Research Article

Association between apurinic/apyrimidinic endonuclease 1 rs1760944 T>G polymorphism and susceptibility of cancer: a meta-analysis involving 21764 subjects

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Background: Previous case−control studies have suggested that apurinic/apyrimidinic endonuclease 1 (APE1) rs1760944 T>G polymorphism may be associated with cancer risk. Here, we carried out an updated meta-analysis to focus on the correlation between APE1 rs1760944 T>G locus and the risk of cancer.

Methods: We used the crude odds ratios (ORs) with their 95% confidence intervals (CIs) to evaluate the possible relationship between the APE1 rs1760944 T>G polymorphism and cancer risk. Heterogeneity, publication bias and sensitivity analysis were also harnessed to check the potential bias of the present study.

Results: Twenty-three independent studies involving 10166 cancer cases and 11598 controls were eligible for this pooled analysis. We found that APE1 rs1760944 T>G polymorphism decreased the risk of cancer in four genetic models (G vs. T: OR, 0.87; 95% CI, 0.83–0.92; P < 0.001; GG vs. TT: OR, 0.77; 95% CI, 0.69–0.86; P < 0.001; GG/TG vs. TT: OR, 0.83; 95% CI, 0.77–0.89, P < 0.001 and GG vs. TT/TG: OR, 0.85; 95% CI, 0.80–0.92, P < 0.001). Results of subgroup analyses also demonstrated that this single-nucleotide polymorphism (SNP) modified the risk among lung cancer, breast cancer, osteosarcoma, and Asians. Evidence of publication bias was found in the present study. When we treated the publication bias with ‘trim-and-fill’ method, the adjusted ORs and CIs were not significantly changed.

Conclusion: In conclusion, current evidence highlights that the APE1 rs1760944 T>G polymorphism is a protective factor for cancer susceptibility. In the future, case−control studies with detailed risk factors are needed to confirm or refute our findings.

Introduction

The incidence and mortality of cancer is increasing worldwide [1−3]. It was estimated that approximately 18.1 million new cancer patients were diagnosed and more than half of them died worldwide during 2018 [1]. The etiology of cancer is complicated. Previous epidemiological studies have indicated that consumption of red meat, fried and salted meat, tobacco smoking and alcohol abuse, diabetes mellitus, obesity, non-alcoholic fatty liver disease, oxidative stress, chronic infection and inflammation can contribute to the development of cancer [4−6]. However, these potential risk factors could not fully explain the etiology of cancer. It is reported that the hereditary factor may influence the susceptibility of cancer [7,8].

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Apurinic/apyrimidinic endonuclease 1 (APE1) is a multifunctional protein which plays an important role in the pathway of base excision repair (BER). APE1 plays a pivotal role in tumor cells involving DNA damage response and regulating transcription factor activation [9]. The observed roles of APE1 protein allude to its potential effect on inflammation, growth, migration and angiogenesis [9–11]. In addition, APE1 may be also implicated in regulating cell cycle, oxidative stress and apoptosis [12]. Recently, some investigations reported that the expression level of APE1 was up-regulated in a number of cancers [13–17]. In addition, glioma cell with higher APE1 expression level was also associated with shorter time to tumor progression after chemo/radiotherapy [18,19]. As well, previous studies reported that the decreased APE1 activity might retard cell growth of ovarian cancer [20] and pancreatic cancer [21].

