RESEARCH ARTICLE

Prognostic Significance of Beta-Catenin Expression in Patients with Esophageal Carcinoma: a Meta-analysis

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Abstract

Many studies have reported β-catenin involvement in the development of esophageal carcinoma (EC), but its prognostic significance for EC patients remains controversial. Therefore, we conducted this meta-analysis to explore the issue in detail. After searching PubMed, EMBASE, Web of Science, and Chinese Biomedical Literature Database, we included a total of ten relevant studies. We pooled the overall survival (OS) data using RevMan 5.2 software. The results showed that aberrant expression of β-catenin was associated with a significant increase of mortality risk (hazard ratio 1.71, 95%CI 1.46-2.01; $p<0.00001$). Subgroup analyses further suggested that aberrant expression of β-catenin resulted in poor OS of EC patients regardless of histological type of EC, study location or criteria for aberrant expression of β-catenin, and the sensitivity analyses revealed that the result was robust. The meta-analysis revealed that aberrant expression of β-catenin could be a predicative factor of poor prognosis for EC patients.

Keywords: β-catenin - esophageal carcinoma - prognosis - meta-analysis

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Introduction

Esophageal carcinoma (EC) is one of the most common malignant tumors worldwide (Jemal et al., 2009), and has even become a global health problem. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two main histopathological types of EC. ESCC is the dominant histologic type in Asian countries, especially in China and Japan, accounting for over 90% of all ECs (Fang et al., 2011; Duan et al., 2012; Wen et al., 2013). While EAC is primarily found in western countries, and the incidence of EAC has been rapidly increasing for several decades (Reed et al., 1993).

Despite recent advances in diagnosis and treatment, the prognosis for EC is generally unfavorable, with a five-year survival rate of merely 15-20% (Xu et al., 2012; Wang et al., 2014), which could owe mainly to the extensive local invasion and regional lymph node metastasis (Wang et al., 1999). It has been demonstrated that the reduced cell-cell and cell-matrix adhesion, which involves with the E-cadherin-catenin complex, is one of the key steps of invasion and metastasis of cancers (Aberle et al., 1996; Montesano., 1996). As a pivotal component of E-cadherin-catenin complex, β-catenin plays important roles in maintaining integrity of cellular structure (Nelson et al., 2004; Ilyas et al., 2005). Moreover, β-catenin is also important in Wnt signaling pathway, which was involved with the transcription of Wnt target genes resulting in cell proliferation, invasion, and metastasis (Nelson et al., 2004; Barker et al., 2006; Wang et al., 2012; Pandurangan et al., 2013). It has been reported that aberrant expression of β-catenin was associated with the poor prognosis of non-small cell lung cancer (NSCLC) (Mei et al., 2013), and colorectal cancer (CRC) (Chen et al., 2013). Many studies also reported that β-catenin was involved in the development of EC, however, its prognostic significance for EC patients remains controversial (Krishnadath et al., 1997; Shiozaki et al., 2000; Hsu et al., 2008; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Situ et al., 2010; Chen et al., 2011; Wang et al., 2011; Lv et al., 2012). Therefore, we conducted this meta-analysis to determine whether β-catenin could be a prognosis factor in EC.

Materials and Methods

Inclusion and exclusion criteria

Studies should be included if they met the following criteria: (1) assessed β-catenin protein expression in the primary EC tissues; (2) evaluated the correlation between β-catenin protein expression and the overall survival (OS) of EC patients; (3) were published as full texts. The exclusion criteria were as follow: (1) letters, reviews, case reports, conference abstracts, editorials; (2) articles had no sufficient data to calculate hazard ratio (HR). Of the

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studies which had duplication data, only the most complete study was included in the analysis.

Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) were followed to conduct the meta-analysis. Using the terms "β-catenin", "beta-catenin", "CTNNB1" and "esophageal carcinoma", we searched PubMed, EMBASE, Web of Science and Chinese Biomedical Literature Database from their start year up to Jan. 2014. The Mesh terms and variations of each term were used and no restriction on language was applied. In addition, we also searched Google Scholar and other databases.

