Pathology - Research and Practice xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Diagnostic value of *RASSF1A* hypermethylation in colorectal cancer: a meta-analysis

Haochang Hu[1], Cong Zhou[1], Bin Li[1], Yanfei Chen, Jie Dai, Yiyi Mao, Tianyi Huang, Hang Yu, Min Chen, Jun Zhao, Shiwei Duan*

Medical Genetics Center, School of Medicine, Ningbo University, Ningbo, Zhejiang, China

ARTICLE INFO

Keywords:
DNA methylation
Colorectal cancer
RASSF1A
Diagnosis
Meta-analysis

ABSTRACT

Purpose: Ras association domain family 1 isoform A (*RASSF1A*), a member of Ras association domain family, plays an important role in tumorigenesis. The goal of our meta-analysis was to assess the diagnostic value of *RASSF1A* hypermethylation in colorectal cancer (CRC).

Methods: PubMed, Embase, CNKI and Wanfang databases were used to conduct literature selection. The association between *RASSF1A* methylation and CRC risk was evaluated by odds ratios (ORs) and 95% confidence intervals (CIs). Summary receiver operating characteristics (SROC) test was used to estimate the diagnostic value of *RASSF1A* methylation for CRC.

Results: A total of 22 articles among 1736 CRC and 811 non-tumor samples were included in the current meta-analysis. Our results showed that *RASSF1A* hypermethylation was found more frequently in CRC than non-tumor samples (OR = 6.02, 95% CI = 4.57–7.93, $P < 0.001$). Our SROC test showed that *RASSF1A* hypermethylation had an area under the curve (AUC) of 0.71 with a pooled sensitivity of 0.33 (95% CI = 0.31–0.36), a pooled specificity of 0.86 (95% CI = 0.84–0.89), a positive-likelihood ratio of 3.18 (95% CI = 1.99–5.09), a negative-likelihood ratio of 0.71 (95% CI = 0.63–0.80), and a diagnostic odds ratio of 5.53 (95% CI = 3.40–9.00). Data mining study indicated that a trend of increased *RASSF1A* expression was found in the CRC cell line C2C12 after 5-AZA treatment.

Conclusions: Our study established that *RASSF1A* hypermethylation might have a potential value in the clinical diagnosis of CRC.

1. Introduction

Colorectal cancer (CRC) is a common malignant tumor, which may increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [1]. Although the use of advanced screening and treatment techniques reduces CRC morbidity and mortality [2], the overall survival rate of CRC patients remains low [3]. The incidence of CRC is heterogeneous. The incidence of CRC among blacks between 50–64 years of age is usually higher than other races in the same age group [4]. And age-adjusted CRC incidence in men is higher than women [5].

As an important epigenetic modification mechanism, DNA methylation is known to be related to the development and progression of human cancers including CRC [6–8]. Aberrant methylation of cytosine-phosphate-guanine island (CGI) in promoter region can suppress the expression of the corresponding gene [9]. This is also a major mechanism of aberrant methylation of CRC-related genes leading to carcinogenesis [10,11]. Accumulating number of studies showed that aberrant methylation of many genes could serve as diagnostic biomarkers for CRC [12–14].

As a putative tumor suppressor gene, Ras association domain family 1 isoform A (*RASSF1A*) is located on chromosome 3p21.3, which often shows loss of heterozygosity in human tumors [15]. RASSF1A is a member of the Ras-binding domain family (RASSF), which binds RAS in

Abbreviations: CRC, colorectal cancer; RASSF1A, ras association domain family 1 isoform A; CNKI, Chinese National Knowledge Infrastructure; SROC, summary receiver operating characteristics; AUC, area under the curve; RASSF, ras association domain family; ORs, odds ratios; CIs, confidence intervals; 5-AZA, 5-Aza-2′-deoxycytidine; GEO, Gene Expression Omnibus; PLR, positive-likelihood ratio; NLR, negative-likelihood ratio; DOR, diagnostic odds ratio; CEA, carcino-embryonic antigen; DAPK, death associated protein kinase; QUADAS, Quality Assessment of Studies of Diagnostic Accuracy

* Corresponding author.
E-mail address: duanshiwei@nbu.edu.cn (S. Duan).

[1] Author HH, author CZ and author BL contributed equally.

https://doi.org/10.1016/j.prp.2018.07.031
Received 18 April 2018; Received in revised form 15 July 2018; Accepted 25 July 2018
0344-0338/ © 2018 Published by Elsevier GmbH.

Please cite this article as: Hu, H., Pathology - Research and Practice (2018), https://doi.org/10.1016/j.prp.2018.07.031

a GTP-dependent manner and subsequently induces apoptosis mediated by RAS [16]. Oliveira C *et al.* demonstrated that *RASSF1A* promoter hypermethylation occurred preferentially in MSI sporadic CRC [17]. Sinha R *et al.* found *RASSF1A* hypermethylation was an indicator of tumor staging and metastasis in CRC [18].Transcriptional silencing of *RASSF1A* by inappropriate promoter methylation has been frequently observed in CRC [19]. And *RASSF1A* hypermethylation could reduce gene expression and display functionally analogous to a homozygous deletion or an inactivating mutation [20]. In addition, increased tumor multiplicity and size has been explored in *RASSF1A* knockout mice [21].

Although *RASSF1A* inactivation caused by the abnormal DNA methylation has been widely studied in CRC [22,23], the characterization of *RASSF1A* methylation in the diagnosis of CRC is still questionable. In this study, we performed a meta-analysis to determine the diagnostic value of *RASSF1A* hypermethylation for CRC.

