Apolipoprotein E Polymorphism and Colorectal Neoplasm: Results from a Meta-Analysis

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Abstract
To investigate the relationship of Apolipoprotein E (APOE) gene polymorphism to colorectal neoplasia (CRN), we performed a systematic review and meta-analysis. Eligible studies were identified through a systematic literature review from PubMed, EMBASE, and the Science Citation Index up to February 2014. A combined analysis was performed, followed by a subgroup analyses stratified by the study design. We used data collected from 8 prospective studies involving respectively a total of 9243 participants and 4310 CRN cases which including 438 patients with colorectal adenoma (CRA), and 3873 patients with colorectal carcinoma (CRC). The pooled data from this meta-analysis indicated there was no significant association between APOE polymorphism and CRN (p2: P = 0.51, OR 1.04 95% CI 0.93 to 1.16; p4: P = 0.72, OR 0.98 95% CI 0.90 to 1.07). Interestingly, subgroup analysis demonstrated there was a significant decreased risk for proximal CRN in patients with APOE e4 (P = 0.0007, OR 0.52 95% CI 0.35 to 0.76). Data showed no significant association between APOE genotype and overall CRN. However, compared with those carry APOE e3 alleles, persons with APOE e4 genotype have significant decreased risk suffering from proximal CRN but not from distal CRN.

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Introduction
Colorectal neoplasm (CRN) is an epithelial polyps which resulted from abnormal proliferation of colonic epithelial cells. Colorectal adenoma (CRA) is recognized as the well-established precursors of colorectal cancer (CRC) [1,2,3]. Generally, CRA can develop into CRC through an adenoma to carcinoma sequence [4]. CRC is the third most common cancer in worldwide, accounting for 8% of all cancers [5]. For the past decades, the mortality rate of CRC has been declined because of screening colonoscopy. Despite the success of screening colonoscopy for CRC prevention, people will be benefitted by identifying additional risk factors for CRC that might facilitate novel prevention strategies.

Apolipoprotein E (APOE) gene polymorphism is demonstrated to be a major factor in lipid metabolism. It is recognized recently that polymorphism of gene encoding APOE to be potential risk factor for CRN [6]. The human APOE gene, which produces three distinct protein isoforms: wild-type APOE E3 (112Cys/158Arg), APOE E2 (112Cys/158Cys), and APOE E4 (112Arg/158Arg), is found located on chromosome 19 [7,8]. Of these isoforms, the most seen one is APOE E3 with a frequency of approximately 70% to 80%, while each isoform of these isoforms has its unique receptor binding activity individually [9,10]. APOE is demonstrated to have the ligand for receptors of the low-density lipoprotein (LDL) receptor family. In addition, APOE plays an important role in the synthesis of very low-density lipoprotein (VLDL) and the process of the VLDL remnants hydrolysis [11]. Accumulated data indicated persons with the E2 allele presented defective receptor-binding ability, had lower plasma cholesterol levels and higher triglyceride levels. However, people with the E4 allele were found have a higher serum level of cholesterol [12,13]. Furthermore, APOE e4 has been implicated in coronary heart disease (CHD), age-related cognitive decline, and Alzheimer’s disease [14,15,16]. It is also demonstrated by a meta-analysis that people with the e4 allele APOE genotypes had a 42% increased risk of CHD than those with the e3 allele [10]. However, the association between APOE genotype and other disease such as CRN is less clear.

Recent studies indicated that APOE may show its activity in CRC development by function in β-catenin localisation, tumor cell metastasis, DNA synthesis, antioxidant abilities, cell proliferation, and angiogenesis [17,18,19,20]. APOE also plays a major role in altering metabolism of cholesterol and bile acids, modulating angiogenesis, carcinogenic cell growth as well as metastasis [20,21,22,23]. Many studies have attempted to clarify the relationship of APOE polymorphism and colorectal tumor risk although the conclusions are still contradictory. A study reported that APOE E4 may be a protective factor for CRC while those with the E2 or E3 genotype had an increased risk of colon carcinoma in males [24]. In addition, a study from Brazil found the e4 genotype only presents in controls [25]. A study from China found subjects with APOE e3/e4 genotype have lower risk suffering from CRA than those with other genotypes [26].
addition, Mrkonjic et al. reported no significant differences in APOE genotype frequencies were observed between CRC cases and unaffected controls [6]. Furthermore, another large sample case-control study did not detect any significant associations between APOE genotype and rectal cancer [27].