APE1 gene is approximately 3 kb in length and is located on chromosome 14q11.2 [22]. A number of variants in APE1 gene are established (https://www.ncbi.nlm.nih.gov/snp/?term=APE1). APE1 rs1760944 (−656T>G) is a promoter locus and has been widely explored. Some functional studies indicated that the APE1 rs1760944 T>G single-nucleotide polymorphism (SNP) might decrease APE1 mRNA and protein expression levels [23,24]. Many case–control studies were conducted to identify the potential association of APE1 rs1760944 T>G polymorphism with the development of cancer. Individuals with APE1 rs1760944 GG variant might reduce 46% glioblastoma risk than those who carried APE1 rs1760944 TT variant [25]. The relationship between APE1 rs1760944 T>G polymorphism and a decreased susceptibility of lung cancer was also found by Lu et al. [24]. A previous study reported that gastric cancer cases carried APE1 rs1760944 GT/GG variants might have a better survival than others with APE1 rs1760944 TT genotype [26]. But the results were conflicting. Two meta-analyses suggested that this SNP was correlated with a decreased susceptibility of cancer in Asian populations and lung cancer [27,28]. Recently, many investigations focused on the association between APE1 rs1760944 T>G polymorphism and the risk of other cancers. The findings were more confusing. The aim of the present study was to carry out a meta-analysis to evaluate whether this SNP was associated with the risk of cancer.

Materials and methods

Literature search parameters

PubMed and Embase databases were exhaustively searched for relevant publications which studied the relationship of APE1 rs1760944 T>G locus with the risk of cancer from the inception up to 17 March 2019. The search strategy was: (polymorphism OR SNP) and (apurinic/apyrimidinic endonuclease 1 or APE1 or APE-1) and (cancer OR carcinoma).

Inclusion criterion

For eligibility, publications were required to meet the following inclusion criteria: (1) case–control studies investigating the relationship between the APE1 rs1760944 T>G locus and the risk of cancer; (2) the diagnosis of cases was confirmed by pathological examination; (3) the frequencies of alleles or genotypes were presented; (4) the paper was written in English or Chinese.

Exclusion criteria

Studies were excluded based on the major exclusion criteria: (1) not case–control design; (2) studies did not provide genotyping data on APE1 rs1760944 T>G polymorphism; and (3) meta-analyses/reviews, comments and letters focusing on the relationships between the APE1 rs1760944 T>G locus and cancer risk.

Data extraction

Two authors (Guowen Ding and Yu Chen) reviewed each eligible study independently. They extracted the following terms from case–control studies, including the first author name, publishing year, country where the study was carried out, ethnicity, the source of control, cancer type, numbers of included cases and controls in each case–control study, genotyping data, the method of polymerase chain reaction, statistical method and evidence of Hardy–Weinberg equilibrium (HWE) evaluation in control group. If the extracted data had any dispute, authors settled these issues following a detailed discussion among all reviewers.

Statistical analysis

HWE in controls was assessed by an online Pearson’s χ² test (http://ihg.gsfc.de/cgi-bin/hw/hwa1.pl). We calculated crude odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the correlation of APE1 rs1760944 T>G polymorphism and cancer risk. The following four genetic models were used, including homozygote model (GG
vs. TT), dominant model (GG/TG vs. TT), recessive model (GG vs. TT/TG) and allele model (G vs. T). Cochran’s Q-statistic and I² test were used to check the heterogeneity among the included studies. The random-effect model was harnessed when I² > 50% or P < 0.10 [29]; otherwise, a fixed-effect model was used [30]. Subgroup analyses were performed to explore the heterogeneity source among the studies. Ethnicity, the source of control and cancer type was considered as the potential source of heterogeneity. Begg’s funnel plots and Egger’s linear regression test were used to detect the potential bias in this meta-analysis. Since significant bias was identified in the present study, non-parametric ‘trim-and-fill’ method was used to evaluate the stability of the observed results. Sensitivity analysis was conducted by one-way method, which deleted each study one by one and re-calculated the pooled ORs and CIs. All statistical analyses were conducted by using STATA 12.0 (Stata Corporation, TX, U.S.A.). A P-value (two-sided) <0.05 was defined as statistically significant.

Results
Characteristics of eligible case–control studies
Figure 1 shows the selection process of the eligible publications. A total of 343 papers were collected. According to the major inclusion criteria, there were 20 papers (including 23 independent case–control studies) focusing on the relationship of APE1 rs1760944 T>G polymorphism with cancer risk [23–25,31–47]. Among them, five investigated lung cancer [24,31–33], three investigated colorectal cancer [34–36], three investigated breast cancer [37–39], three investigated cervical cancer [40,41], two investigated osteosarcoma [23], two investigated nasopharyngeal carcinoma [42,43] and five investigated other cancers (bladder cancer [44], glioblastoma [25], renal cell carcinoma [45], prostate cancer [46] and ovarian cancer [47]). Additionally, twenty-one had Asian and two had Caucasian ethnicities. In all included studies, χ² test was used to calculate the pooled ORs and CIs. The detailed characteristics of the included case–control studies are shown in Table 1. The number of each genotype and HWE are presented in Table 2.

Quantitative synthesis
A total of 23 independent case–control studies with 10166 cancer cases and 11598 controls were included to explore the potential correlation of APE1 rs1760944 T>G polymorphism with the susceptibility of cancer [23–25,31–47]. We found that APE1 rs1760944 T>G polymorphism conferred statistical evidence of the relationship between APE1 rs1760944 T>G locus and a decreased risk of cancer (G vs. T: OR, 0.87; 95% CI, 0.83–0.92 P < 0.001; GG vs. TT: OR, 0.77; 95% CI, 0.69–0.86; P < 0.001; GG/TG vs. TT: OR, 0.83; 95% CI, 0.77–0.89, P < 0.001 and GG vs. TT/TG: OR, 0.85; 95% CI, 0.80–0.92; P < 0.001; Table 3).

When we conducted subgroup analyses according to the different populations, the findings indicated that APE1 rs1760944 T>G polymorphism might be a protective factor for the development of cancer in Asian population (G vs. T: OR, 0.86; 95% CI, 0.82–0.91 P < 0.001; GG vs. TT: OR, 0.75; 95% CI, 0.67–0.84; P = 0.001; GG/TG vs. TT: OR, 0.82; 95% CI, 0.76–0.89, P < 0.001 and GG vs. TT/TG: OR, 0.83; 95% CI, 0.78–0.90, P < 0.001; Figure 2).

When we conducted subgroup analyses according to cancer type, the results suggested that APE1 rs1760944 T>G polymorphism decreased the risk of lung cancer (G vs. T: OR, 0.83; 95% CI, 0.78–0.90, P < 0.001; GG vs. TT: OR, 0.68; 95% CI, 0.59–0.79; P < 0.001; GG/TG vs. TT: OR, 0.80; 95% CI, 0.72–0.90, P < 0.001 and GG vs. TT/TG: OR, 0.77; 95% CI, 0.68–0.87, P < 0.001), breast cancer (G vs. T: OR, 0.83; 95% CI, 0.73–0.95, P = 0.005; GG vs. TT: OR, 0.75; 95% CI, 0.57–0.98; P = 0.034 and GG/TG vs. TT: OR, 0.71; 95% CI, 0.59–0.86, P < 0.001), and osteosarcoma (G vs. T: OR, 0.69; 95% CI, 0.57–0.83 P < 0.001; GG vs. TT: OR, 0.51; 95% CI, 0.35–0.75; P = 0.001; GG/TG vs. TT: OR, 0.61; 95% CI, 0.47–0.80, P < 0.001 and GG vs. TT/TG: OR, 0.64; 95% CI, 0.45–0.91, P = 0.014).

Publication bias and non-parametric ‘trim-and-fill’ method
In the present study, Begg’s and Egger’s tests were used to assess the potential bias among the eligible studies. Evidence of bias was found in the present study (G vs. T: Begg’s test P = 0.055, Egger’s test P = 0.013; GG vs. TT: Begg’s test P = 0.037, Egger’s test P = 0.080; GG/TG vs. TT: Begg’s test P = 0.051, Egger’s test P = 0.016; GG vs. TT/TG: Begg’s test P = 0.055, Egger’s test P = 0.174; Figure 3).