Study screening and data extraction

Each study was screened by two reviewers independently to determine whether it met the inclusion criteria or not, and any disagreement was resolved by consensus. For each included study, two reviewers independently extracted the following data using a standard form: first author, year of publication, source of cases, number of cases, test method, criteria for aberrant expression of β-catenin, and patient survival results.

Methodological assessment

Using the Newcastle-Ottawa quality assessment scale (Stang et al., 2010), two reviewers evaluated the methodological quality of each included study. 0-9 stars were assigned to each study based on three categories (selection, comparability and outcome).

Statistical analysis

HR with 95% confidence interval (CI) was used to estimate the association between β-catenin expression and the OS of EC patients. For studies which had not given those HRs directly, they were estimated from available data using the methods reported by Tierney et al. (2007) and Zhang et al. (2012). The χ^2 test and the I^2 statistic were used to evaluate the heterogeneity among studies. $p<0.1$ or $I^2>50\%$ was considered to be significant for heterogeneity, and a random-effects model was used to conduct the meta-analysis, otherwise, a fixed-effects model was used. Subgroup analyses were performed by histology of EC, study location, and criteria of aberrant expression of β-catenin. Sensitive analyses were also carried out to determine whether the publication year, sample size of study, the method of HR estimate or HR calculation affected the robustness of the result. A funnel plot recommended by the Cochrane Handbook (Higgins et al., 2011) was made to explore whether publication bias existed in the meta-analysis or not. All statistical analyses were conducted using Review Manager 5.2.

Results

Study selection and characteristics

Using the search strategy as described above, we identified a total of 921 articles. Figure 1 details the selection process. Finally, ten studies (Krishnadath et al., 1997; Shiozaki et al., 2000; Hsu et al., 2008; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Situ et al., 2010; Chen et al., 2011; Wang et al., 2011; Lv et al., 2012) investigating the correlation between β-catenin expression and the OS of EC patients were included in the meta-analysis, of which nine studies (Shiozaki et al., 2000; Hsu et al., 2008; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Situ et al., 2010; Chen et al., 2011; Wang et al., 2011; Lv et al., 2012) investigated Asian patients, and one (Krishnadath et al., 1997) investigated European patients. The studies were conducted between 1997 and 2012, and the number of patients they investigated ranged from 40 to 227. Nine studies (Shiozaki et al., 2000; Hsu et al., 2008; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Situ et al., 2010; Chen et al., 2011; Wang et al., 2011; Lv et al., 2012) investigated patients with ESCC, and one (Krishnadath et al., 1997) investigated EAC. Although all the studies used immunohistochemical analysis to examine the expression of β-catenin, they made different criteria of β-catenin aberrant expression. HRs with 95% CIs were reported directly in three studies (Hsu et al., 2008; Situ et al., 2010; Lv et al., 2012), calculated from available data in six studies (Krishnadath et al., 1997; Shiozaki et al., 2000; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Wang et al., 2011), and extrapolated from Kaplan-Meier curves in one study (Chen et al., 2011). As for the statistical methods used to calculate HRs, four studies used multivariate analysis (Shiozaki et al., 2000; Hsu et al., 2008; Situ et al., 2010; Lv et al., 2012), and the others used univariate analysis. (Table 1)

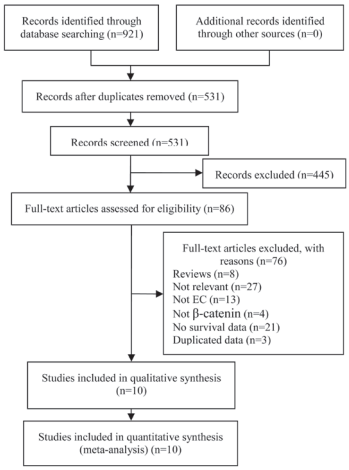

Figure 1. Flow Chart of Included Studies

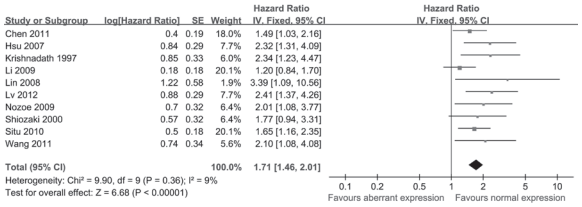

Figure 2. Meta-Analysis of Effects of Beta-Catenin on Overall Survival of Patients with Esophageal Carcinoma

Methodological quality of the included studies

The methodological quality of the included studies was assessed by using the Newcastle-Ottawa quality assessment scale for cohort study. The stars achieved by

Table 1. Main Characteristics of All Studies Included in the Meta-analysis

Author	Year	Location; country/region	No. of specimens	Histology of EC	Method	Criteria of β-catenin aberrant expression	No. of aberrant expression (%)	HR estimate	Quality score
Chen et al.	2011	China	211	SCC	IHC	Cytoplasm staining; score≥5	136 (64.5%)	Curve (U)	5
Hsu et al.	2007	Taiwan	68	SCC	IHC	Membrane staining; score≤2	43 (63.2%)	R (M)	6
Krishnadath et al.	1997	Netherlands	65	AC	IHC	Membrane staining; positive cells≤90%	42 (64.6%)	A (U)	7
Li et al.	2009	Taiwan	121	SCC	IHC	Cytoplasm staining; positive cells≥25%	22 (18.2%)	A (U)	7
Lin et al.	2008	China	50	SCC	IHC	Membrane staining; score≤2	26 (52%)	A (U)	6
Lv et al.	2012	China	70	SCC	IHC	NR	NR	R (M)	7
Nozoe et al.	2009	Japan	69	SCC	IHC	Membrane staining; positive cells<50%	36 (52.2%)	A (U)	6
Shiozaki et al.	2000	Japan	77	SCC	IHC	Cytoplasm or nuclear staining; positive cells≥10%	42 (54.5%)	A (M)	7
Situ et al.	2010	China	227	SCC	IHC	Membrane and cytoplasm staining; immunohistochemistry score≥1.3333	144 (63.4%)	R (M)	8
Wang et al.	2011	China	40	SCC	IHC	Membrane staining; positive cells<70%	22 (55%)	A (U)	6

*EC, esophagus cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma; IHC, immunohistochemistry; NR, not reported; HR, hazard ratio; R, reported; Curve, Kaplan-Meier curve; A, available data; M, multivariate analysis; U, univariate analysis

Table 2. Subgroup Analysis and Sensitive Analysis on the Outcome of Overall Survival

	No. of Studies	No. of patients	Heterogeneity	Statistical model used	HR (95% CI), P value
Histology of esophageal cancer					
Squamous carcinoma	9	933	p=0.35; I^2=11%	Fixed	1.68 (1.43, 1.98), p<0.00001
Adenocarcinoma	1	65	NA	Fixed	2.34 (1.23, 4.47), p=0.01
Study location					
Asia	9	933	p=0.35; I^2=11%	Fixed	1.68 (1.43, 1.98), p<0.00001
Europe	1	65	NA	Fixed	2.34 (1.23, 4.47), p=0.01
Criteria of aberrant expression of β-catenin					
Reduced expression in membrane	5	292	p=0.95; I^2=0%	Fixed	2.26 (1.67, 3.06), p<0.00001
Overexpression in cytoplasm/nuclear	3	409	p=0.50; I^2=0%	Fixed	1.38 (1.09, 1.57), p=0.007
No. of patients					
<100	7	439	p=0.97; I^2=0%	Fixed	2.20 (1.73, 2.82), p<0.00001
>100	3	559	p=0.44; I^2=0%	Fixed	1.43 (1.16, 1.76), p=0.0007
HR estimate					
Reported	3	365	p=0.42; I^2=0%	Fixed	1.93 (1.48, 2.51), p<0.00001
Available data calculated	6	422	p=0.24; I^2=26%	Fixed	1.65 (1.31, 2.09), p<0.0001
Kaplan-Meier curve	1	211	NA	Fixed	1.49 (1.03, 2.16), p=0.04
Statistical method used to calculate HR					
Multivariate analysis	4	442	p=0.61; I^2= %	Fixed	1.90 (1.49, 2.43), p<0.00001
Univariate analysis	6	556	p=0.23; I^2=27%	Fixed	1.59 (1.29, 1.96), p<0.0001