As the contrary conclusions of APOE gene polymorphism in CRN, for the first time, we performed a systematic review and meta-analysis focusing on the APOE genotype of possible relevance to colorectal carcinogenesis.

Materials and Methods

Search strategy

The published Quality of Reporting of Meta-analysis (QUOROM statement) was followed in our study [28]. Electronic databases which included PubMed, EMBASE, and the Science Citation Index were searched for identification of studies on APOE polymorphisms and CRN published up to February 2014. The following search terms were used: “colorectal neoplasm”, “colorectal cancer”, “colorectal adenoma”, “polymorphisms”, “apolipoprotein E” or “Apo E” or “apoE” or “APOE”. Additionally, the reference lists of relevant publications were also screened for additional relevant studies. As a prerequisite, only those studies published in English language and focused on human subjects were identified.

Inclusion criteria

Studies included in this meta-analysis according to following criteria: 1) evaluation of APOE polymorphism in association with CRN (including CRC and CRA); 2) study design was “cohort” or “prospective” or “follow-up” or “cross sectional” or “case–cohort” or “nested case–control”; 3) allele counts of APOE polymorphisms of cases and controls could be extracted. Studies were excluded if the data were not sufficient to perform meta-analysis. In addition, review articles or published abstracts from meeting were excluded. Furthermore, articles selected for meta-analysis had no overlap of subjects with other studies.
Table 2. Allele frequencies and percentage of apolipoprotein E polymorphisms carriers among CRN cases and controls.

| Study/first author       | Ethnicity | Source of controls | Type of lesion | Cases | Controls |
|--------------------------|-----------|--------------------|----------------|-------|----------|
|                          |           |                    |                | allele frequencies | allele frequencies |
|                          |           |                    |                |       |          |
| Shinomiya S, et al.      | Asians    | Hospital           | colorectal adenoma | 205   | 69       |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Souza DRS, et al.        | Brazilian | Hospital           | colorectal adenoma | 87    | 12       |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Zhoungyin Z, et al.      | Chinese   | Hospital           | colorectal adenoma | 98    | 5        |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Butler WJ, et al.        | Caucasians| Population        | colorectal adenoma | 219   | 13       |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Kervinen K, et al.       | Caucasians| Population        | colorectal neoplasm | 257   | 122      |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Slattery ML, et al.      | Mainly Caucasians | Not reported | colorectal adenoma | 2333  | 777      |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Watson MA, et al.        | Caucasians| Population        | colorectal adenoma | 206   | 59       |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |
| Mrkonjic M, et al.       | Mainly Caucasians | Hospital         | colorectal adenoma | 906   | 147      |
|                          |           |                    |                | cases  | controls |
|                          |           |                    |                |       |          |

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Studies included in this meta-analysis were reviewed twice by using a standardized form for data extraction. Two authors (Y. Tian and J. Wang) independently carefully drew all the studies. Data were collected on the first author’s name, year of publication, source of control group (population based or hospital based), study design, ethnicity of patients and controls, country of origin, and numbers of APOE alleles among patients and controls. The data was extracted from each publication by a standardized protocol.