Since bias was found, we used non-parametric ‘trim-and-fill’ method to evaluate the stability of results. When we treated the publication bias, the adjusted ORs and CIs were not significantly changed (Figure 4).

Sensitivity analysis
In this meta-analysis, sensitivity analysis was conducted by one-way method, which deleted an individual case–control study one by one and re-calculated the pooled ORs and CIs. No single case–control study significantly influenced the final decision (Figure 5).
Figure 1. Flow diagram of included and excluded processes

**Heterogeneity**

We found significant heterogeneity in all genetic models. Considering the potential factors for heterogeneity, subgroup analysis was conducted to identify its major source. In this meta-analysis, Asians, cervical cancer and population-based studies contribute to the major sources of heterogeneity.

**Discussion**

The APE1 rs1760944 T>G has been frequently investigated due to its potential role in the development of cancer; however, the results are conflicting. To shed light on this issue, we performed an extensive meta-analysis. The results highlighted that APE1 rs1760944 T>G polymorphism decreased the risk of cancer. Results of subgroup analyses demonstrated that this SNP still significantly modified the risk among lung cancer, breast cancer, osteosarcoma patients and Asians.
 Rs1760944 T>G is a promoter SNP in the APE1 gene and may affect the binding of transcription factors. Since 2007, a number of case–control studies were performed to assess the potential relationship of APE1 rs1760944 T>G polymorphism with the risk of cancer, but the observations were controversial. Several investigations suggested that APE1 rs1760944 T>G SNP decreased the susceptibility of cancer [23,24,31,32,37,38,40,42,44,46]. However, other case–control studies suggest null correlation between the APE1 rs1760944 T>G SNP and cancer risk [25,33–36,39,41,43,45,47]. How can we obtain an extensive evaluation of the relationship between APE1 rs1760944 T>G SNP and cancer risk. Overall, we found that APE1 rs1760944 T>G polymorphism decreased the risk of cancer in four genetic models. When we conducted subgroup analyses, we found that APE1 rs1760944 T>G polymorphism decreased the risk of lung cancer, breast cancer, osteosarcoma and Asians. To the best of our knowledge, the association might be confounded by some potential bias (e.g. publication bias, heterogeneity and lack of accordance with HWE in controls). Thus, we subsequently performed subgroup analyses. The

