disease, rather than poor genotyping [67]; (2) studies
with insufficient information to determine whether the
controls were in HWE were eligible for a meta-analysis,
but the influence of these studies on the pooled result was
examined in subgroup analyses. Second, the quality of
each study was assessed according to the NOS specific
to case-control study [45]. The NOS evaluates the quality
of a study in three domains: selection, comparability,
and exposure. For each study, a maximum score of
4 is assigned for selection, 2 for comparability, and 3 for
exposure. A study is considered low (or high) quality if
total NOS score is < 6 (or ≥ 6). Because the NOS score is
a continuum, distinction between high and low quality is
inevitably arbitrary. Due to the subjective nature, the NOS
score was used as a stratification factor in the subgroup
analysis to evaluate whether the results of the meta-analysis
depended on the quality of the included studies [68].

Procedures of meta-analyses

To clarify whether there was a joint effect between
the rs1801516 polymorphism and radiation exposure
in carcinogenesis, we performed three steps: 1). meta-
analysis of the rs1801516 polymorphism and cancer risk
in individuals in the presence of radiation exposure; 2).
meta-analysis of the rs1801516 polymorphism and cancer
risk in individuals in the absence of radiation exposure;
of China (Grant No. 81300724 to YGZ), Doctoral Program for New Teachers of China’s Ministry of Education (Grant No. 20120061120087 to YGZ). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES


