EBioMedicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Is Ep-CAM Expression a Diagnostic and Prognostic Biomarker for Colorectal Cancer? A Systematic Meta-Analysis

Susu Han [1], Shaoqi Zong [1], Qi Shi, Hongjia Li, Shanshan Liu, Wei Yang, Wen Li *, Fenggang Hou *

Oncology Department of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai TCM University, 274 Zhijiang Road, Shanghai 200071, People's Republic of China

ARTICLE INFO

Article history:
Received 13 April 2017
Received in revised form 11 May 2017
Accepted 22 May 2017
Available online xxxx

Keywords:
Ep-CAM
Expression
CRC
Prognosis
Diagnosis
Biomarker

ABSTRACT

Background: Cancer stem cell (CSC) epithelial cell adhesion molecule (Ep-CAM) is frequently expressed in colorectal cancer (CRC). However, the clinical significance of Ep-CAM expression in CRC is not clear. This study evaluated whether Ep-CAM provided valuable insight as a molecular biomarker for CRC diagnosis and prognosis and the potential of Ep-CAM as a novel therapeutic target in CRC.

Methods: Publications were selected online using electronic databases. The pooled odds ratios (ORs) or hazard ratios (HRs) with their 95% confidence intervals (95% CIs), and the combined sensitivity, specificity, and area under the curve (AUC) were calculated and summarized.

Results: Eleven eligible articles published in English involving 4561 cases were analyzed in this study. Ep-CAM expression was significantly higher in CRC compared with normal controls, and its overexpression was negatively linked to tumor differentiation, tumor stage, vascular invasion, depth of tumor invasion, lymph node metastasis, distant metastasis, and tumor budding in CRC patients. The loss of Ep-CAM expression positively correlated with these characteristics. Multivariate analysis of loss of Ep-CAM expression correlated with a poor prognosis in disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). The pooled sensitivity, specificity and AUC values of Ep-CAM expression in patients with CRC vs. normal controls were 0.93, 0.90, and 0.94, respectively.

Conclusions: The present findings suggest that Ep-CAM expression may be associated with CRC carcinogenesis, while the loss of Ep-CAM expression is correlated with the progression, metastasis, and poor prognosis of CRC. Ep-CAM expression may be a useful biomarker for the clinical diagnosis of CRC.

1. Introduction

Colorectal cancer (CRC) is the fifth most frequent malignancy and the fifth leading cause of death in all human cancers in China (Chen et al., 2016). Global cancer statistics noted approximately 1.4 million new cases were clinically diagnosed with CRC in 2002 and an estimated 693,900 deaths occurred due to CRC worldwide (Torre et al., 2015). CRC is a major public health problem because approximately 50% of CRC cases develop metastasis and exhibit a poor survival rate despite advances in early detection and treatment (Aranda et al., 2015; Ferlay et al., 2015; Van Cutsem et al., 2010). Therefore, there is a need for a potential biological marker that allows early detection and predicts clinical prognosis of CRC.

A special subpopulation of cancer cells, known as cancer stem cells (CSCs), drive cancer progression. CSCs self-renew, uncontrollably proliferate, differentiate, and form the bulk of the tumor (Majumdar et al., 2012; Chandler and Lagasse, 2010). CSCs also regulate the development, progression, and metastasis of cancer (da Silva-Diz et al., 2016, Sampetrean and Saya, 2013, Nguyen et al., 2012). Multiple studies reported evidence of CSCs in CRC (Patman, 2016; Zeuner et al., 2014). Epithelial cell adhesion molecule (Ep-CAM), also known as epithelial-specific antigen (ESA) or CD326, is a transmembrane glycoprotein cell adhesion molecule that is encoded by the Ep-CAM gene mapped to chromosomal region 4q (Balzar et al., 1999; Linnenbach et al., 1989). This cell adhesion molecule plays a key role in Ca^{2+}-independent cell-to-cell adhesion (Litvinov et al., 1994). Ep-CAM correlates with cell proliferation, migration, invasion, motility, and signal transduction (Subramanian et al., 2015; Maetzel et al., 2009). Studies suggest that Ep-CAM is associated with epithelial-to-mesenchymal transition (EMT) and enhances tumor-initiating capacity (Gupta et al., 2009; Morel et al., 2008). Ep-CAM is overexpressed in many types of cancers, such as breast cancer, ovarian cancer, and head and neck squamous cell

Abbreviations: CRC, colorectal cancer; CSC, cancer stem cell; Ep-CAM, epithelial cell adhesion molecule; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; AUC, area under the curve; DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival; ESA, epithelial-specific antigen; EMT, epithelial-to-mesenchymal transition; CTC, circulating tumor cell; PRISMA, the preferred reporting items for systematic reviews and meta-analyses; IHC, immunohistochemistry.