Table 1 Characteristics of all included studies in the meta-analysis

| Author          | Year | Country | Ethnicity | The type of cancer | Genotyping method | Source of control | Sample size (case/control) | Statistical methods |
|-----------------|------|---------|-----------|--------------------|-------------------|-------------------|--------------------------|---------------------|
| Berndt et al.   | 2007 | U.S.A.  | Caucasians| Advanced colorectal adenoma | Taqman            | PB                | 767/720                  | χ² test             |
| Lu et al.       | 2009 | China   | Asians    | Lung cancer        | Illumina          | PB                | 500/517                  | χ² test, SPSS 15.0  |
| Lo et al.       | 2009 | China   | Asians    | Lung cancer        | MassARRAY        | HB                | 730/730                  | χ² test, SAS        |
| Lu et al.       | 2009 | China   | Asians    | Lung cancer        | Illumina          | HB                | 572/547                  | χ² test, SPSS 15.0  |
| Wang et al.     | 2010 | China   | Asians    | Bladder cancer     | PCR-RFLP         | HB                | 234/253                  | χ² test, SAS        |
| Zhou et al.     | 2011 | China   | Asians    | Gibioblastoma      | MALDI-TOF        | HB                | 766/824                  | χ² test, SPSS 15.0  |
| Li et al.       | 2011 | China   | Asians    | Lung cancer        | PCR-CTPP         | HB                | 455/443                  | χ² test, SPSS 16.0  |
| Cao et al.      | 2011 | China   | Asians    | Renal cell carcinoma | TaqMan            | HB                | 612/632                  | χ² test, t test, SAS|
| Wang et al.     | 2013 | China   | Asians    | Cervical cancer    | PCR-RFLP         | HB                | 306/306                  | χ² test, t test, SAS|
| Jing et al.     | 2013 | China   | Asians    | Prostate cancer    | PCR-RFLP         | HB                | 198/159                  | χ² test, SPSS 16.0  |
| Kang et al.     | 2013 | China   | Asians    | Breast cancer      | TaqMan            | HB                | 500/799                  | χ² test, SAS        |
| Pan et al.      | 2013 | China   | Asians    | Lung cancer        | PCR-LDR          | HB                | 819/803                  | χ² test, Open-source R software |
| Zhang et al.    | 2013 | China   | Asians    | Ovarian cancer     | DNA sequence      | HB                | 124/141                  | χ² test, SPSS 16.0  |
| Li et al.       | 2013 | China   | Asians    | Nasopharyngeal carcinoma | PCR-CTPP        | HB                | 231/300                  | χ² test, SPSS 16.0  |
| Zhang et al.    | 2014 | China   | Asians    | Colorectal cancer  | PCR-CTPP          | HB                | 247/300                  | χ² test, SPSS 19.0  |
| Luo et al.      | 2014 | China   | Asians    | Breast cancer      | PCR-CTPP          | HB                | 194/245                  | χ² test, SPSS 16.0  |
| Mashayekhi et al.| 2015| Iran    | Caucasians| Breast cancer      | T-ARMS-PCR       | HB                | 150/150                  | χ² test, Medcalc software 12.1 |
| Lai et al.      | 2016 | China   | Asians    | Colorectal cancer  | High resolution melting assay | HB    | 727/736                  | χ² test, SAS 9.2   |
| Meng et al.     | 2017 | China   | Asians    | Cervical cancer    | TaqMan            | HB                | 571/657                  | χ² test             |
| Meng et al.     | 2017 | China   | Asians    | Cervical cancer    | TaqMan            | HB                | 608/1165                 | χ² test, SPSS 22.0, GraphPad Prism 6.0 |
| Xiao et al.     | 2017 | China   | Asians    | Osteosarcoma       | TaqMan            | HB                | 172/256                  | χ² test, GraphPad Prism 6.0 |
| Xiao et al.     | 2017 | China   | Asians    | Osteosarcoma       | TaqMan            | HB                | 206/360                  | χ² test, GraphPad Prism 6.0 |
| Lu et al.       | 2017 | China   | Asians    | Nasopharyngeal carcinoma | MassARRAY      | HB                | 477/558                  | χ² test, SPSS 17.0  |

Abbreviations: MALDI-TOF MS, matrix-assisted laser desorption/ionization time of flight mass spectrometry; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; PCR-LDR, polymerase chain reaction-ligase detection reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; T-ARMS-PCR, tetra-primer amplification refractory mutation system-polymerase chain reaction.
findings suggested that the \textit{APE1} rs1760944 T\( \rightarrow \)G polymorphism might be a protective effect on the development of cancer in Asians only, but not Caucasians. In the present study, one case–control study was incongruent with HWE [37]. When we deleted it and re-calculated the pooled ORs and CIs, the significant relationship was not changed. In the present study, we conducted non-parametric ‘trim-and-fill’ method to explore the potential influence of publication bias. We found that the bias of publication might not alter the findings. We also found that \textit{APE1} rs1760944 T\( \rightarrow \)G polymorphism still significantly decreased the risk of some type of cancers.