Statistical analysis

The associations between APOE polymorphisms and CRN were evaluated by using the software Review Manager (V5.1) for windows (Oxford, England, UK). We first analyzed the risk of the e2 and e4 alleles compared with the wild-type e3 allele for the development of CRN. Second, the association between APOE polymorphisms and susceptibility to CRC was estimated. Finally, we performed the meta-analysis of the relationship of the e2 carriers and e4 carriers and CRA risk. A statistical test for heterogeneity was performed based on the Q statistic test with a p-value less than 0.05 was considered as significant heterogeneity between studies to account for the possibility of heterogeneity across studies [29]. The data were analyzed by using both fixed effects and random effects models. The fixed-effects method by Mantel and Haenszel was used in the condition of no significant heterogeneity [30], while the random-effects method by DerSimonian and Laird [31] was more appropriate when heterogeneity was present. Publication bias analysis was measured using Stata 11.0 (Stata Corp, College Station, TX) with Begg and Egger tests [32,33].

Results

Study characteristics

Seventy-two papers relevant to the words searched were retrieved (Figure 1). Through the step of screening the title, 30 duplicated articles were excluded with initial assessment. The rest 42 articles were reviewed and an additional 24 trials were excluded because of clearly not relevant, leaving 18 studies for detailed review. Of these, 10 records were excluded because they did not match the detailed criteria. At last, we identified 8 eligible studies, published from 1996 to 2009, that reported on polymorphisms of APOE and risk of CRN [6,24,25,26,34,35,36,37]. Studies were carried out in Japan, Brazil, China, Australia, Finland, USA, UK and Canada. Characteristics of the studies included in the meta-analysis with APOE polymorphisms and CRN is provided through Table 1. Table 2 showed the allele frequencies and percentage of APOE polymorphism carriers among CRN cases and controls. Appropriate genotyping methods for APOE were stated in all studies, all of which was polymerase chain reaction restriction fragment length polymorphism except 1 study [35] using immunoblotting techniques. The deviation from Hardy–Weinberg equilibrium was assessed by the HWE program, and the results indicated that the genotype distribution of control population in most of the eight included studies were in Hardy–Weinberg equilibrium except one study [25].

Overall analyses on the association of APOE polymorphisms and CRN

The meta-analysis of the APOE alleles and the risk of CRN was performed firstly. All 8 studies were eligible for assessing the impact of at least one of APOE alleles on the CRN risk [6,24,25,26,34,35,36,37]. Comparison of prevalence of the e2 vs. e3 alleles among cases and controls showed no statistically significant heterogeneity between studies (Q = 6.03, p = 0.54, I² = 0%, Figure 2A). The fixed-model was then used. Among the populations in the included studies, the presence of e2 allele conferred no risk for CRN (OR, 1.04; 95% CI, 0.93 to 1.16; p = 0.51, Figure 2A). In addition, the association of e4 carriers vs. e3 alleles between cases and controls was estimated. Because there was no statistical heterogeneity between studies (Q = 10.52, p = 0.16, I² = 33%, Figure 2B), the fixed effects mode was applied. The pooled data indicated presence of the e4 allele indicated no decreased risk of CRN, in comparison with the e3 allele (OR 0.98 95% CI 0.90 to 1.07, p = 0.72; Figure 2B). Our data also showed that individuals with the e2 had similar risk of CRN compared
with those with the e4 (OR 1.04, 95% CI 0.92 to 1.19, p = 0.52). (Figure 2). Results of genotypic models for comparisons of E2, E3 and E4 genotypes in both dominant and recessive models were presented in table 3.

Overall analyses on the association of APOE polymorphisms and CRC

There were a total of 6 studies evaluating the association between APOE polymorphisms and CRC. Five studies of the e2 vs. e3 alleles were enrolled in this analysis [6,24,25,34,35,37]. The combined results based on these 6 studies showed that, compared with those with e2 alleles, there was no significant risk of CRC of individuals with the e3 alleles (OR 1.03, 95% CI 0.92 to 1.16, p = 0.60, Figure 3, A). Fixed effects mode was used because there was no heterogeneity between studies (Q = 5.77, p = 0.33, I² = 13%, Figure 3, A). There were 6 studies of the e4 vs. e3 alleles were enrolled in this analysis [6,24,25,34,35,37]. The pooled data indicated that, compared with those with e4 alleles,

Table 3. Comparisons of apolipoprotein E genotype and CRN risk.