* Corresponding authors.
E-mail addresses: 13917367207@163.com (W. Li), fghou555@126.com (F. Hou).

[1] SH and SZ are co-first authors of this study.

http://dx.doi.org/10.1016/j.ebiom.2017.05.025

cancer (Moldenhauer et al., 2012). Some studies demonstrated that Ep-CAM overexpression was an unfavorable prognostic marker in breast cancer and gallbladder carcinoma (Varga et al., 2004; Gastl et al., 2000). Ep-CAM is a CSC marker, and it is frequently expressed or overexpressed in CRC (Dalerba et al., 2007; Mosolits et al., 2004). Ep-CAM is defined as a universal molecular marker for circulating tumor cell (CTC) detection, which is termed the "post-Ep-CAM era" (Nicolazzo et al., 2015; Raimondi et al., 2015). Therefore, it is important to investigate Ep-CAM further.

Some studies demonstrated inconsistent and controversial conclusions of Ep-CAM expression in CRC patients. For example, Kuhn et al. reported that Ep-CAM expression was not associated with tumor stage or grade (Kuhn et al., 2007). Gosens et al. reported that the loss of Ep-CAM expression was significantly associated with tumor grade and trended towards a correlation with tumor stage (Gosens et al., 2007). Therefore, the present study assessed whether Ep-CAM expression correlated with an increased risk of CRC vs. benign colonic lesions and normal controls. We also analyzed whether Ep-CAM overexpression or the loss of Ep-CAM expression was associated with the prognostic effect and clinicopathological features of CRC. Finally, we evaluated the use of Ep-CAM expression as a biomarker for the early diagnosis of CRC.

2. Materials and Methods

2.1. Literature Search

A comprehensive literature search (PubMed, EMBASE, EBSCO, Web of Science, and Cochrane Library databases) was performed to identify relevant publications on Ep-CAM expression in CRC patients prior to January 16th, 2017. The articles were identified using the following search terms and key words: 'Ep-CAM', 'epithelial cell adhesion molecule', 'EpCAM', 'CD326', 'GA733', 'CO17-1A', 'EGP', 'KS1-4', 'ESA', 'MOC31', 'BerEP4', and 'colorectal cancer' 'colorectal tumor', 'colorectal carcinoma', 'colorectal neoplasm', 'CRC' and 'expression'. The reference lists of the included articles were also screened to obtain other potential studies. This study was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement criteria (Moher et al., 2009) (Table S1).

2.2. Selection Criteria

Eligible studies were selected based on the following inclusion criteria: 1) patients were limited to a diagnosis of CRC; 2) articles were published in English with the full text; 3) Ep-CAM was considered as a positive expression, overexpression or a loss of the expression; 4) articles provided sufficient information to evaluate the correlation of Ep-CAM expression between CRC and nonmalignant controls; 5) articles provided sufficient data to assess the relationship of Ep-CAM expression with the clinicopathological characteristics of patients with CRC; and 6) the pooled hazard ratios (HRs) and their 95% confidence intervals (CIs) were extracted to evaluate the prognostic role when the data from the original papers were available. The most complete paper containing the most information was selected when authors published several articles using duplicated data.

2.3. Data Extraction

The following data were collected from eligible studies: first author's surname, year of publication, country, ethnic population, age, detection method, clinical stage, staining patterns, cut-off values, Ep-CAM expression (overexpression or loss), expression frequency, number of cases and controls, survival data of multivariate analysis, and clinicopathological features. The clinicopathological characteristics included tumor differentiation (poor vs. well/moderate), tumor stage (3–4 vs. 1–2), vascular invasion (yes vs. no), depth of tumor invasion (pT3–4 vs. pT1–2), lymph node metastasis (yes vs. no), distant metastasis (yes vs. no), tumor budding (yes vs. no), and tumor location (colon vs. rectum). Loss of Ep-CAM expression consisted of complete and partial loss.