It was found that inhibition of APE1 activity might reduce cell growth of ovarian cancer [20] and pancreatic cancer [21]. In addition, Luo et al. [48] identified that a decreased APE1 activity could also significantly retard the proliferation of endothelial cells, suggesting its stimulative effect on the development of cancer. Several studies indicated that \textit{APE1} rs1760944 G allele decreased \textit{APE1} mRNA and protein expression levels [23,24]. Additionally, Lu et al. [24] reported that \textit{APE1} rs1760944 G allele was associated with a decreased level of APE1 mRNA by reducing the binding affinity of some transcription factors. Although the pathway of the relationship between \textit{APE1} rs1760944 T\( \rightarrow \)G and cancer risk has been not confirmed, it is speculated that this SNP may alter the susceptibility of cancer through the mechanism mentioned above. All observations and speculations should be verified with new molecular studies.

Some limitations of the current analysis should be noted. First, in this meta-analysis, only published literature was eligible and included, and some presumable unpublished studies might be neglected and discarded. Second, heterogeneity and publication bias were apparent, which could distort the pooled results. Our findings should be interpreted with cautions. Third, for lack of sufficient data (e.g., smoking, drinking, age, sex and vegetable and fruit intake and other environmental factors), we only conducted a crude assessment. Finally, only \textit{APE1} rs1760944 T\( \rightarrow \)G polymorphism was included to assess the association with the risk of cancer; other functional loci in \textit{APE1} gene should not been ignored.

In summary, this updated meta-analysis highlights that the \textit{APE1} rs1760944 T\( \rightarrow \)G polymorphism may play a protective role in the development of cancer. Further studies in different race are needed to confirm or refute our findings.

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Table 3 Results of the meta-analysis from different genetic models