*HR, hazard ratio; CI, confidence interval; NA, not applicable

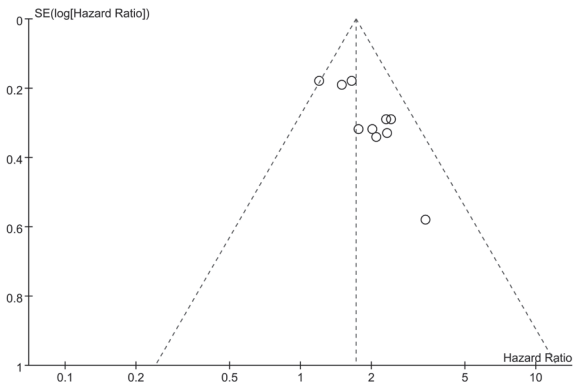

Figure 3. Funnel Plot for the Outcome of Overall Survival

each study ranged from 5 to 8; one study (Chen et al., 2011) achieved 5 stars, four studies (Hsu et al., 2008; Lin et al., 2008; Nozoe et al., 2009; Wang et al., 2011) achieved 6, four studies (Krishnadath et al., 1997; Shiozaki et al., 2000; Li et al., 2009; Lv et al., 2012) achieved 7, and one study (Situ et al., 2010) achieved 8.

Meta-analysis results

All the studies reported the outcome of OS and had available data to calculate HRs. As no significant heterogeneity existed among them (P=0.36, I^2=9%), a fixed-effects model was used to pool the data, and the results showed that aberrant expression of β-catenin was associated with a significant increase of mortality risk (HR 1.71, 95% CI 1.46-2.01), as shown in Figure 2.

As shown in Table 2, the results of subgroup analyses

showed that aberrant expression of β-catenin resulted in poor OS of EC patients regardless of histological type of EC, study location or criteria of aberrant expression of β-catenin. The results of sensitive analyses showed that the publication year, sample size of study, the method of HR estimate or HR calculation did not alter the significant prognostic impact of aberrant expression of β-catenin.

Figure 3 shows the funnel plot for the outcome of OS, and it showed no asymmetry exhibiting, demonstrating that there was probably no publication bias.

Discussion

The migration of cancer cells from the cancer nest is an initial event in the formation of tumor metastasis (Nagano et al., 2004). Previous investigations have demonstrated that the reduced cell-cell and cell-matrix adhesion was one of the key steps of invasion and metastasis of cancers (Aberle et al., 1996; Montesano et al., 1996), and the expression of adhesion molecules, which prevent cancer cells from detaching, is a potential indicator of prognosis in patients and/or of less invasive behavior in gastrointestinal cancer types, including EC (Xu et al., 2014).

Cadherins, belong to a family of transmembrane glycoproteins, are adhesion molecules responsible for homophilic interaction of calcium-dependent cell-cell adhesion (Zhao et al., 2003). Among them, E-cadherin is a classical cadherin that forms the functional component of adherens junctions between epithelial cells (Hirohashi et al., 1998), and β-catenin, is a multifunctional protein which links E-cadherin and α-catenin to cytoskeleton to constitute E-cadherin-catenin complex (Ilyas et al., 1997; Wijnhoven et al., 2000). The complex plays important roles in maintaining integrity of cellular structure (Yagi et al., 2000; Ivanov et al., 2001). Reduced expression of one or more components of this complex in tumor cells could destroy the junctional structure, result in loss of intercellular adhesion and consequently facilitate tumor differentiation and metastasis (Saad et al., 2013; Yu et al., 2014). It has been reported that reduced membranous β-catenin expression was related to poor survival and prognosis in a portion of cancers (Krishnadath et al., 1997; Wang et al., 2011; Guan et al., 2012; Mei et al., 2013).