| Comparisons          | Pooled OR (95% CI) | P value | I² (%) |
|----------------------|--------------------|---------|--------|
| E2 vs E3 for CRN     |                    |         |        |
| E2/2 vs E3/3         | 0.99 (0.56, 1.77)  | 0.99    | 0      |
| E2/3 vs E3/3         | 1.07 (0.94, 1.22)  | 0.82    | 40     |
| E2/2+E2/3 vs E3/3    | 1.07 (0.94, 1.22)  | 0.32    | 22     |
| E2/2 vs E2/3+E3/3    | 1.00 (0.56, 1.77)  | 0.99    | 0      |
| E4 vs E3 for CRN     |                    |         |        |
| E4/4 vs E3/3         | 0.93 (0.69, 1.26)  | 0.64    | 0      |
| E4/3 vs E3/3         | 1.01 (0.91, 1.12)  | 0.90    | 41     |
| E4/4+E4/3 vs E3/3    | 1.00 (0.90, 1.11)  | 0.99    | 40     |
| E4/4 vs E3/4+E3/3    | 0.93 (0.69, 1.25)  | 0.62    | 0      |
| E2 vs E3 for CRC     |                    |         |        |
| E2/2 vs E3/3         | 0.99 (0.55, 1.78)  | 0.97    | 0      |
| E2/3 vs E3/3         | 1.07 (0.94, 1.22)  | 0.32    | 52     |
| E2/2+E2/3 vs E3/3    | 1.07 (0.94, 1.22)  | 0.33    | 38     |
| E2/2 vs E2/3+E3/3    | 0.99 (0.55, 1.78)  | 0.98    | 0      |
| E4 vs E3 for CRC     |                    |         |        |
| E4/4 vs E3/3         | 0.93 (0.69, 1.26)  | 0.64    | 0      |
| E4/3 vs E3/3         | 1.01 (0.91, 1.13)  | 0.78    | 30     |
| E4/4+E4/3 vs E3/3    | 1.01 (0.91, 1.13)  | 0.78    | 30     |
| E4/4 vs E3/4+E3/3    | 0.93 (0.69, 1.25)  | 0.62    | 0      |
| E2 vs E3 for CRA     |                    |         |        |
| E2/2 vs E3/3         | 0.87 (0.11, 6.91)  | 0.89    | 0      |
| E2/3 vs E3/3         | 1.43 (0.69, 2.97)  | 0.33    | 0      |
| E2/2+E2/3 vs E3/3    | 1.42 (0.70, 2.86)  | 0.33    | 0      |
| E2/2 vs E2/3+E3/3    | 0.85 (0.11, 6.74)  | 0.88    | 0      |
| E4 vs E3 for CRA     |                    |         |        |
| E4/4 vs E3/3         | 0.81 (0.30, 2.18)  | 0.67    | 0      |
| E4/3 vs E3/3         | 0.70 (0.50, 0.98)  | 0.04    | 0      |
| E4/4+E4/3 vs E3/3    | 0.71 (0.51, 0.98)  | 0.04    | 6      |
| E4/4 vs E3/4+E3/3    | 0.88 (0.32, 2.36)  | 0.79    | 0      |
| E2 vs E3 for proximal CRN |               |         |        |
| E2/2 vs E3/3         | 0.67 (0.03, 16.67)| 0.81    | 0      |
| E2/3 vs E3/3         | 1.99 (1.08, 3.68)  | 0.03    | 0      |
| E2/2+E2/3 vs E3/3    | 0.64 (0.03, 15.81)| 0.78    | 0      |
| E2/2 vs E2/3+E3/3    | 1.90 (1.03, 3.49)  | 0.04    | 0      |
| E4 vs E3 for distal CRN |                |         |        |
| E4/4 vs E3/3         | 0.30 (0.06, 1.58)  | 0.15    | 0      |
| E4/3 vs E3/3         | 0.70 (0.46, 1.07)  | 0.10    | 61     |
| E4/4+E4/3 vs E3/3    | 0.64 (0.42, 0.97)  | 0.04    | 61     |
| E4/4 vs E3/4+E3/3    | 0.32 (0.06, 1.73)  | 0.19    | 0      |
| E2 vs E3 for distal CRN |               |         |        |
| E2/2 vs E3/3         | 1.08 (0.07, 17.43)| 0.96    | 0      |
| E2/3 vs E3/3         | 1.48 (0.89, 2.45)  | 0.13    | 0      |
| E2/2+E2/3 vs E3/3    | 1.46 (0.89, 2.41)  | 0.13    | 0      |
| E2/2 vs E2/3+E3/3    | 1.05 (0.06, 16.93)| 0.97    | 0      |
| E4 vs E3 for distal CRN |                |         |        |
| E4/4 vs E3/3         | 0.90 (0.66, 1.22)  | 0.49    | 82     |
| E4/3 vs E3/3         | 1.44 (0.68, 3.08)  | 0.34    | 0      |
| E4/4+E4/3 vs E3/3    | 0.94 (0.70, 1.27)  | 0.70    | 81     |
| E4/4 vs E3/4+E3/3    | 12.01 (6.84, 21.10)| 0.0001  | 48     |