2.4. Statistical Analysis

Data were analyzed using Stata software (version 12.0, Stata Corporation, College Station, TX, USA). The combined odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to determine the relationship of Ep-CAM expression between CRC and nonmalignant controls. The associations of Ep-CAM overexpression or loss of Ep-CAM expression with the clinicopathological features of CRC were also calculated using pooled ORs with 95% CIs. The overall hazard ratios (HRs) with 95% CIs were used to determine the impact of Ep-CAM expression on the survival of CRC patients, if possible. Between-study heterogeneity was measured using the Cochran's Q statistic (Zintzaras and Ioannidis, 2005). The random-effects model was used to increase the reliability of the results in the present analysis (heterogeneity: $P < 0.1$). A sensitivity analysis was performed to determine the influence of one study on the results and heterogeneity via omission of a single study when the pooled results with greater than two studies had substantial heterogeneity ($P < 0.1$) (Higgins et al., 2003; Lau et al., 1997). Potential publication bias was assessed using Egger's test for the results with greater than or equal to ten studies (Egger et al., 1997). The pooled sensitivity, specificity, and the summary receiver operator characteristic (SROC) curve (AUC) values were calculated and constructed according to the bivariate analysis to evaluate the performance of the diagnostic capacity of Ep-CAM expression to CRC in this study (Reitsma et al., 2005; Jones and Athanasiou, 2005).

3. Results

3.1. Characteristics of the Included Studies

Fig. 1 shows the detailed selection procedure used for the potential literature. The abovementioned inclusion criteria resulted in 11 eligible studies published in English from 2005 to 2016 (Kim et al., 2016; Chai et al., 2015; Zhou et al., 2015; Kim et al., 2014; Goossens-Beumer et al., 2014; Lugli et al., 2010; Paret et al., 2007; Kuhn et al., 2007; Gosens et al., 2007; Went et al., 2006; Karanikiotis et al., 2005) for the meta-analysis, which included 4103 CRC patients and 458 controls. Five studies of 331 patients with CRC and 458 controls analyzed the relationship of Ep-CAM expression between CRC and controls (Chai et al., 2015; Zhou et al., 2015; Paret et al., 2007; Kuhn et al., 2007; Karanikiotis et al., 2005). Six studies analyzed the correlation of Ep-CAM overexpression or loss with

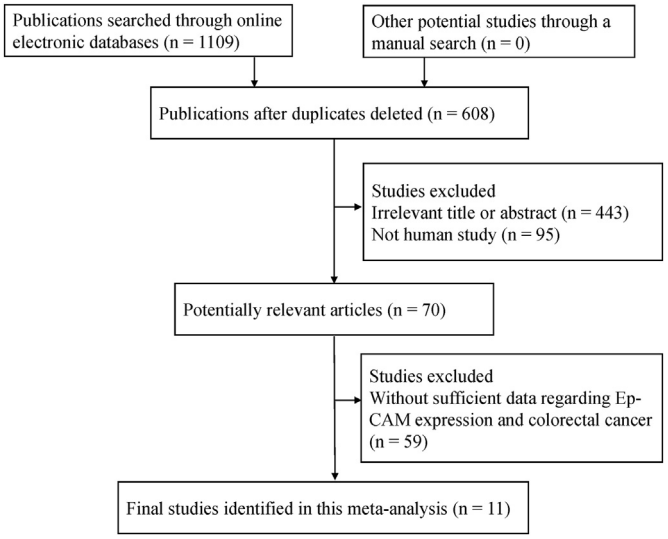

Fig. 1. Flow chart of the selection procedure.

Please cite this article as: Han, S., et al., Is Ep-CAM Expression a Diagnostic and Prognostic Biomarker for Colorectal Cancer? A Systematic Meta-Analysis, EBioMedicine (2017), http://dx.doi.org/10.1016/j.ebiom.2017.05.025