| Number of cases/controls | G vs. T | GG vs. TT | GG/TG vs. TT | GG vs. TT/TG |
|-------------------------|---------|-----------|--------------|--------------|
|                         | OR (95% CI) | P | \( \chi^2 \) | P (Q-test) | OR (95% CI) | P | \( \chi^2 \) | P (Q-test) | OR (95% CI) | P | \( \chi^2 \) | P (Q-test) |
| Total                   | 0.87 (0.83–0.92) | <0.001 | 43.9% | 0.015 | 0.77 (0.69–0.86) | <0.001 | 39.4% | 0.031 | 0.83 (0.77–0.89) | <0.001 | 35.8% | 0.046 | 0.85 (0.80–0.92) | <0.001 | 26.8% | 0.121 |
| HWE                     | Yes      | 0.87 (0.82–0.92) | <0.001 | 46.4% | 0.111 | 0.77 (0.69–0.85) | <0.001 | 41.1% | 0.026 | 0.83 (0.77–0.90) | <0.001 | 35.1% | 0.054 | 0.85 (0.79–0.91) | <0.001 | 24.4% | 0.151 |
|                         | No       | 0.84 (0.60–1.17) | 0.310 | - | - | 1.21 | 0.44 | 3.34 | 0.710 | - | - | 0.60 | 0.37 | 0.97 | - | - | 1.78 | 0.68 | 4.64 | 0.241 | - | - |
| Ethnicity               | Yes      | 810/824 | 1.00 | 0.87 (1.15) | 0.994 | 20.0% | 0.264 | 1.09 | 0.81 | 1.48 | 0.573 | 0.0% | 0.832 | 0.42 | 0.47 | 1.45 | 0.502 | 75.1% | 0.045 | 1.07 | 0.86 | 1.33 | 0.539 | 11.5% | 0.288 |
|                         | No       | 9187/10713 | 0.86 (0.82–0.91) | <0.001 | 42.4% | 0.024 | 0.75 | 0.67 | 0.84 | 0.001 | 36.3% | 0.054 | 0.82 | 0.76 | 0.89 | - | - | - | 0.0% | 0.396 | 0.967 | 0.801 | 0.17 |
| Cancer type             | Colorectal cancer | 1628/1705 | 0.97 | 0.88 | 1.07 | 0.607 | 0.0% | 0.396 | 0.96 | 0.682 | 0.0% | 0.510 | 0.93 | 0.388 | 15.3% | 0.307 | 1.00 | 0.983 | 0.0% | 0.873 |
|                         | Lung cancer | 3071/3038 | 0.83 | 0.78 | 0.90 | 0.001 | 0.0% | 0.717 | 0.66 | 0.59 | 0.79 | <0.001 | 0.0% | 0.702 | 0.80 | 0.72 | 0.90 | <0.001 | 0.0% | 0.795 | 0.0% | 0.83 |
|                         | Cervical cancer | 1485/2128 | 0.93 | 0.79 | 0.99 | 0.361 | 61.4% | 0.075 | 0.89 | 0.96 | 0.367 | 51.5% | 0.127 | 0.90 | 0.416 | 62.3% | 0.071 | 0.93 | 0.433 | 0.0% | 0.438 |
|                         | Breast cancer | 809/1194 | 0.83 | 0.73 | 0.95 | 0.005 | 4.3% | 0.352 | 0.75 | 0.57 | 0.98 | 0.034 | 37.6% | 0.202 | 0.71 | 0.59 | 0.86 | <0.001 | 0.0% | 0.635 | 0.0% | 0.72 |
|                         | Nasopharyngeal cancer | 708/858 | 0.89 | 0.70 | 1.14 | 0.355 | - | - | 0.71 | 0.43 | 1.20 | 0.204 | - | - | 0.84 | 0.59 | 1.18 | 0.316 | 58.5% | 0.120 | 0.65 | 0.41 | 1.03 | 0.064 | - | - |
|                         | Osteosarcoma | 378/616 | 0.69 | 0.57 | 0.83 | <0.001 | 0.0% | 0.701 | 0.51 | 0.35 | 0.75 | 0.001 | 0.0% | 0.823 | 0.61 | 0.47 | 0.80 | <0.001 | 0.0% | 0.748 | 0.0% | 0.86 |
|                         | Others | 1918/1998 | 0.87 | 0.75 | 1.02 | 0.080 | 58.0% | 0.049 | 0.77 | 0.57 | 1.03 | 0.083 | 54.7% | 0.065 | 0.80 | 0.78 | 1.02 | 0.109 | 47.8% | 0.105 | 0.87 | 0.74 | 1.02 | 0.079 | 22.3% | 0.273 |
| Source of control       | Control | 1160/1191 | 0.92 | 0.73 | 1.17 | 0.506 | 75.6% | 0.043 | 0.80 | 0.50 | 1.40 | 0.494 | 78.5% | 0.031 | 0.93 | 0.485 | 28.9% | 0.236 | 0.84 | 0.54 | 1.31 | 0.448 | 80.5% | 0.024 |
|                         | Population-based | 8637/10346 | 0.87 | 0.82 | 0.92 | <0.001 | 41.3% | 0.028 | 0.76 | 0.68 | 0.85 | <0.001 | 35.5% | 0.059 | 0.82 | 0.75 | 0.88 | <0.001 | 36.7% | 0.048 | 0.85 | 0.79 | 0.92 | <0.001 | 18.3% | 0.226 |

Bold values are statistically significant (P < 0.05).
Figure 2. Meta-analysis for the association of cancer risk with the APE1 rs1760944 T>G polymorphism (random-effect, allele comparing model)

Author Contribution
Conceived and designed the experiments: S.C. Performed the experiments: G.D., Y.C. and H.P. Analyzed the data: W.T. and H.Q. Contributed reagents/materials/analysis tools: S.C. Wrote the manuscript: G.D., Y.C. and W.T.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Figure 3. For APE1 rs1760944 T>G polymorphism, Begg's funnel plot analysis for publication bias (allele comparing model).

Figure 4. For APE1 rs1760944 T>G polymorphism, filled funnel plot of meta-analysis (allele comparing model).
Figure 5. Sensitivity analysis of the influence in G vs. T genetic model (random-effects estimates)

Abbreviations
APE1, apurinic/apyrimidinic endonuclease 1; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single-nucleotide polymorphism.

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