2. Materials and methods

2.1. Literature selection

The PubMed, Embase, CNKI, and Wanfang databases were used to select candidate documents. We retrieved eligible documents updated before September 2017 by setting keyword combinations "(Ras Association Domain Family Member 1 A or RASSF1A or Ras Association Domain Family Member 1 or RASSF1) and (colorectal cancer or colorectal tumor or colorectal carcinoma or colorectal neoplasm) and (methylation or epigene*)". The studies included in the meta-analysis should meet the following criteria: (1) the study should be the original association study of CRC with *RASSF1A* methylation; (2) the study should have a case-control cohort or a subgroup based on race, gender, or age; (3) The control sample should be a normal sample of adjacent non-cancer tissue from a healthy person or CRC patient; (4) The study had sufficient data to calculate the odds ratio (OR) and 95% confidence interval (CI), true positive, false positives, true negatives and false negatives; (5) Repetitive studies should be excluded to avoid data overlap.

2.2. Data extraction and quality assessment

HH, CZ, and BL extracted information from the eligible literature for the first author's name, publication year, patient race, sample size and type, methylation status, and information specific to the subgroup. Two authors (CZ and BL) independently assessed the quality of 22 studies based on QUADAS [24]. All extracted data was checked by the authors (CZ and BL) repeatedly.

2.3. Data mining study

The expression data of the CRC cell line (C2C12) with and without 10 μm 5-Aza-2′-deoxycytidine (5-AZA) treatment was obtained from Gene Expression Omnibus (GEO) DataSets (GSE30192; https://www.ncbi.nlm.nih.gov/gds/). Two records were retrieved as parallel experiments (1441737_s_at, 1448855_at).

2.4. Statistical analysis

The meta-analysis was performed by Review Manager 5, Meta-Disc 1.4 and Stata SE12.0 software. The association between *RASSF1A* methylation and CRC risk was assessed by odds ratio (OR) and 95% confidence interval (CI). The heterogeneity of the study was estimated by the I^2 statistic in the meta-analysis ($P < 0.1$ or $I^2 > 50\%$ considered heterogeneity). When $I^2 < 50\%$, a fixed effect model was used for meta-analysis, otherwise a random effects model was used [25]. Subgroup meta-analysis were performed to explore the source of heterogeneity. True positive, true negative, false positive and false negative from each eligible study were extracted for diagnostic meta-analysis. Summary receiver operator characteristic (SROC) curve and forest plots of pooled sensitivity, specificity, positive-likelihood ratio (PLR), negative-likelihood ratio (NLR), and diagnostic odds ratio (DOR) were made to estimate the diagnostic performance of *RASSF1A* methylation. Deeks' funnel plot asymmetry test was performed to assess the potential publication bias [26]. An independent-samples T test was used to assess the expression differences pre-treatment and post-treatment of 5-AZA in GEO datasets. *P* values were derived from two-tailed tests, and $P < 0.05$ was considered statistically significant.

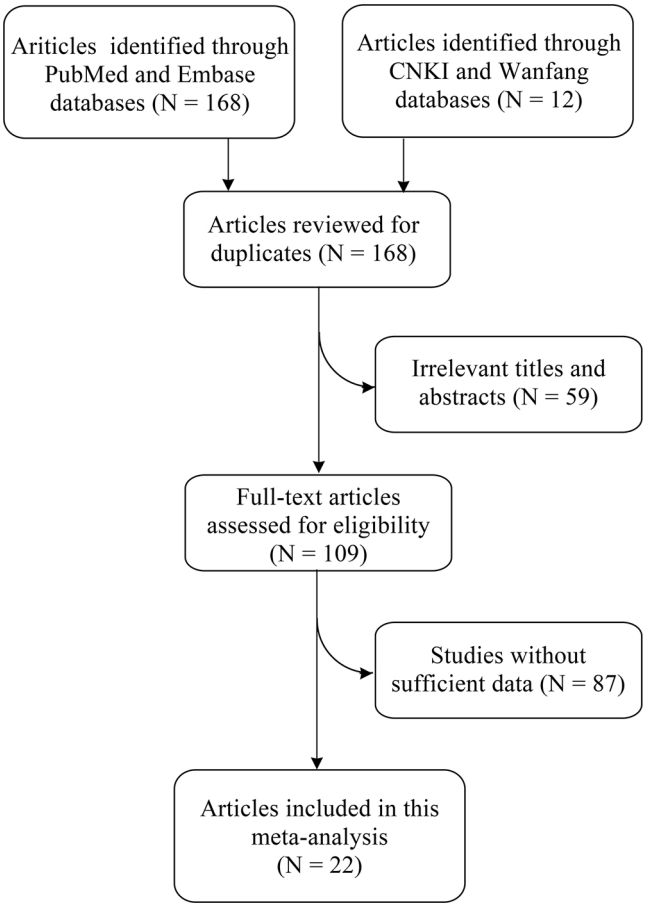

Fig. 1. Flow diagram of eligible studies selection in present meta-analysis.

3. Results

3.1. Search results and studies characteristics

A total of 168 articles were initially selected without duplicate from online literature databases including PubMed, Embase, CNKI and Wanfang. And 59 articles were excluded subsequently for irrelevant titles and abstracts. Eventually, 22 articles involving 1736 CRC and 811 non-tumor samples were found to be eligible for the following meta-analysis (Fig. 1). The 22 articles were published in English or Chinese. There were 13, 8 and 1 studies conducted among Asians, Caucasians, and Africans, respectively. And 18 studies were based on tissue samples, and 4 studies were based on blood samples. More particular information of the eligible articles was shown in Table 1.

3.2. Quality assessment of included studies

The QUADAS assessment tool with 14 evaluation items was applied to assess the quality of the 22 articles (Supplementary Table 1). And 8 out of 22 studies didn't mention the time period between reference

Download English Version:

https://daneshyari.com/en/article/10157729

Download Persian Version:

https://daneshyari.com/article/10157729

Daneshyari.com