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Apolipoprotein E Polymorphism and CRN
there was no significant risk of CRC of individuals with the ε3 alleles (OR 1.00, 95% CI 0.92 to 1.10, p = 1.00; Figure 3, B). Fixed effects mode was used as there was no heterogeneity between studies (Q = 7.12, p = 0.21, I² = 30%, Figure 3, B). We found that, in comparison with the ε4 carriers, ε2 carriers had a similar risk for CRC development (OR 1.00, 95% CI 0.87 to 1.15, p = 1.00). Table 3 showed the analysis of of E2, E3 and E4 genotypes comparisons in both dominant and recessive models were presented in table 3.

Overall analyses on the association of APOE polymorphisms and CRA

There were a total of 3 studies of the ε2 vs. ε3 alleles for CRA were enrolled in this analysis [26,35,36]. The combined results based on these 3 studies did not provide evidence of significant risk of CRA of individuals with the ε2 alleles when compared with those with ε3 alleles (OR 1.16, 95% CI 0.75 to 1.79, p = 0.50; Figure 4, A). Fixed effects mode was used as there was no heterogeneity between studies (Q = 1.76, p = 0.42, I² = 0%, Figure 4, A). Three studies of the ε4 vs. ε3 alleles for CRA were enrolled in this analysis [26,35,36]. The pooled data did not support the concept that individuals with the ε4 alleles presented significant decreased risk of CRA, compared with those with ε3 alleles (OR 0.79, 95% CI 0.59 to 1.06, p = 0.12; Figure 4, B). Fixed effects mode was applied because the absence of heterogeneity between studies (Q = 1.14, p = 0.56, I² = 0%, Figure 4, B). In addition, we found there was no difference in CRA risk among individuals with the ε2 or ε4 genotypes (OR 1.48, 95% CI 0.89 to 2.45, p = 0.13). Results of genotypic models for comparisons of E2, E3 and E4 genotypes in both dominant and recessive models were indicated in table 3.

Figure 3. Forest plots of the meta-analysis of associations between alleles of APOE polymorphism and CRC (colorectal cancer) risk (A, ε2 versus ε3; B, ε4 versus ε3).
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Figure 4. Forest plots of odds ratio with 95% CI for APOE polymorphism and CRA (colorectal adenoma) risk (A, ε2 versus ε3; B, ε4 versus ε3).
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Overall analyses on the association of APOE polymorphisms and proximal CRN

There were 3 studies with extractable data evaluated the association between APOE polymorphisms and proximal CRN [24,35,36]. Subgroup analysis based on these 3 studies showed that, compared with those with e2 alleles, there was no significant risk of proximal CRN of individuals with the e3 alleles (OR 1.35, 95% CI 0.87 to 2.09, p = 0.18, Figure 5, A). Fixed effects mode was used because there was no heterogeneity between studies (Q = 0.32, df = 2 (P = 0.89); I^2 = 0%, Figure 5, A). However, data from this subgroup analysis demonstrated the significant decreased risk of proximal CRN of individuals with the e4 alleles when compared with those with e3 alleles (OR 0.52, 95% CI 0.35 to 0.76, p = 0.0007; Figure 5, B). Fixed effects mode was used as there was no heterogeneity between studies (Q = 4.82, p = 0.09, I^2 = 58%, Figure 5, B). In addition, data of genotypic models for comparisons of E2, E3 and E4 genotypes in both dominant and recessive models were presented in table 3.