Unlike the other catenins, β-catenin is also a member in Wnt signaling (Zhang et al., 2012). Under normal circumstances, β-catenin maintains a low cytoplasmic concentration through the destruction complex that is composed of the adenomatous polyposis coli tumor suppressor gene, scaffolding protein Axin, glycogen synthase kinase 3β, and casein kinase I (Corrigan et al., 2009). However, when the Wnt signaling pathway is activated, the destruction complex is dissolved and β-catenin accumulates in the cytoplasm and enters the nucleus, subsequently activates transcription of Wnt target genes and leading to cell proliferation, invasion, and metastasis (Barker et al., 2006; Wang et al., 2012; Pandurangan et al., 2013). Thus, the overexpression of β-catenin in the cytoplasm and nucleus is an indicator of an active Wnt signaling pathway and a useful biomarker associated with poor prognosis of cancers.

Generally speaking, aberrant β-catenin expression, either reduced expression in membrane or increased expression in cytoplasm/nuclear, contributes to tumorigenesis, and many systematic reviews have reported that β-catenin participated in the development of cancers, and resulted in poor prognosis. Mei et al. conducted a meta-analysis (Mei et al., 2013) including 12 studies (covering 1,964 patients with NSCLC), and reported that reduced β-catenin expression in the membranes had an adverse impact on OS in NSCLC patients (HR 1.91, 95%CI: 1.60-2.28). A meta-analysis conducted by Chen et al. (Chen et al., 2013) analyzed 18 studies (involving 3,665 CRC patients) and the results suggested that β-catenin overexpression in the nucleus was significantly associated with advanced stage CRC (odds ratio [OR] 0.71, 95% CI: 0.53-0.94) and metastasis of CRC (OR 0.49,95% CI: 0.25-0.96), and also associated with unfavorable disease free survival (HR 1.87, 95% CI: 1.28-2.71) and OS (HR 1.55, 95% CI: 1.12-2.14) for CRC patients.

The correlation between β-catenin expression and the prognosis of EC was also explored by many studies (Krishnadath et al., 1997; Shiozaki et al., 2000; Hsu et al., 2008; Lin et al., 2008; Li et al., 2009; Nozoe et al., 2009; Situ et al., 2010; Chen et al., 2011; Wang et al., 2011; Lv et al., 2012), however, their conclusions were inconsistent. Since the prognostic value of β-catenin for EC patients remains controversial, a meta-analysis was needed to explore the issue clearly. The present study pooled the survival data of 998 EC patients that from ten studies, and found that aberrant expression of β-catenin was associated with a significant increase of mortality risk of EC patients (HR 1.71, 95% CI 1.46-2.01), which suggested that β-catenin could be a prognostic factor in EC. The results of subgroup analyses showed that aberrant β-catenin expression also was associated with unfavorable survival for either ESCC patients, EAC patients, or Asian patients, European patients. The subgroup analysis also revealed that either reduced expression in membrane or increased expression in cytoplasm/nuclear was a useful biomarker for poor prognosis of EC. Sensitive analyses were conducted to determine the robustness of the results. We found that the publication year, sample size of study, the methods of HR estimate or HR calculation did not alter the significant prognostic impact of aberrant expression of β-catenin, which suggested that the result was robust.

Our findings should be considered within the limitations of the study. Firstly, only one study (Krishnadath et al., 1997) focused on EAC patients in Europe, which made it difficult to draw a firm conclusion on the prognostic value of β-catenin for EAC or for European patients. Secondly, the criteria for defining aberrant expression of β-catenin differed from each other among the included studies, hence, so we could not conduct subgroup analysis to determine the optimal cut-off value.

In conclusion, our meta-analysis revealed that aberrant expression of β-catenin could be a predicative factor of poor prognosis for EC patients. However, high-quality studies are still needed, especially studies focus on EAC patients in European countries.

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