Overall analyses on the association of APOE polymorphisms and distal CRN

Subgroup analysis was also performed to compare prevalence of the e2 vs. e3 alleles among distal CRN cases and controls. Pooled data from the available 3 studies [24,35,36] showed the presence of e2 allele conferred no risk for distal CRN (OR, 1.08; 95% CI, 0.74 to 1.56; p = 0.70, Figure 5, C). The fixed-model was then used as there was no statistically significant heterogeneity between studies (Q = 1.66, p = 0.44, I^2 = 0%, Figure 5, C). In addition, the association of e4 carriers vs. e3 alleles between distal CRN cases and controls was estimated. Because there was no statistical heterogeneity between studies (Q = 3.46, p = 0.18, I^2 = 42%, Figure 5, D), the fixed effects mode was applied. The pooled data indicated presence of the e4 allele indicated no decreased risk of distal CRN, in comparison with the e3 allele (OR 1.12, 95% CI 0.89 to 1.41, p = 0.32; Figure 5, D). Additionally, genotypic analysis for comparisons of E2, E3 and E4 genotypes in both dominant and recessive models were presented in table 3.

Publication bias

We also evaluated the publication bias by testing funnel plots for obvious asymmetry. No publication bias was found from either
visualization of the funnel plot or statistics of. Our data indicated there was no statistical evidence of publication bias (Egger’s, P = 0.7, Begg’s P = 0.805) (Figure 6).

Discussion

Eight eligible studies at last included in this meta-analysis, and 5 studies of them suggested APOE ε4 is a protective factor. In this meta-analysis, we used a total of 9243 subjects and 4310 CRN cases which including 438 patients with CRA, and 3873 patients with CRC from 8 publications to evaluate the association of APOE gene polymorphism with CRN. This meta-analysis suggested that having an APOE allele doesn’t increase the risk of CRN. Although APOE ε4 has been considered to be a protective factor in CRN [25,34], our results indicated there was no association between a ε4 allele and CRA development.

APOE seems to be involved in immunoregulation [38] and inhibiting endothelial cell proliferation [20], which may directly affect the adenoma to carcinoma process. It was suggested that APOE may influence CRC development through three potential pathways: cholesterol and bile metabolism, triglyceride and insulin regulation, and the prolonged inflammation [37]. Due to different affinity to its receptors, APOE can influence hepatic cholesterol processing by enhancing cholesteryl ester hydrolysis [39], and people with the allele ε4 were found to have an increased intestinal absorption of cholesterol [40] and to have a lower biliary excretion of deoxycholic acid [41]. It was speculated APOE ε4, which is associated with more intracellular release of free than that of ε3 [42] and lower concentrations of fecal bile acids in the gastrointestinal tract, has its protective role against CRC [35].

The APOE ε4 allele appears to be associated with an increased risk of gallstones and breast cancer [43,44]. Our present data indicated that the APOE gene polymorphisms were similar between patients with CRN and controls. Our data also demonstrated APOE ε4 did not affect the overall risk for CRA, there was not a protective effect in patients with ε4 when compared to those with ε3. Despite the genetic factors has been suggested to be important for the susceptibility to CRN, other factor like racial differences may also play a role. First, genetic heterogeneity may be a reason for the conflicting results. In people of European ancestry, APOE genotype showed a positive dose-response association with LDL-C [45] while study of Brazilian individuals indicated that the presence of the ε4 genotype may be a protective effect against CRC [25]. In addition, the allele ε4 is much less frequent in Japanese than in Caucasians, and it was reported Finns seem to have a particularly high frequency of the allele ε4 [46,47]. In our meta-analysis, the included 8 studies are from Japan, Brazil, China, Australia, Finland, USA, UK, and Canada respectively on evaluating the APOE polymorphisms in relation to CRN. In addition, our data indicated the contribution of APOE polymorphisms to CRN susceptibility varies in different studies. For ethnic diversity, distinct environmental factors and eating habits characterize populations, analyze the allelic and genotypic distributions of the APOE and their association with CRA or CAC should characterize the histories and habits of people.

We also evaluated association of genetic variants of APOE with proximal and distal CRN. Three of the 8 included studies involving evaluated the presence of APOE polymorphisms to different parts of the colorectal tumors [24,35,36]. Although APOE ε4 did not affect the overall risk for CRN, there was a trend towards a protective effect in patients with right-sided cancer when compared to those with left-sided carcinoma [34,48]. However, the degree of this protection was less prominent reported by Kervinen et al. from Finland [35]. Our meta-analysis data demonstrated, compared with those carry APOE ε3 alleles, persons with APOE ε4 genotype have significant decreased risk suffering from proximal CRN but not from distal CRN. Several reasons for the protective association between the allele ε4 of APOE and proximal colon adenomas have been reported in past years. A proposed mechanism involving in this different effect between proximal and distal CRN is the decreased levels of fecal bile acids which may result in relative lower levels of cell proliferation in the proximal colon [41]. A potential mechanism for this effect is the low levels of fecal bile acids which may result in lower levels of epithelial proliferation in the proximal colon [41]. Serum cholesterol acids are positively related to the risk of CRN [49,50] and patients with colorectal adenomas indicated high serum deoxycholic acid levels [22]. However, in patients with the ε4 allele of APOE, the levels of biliary deoxycholic acid are relatively low [41], which may be associated with the low incidence of adenoma and carcinoma. This has been confirmed by the results that APOE has the ability in inhibiting endothelial proliferation [20] and APOE shows its ability in immunoregulation [51]. It seems that the alterations in luminal cholesterol delivery and fecal bile acid are involved in the protective association of the allele ε4 and proximal CRN development [35,52]. APOE genotypes has been reported implicated in the breast cancer [33]. APOE ε4 allele is found to be a low-penetrant risk factor for development of breast cancer [43]. The possible biological mechanisms of the association between APOE ε4 genotype and carcinoma of the proximal colon and breast is subjects carrying APOE ε4 genotype less than half of the risk of tumor cell proliferation [20].

CRN incidences differ considerably between Western and non-Western countries. In recent years, a dramatic increase in CRC incidence has been reported in several Asian countries. Two studies from Asia included in our meta-analysis [26,36] found APOE ε4 was protective factor for CRN. Immigration studies have suggested that environmental factors rather than genetic susceptibility are primarily responsible for the secular trends of CRC incidence rates and international variability. It is more likely that the interaction of genetic susceptibility and environmental factors is the causation of colorectal carcinomas and adenomas. Therefore, not only the main effect of a gene but also the influence of gene-environment interactions on cancer risk are important from the public health perspective [34].

We must confess that some limitations of this study were still inherited from the published studies. First, many of the studies included in the analysis were published a decade ago, recent advance of this issue is limited. Second, selection bias may play a role in this meta-analysis. Third, due to the limited patients included in this study, it was impossible for us to perform the subgroup analysis. Last but not the least is that account of potential confounding factors which might be associated with the risk of CRN.

In conclusion, the pooled data showed no significant association between APOE genotype and CRN. However, compared with those carry APOE ε3 alleles, persons with APOE ε4 genotype have significant decreased risk suffering from proximal CRN but not from distal CRN. Due to the small number of studies addressing the association of APOE polymorphisms and CRN, the conclusion whether APOE ε3 and ε2 increase or decrease the susceptibility to CRN requires further investigation. The mechanism of the involvement of APOE in carcinogenesis is still not clear and further studies with larger samples are necessary to confirm this in population.
