

## Original Article

# Prognostic value of rsf-1/hbxap in human solid tumors: a meta-analysis of cohort studies

Jiayuan Wu<sup>1\*</sup>, Liren Hu<sup>2\*</sup>, Fenping Wu<sup>3</sup>, Taiping He<sup>4</sup>

<sup>1</sup>Department of Nutritional, The Affiliated Hospital of Guangdong Medical College, Zhanjiang, Guangdong Province, China; <sup>2</sup>Department of Epidemiology and Health Statistics, School of Public Health, Guangdong Medical College, Zhanjiang, Guangdong Province, China; <sup>3</sup>Department of Radiotherapy, The Seventh People's Hospital of Chengdu, The Oncology Hospital of Chengdu, Chengdu, Sichuan Province, China; <sup>4</sup>School of Public Health, Guangdong Medical College, Dongguan, Guangdong Province, China. \*Equal contributors.

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**Abstract:** Purpose: Recent studies have investigated remodeling and spacing factor 1 (Rsf-1) as a molecular marker in various solid tumors. However, whether or not Rsf-1 exerts a negative or positive effect on the survival of patients with solid cancers remains controversial. Therefore, this study aims to determine whether or not Rsf-1 may be a predicative marker of poor prognosis and aggressive tumor progression. Methods: We conducted a meta-analysis of 11 cohort studies (n = 1620 patients) to evaluate the relationship between Rsf-1 and clinical outcome. We included studies with data on overall survival (OS), disease-specific survival (DSS), recurrent-free survival (RFS), metastasis-free survival (MFS), and hazard ratios (HRs) with 95% confidence intervals (CIs). Results: High Rsf-1 expression was significantly associated with poor survival in solid tumors. Overall, the combined HR for OS was 1.49 (95% CI = 1.21-1.84,  $P < 0.001$ ), DSS 3.07 (95% CI = 1.67-5.62,  $P < 0.001$ ), RFS 2.51 (95% CI = 1.12-5.63,  $P = 0.025$ ), and MFS 2.14 (95% CI = 1.49-3.06,  $P < 0.001$ ). In addition, Rsf-1 overexpression was significantly associated with tumor stage (OR = 4.13, 95% CI = 2.84-6.00,  $P < 0.001$ ), primary tumor (OR = 2.09, 95% CI = 1.58-2.75,  $P < 0.001$ ), nodal status (OR = 1.95, 95% CI = 1.40-2.72,  $P < 0.001$ ), and histological grade (OR = 3.09, 95% CI = 2.10-4.54,  $P < 0.001$ ). Conclusions: Rsf-1 may be a predicative marker of poor prognosis and aggressive tumor progression.

**Keywords:** Rsf-1, tumor, prognosis, meta-analysis

## Introduction

Gene amplification is a molecular genetic hallmark that plays fundamental roles in oncogenic activation in human cancers. This process participates in distinct genomic events, including transcriptional regulation, DNA synthesis, damage repair, methylation, and recombination [1]. Identifying new cancer-associated genes is important to illuminate the molecular etiology of neoplastic diseases and to develop new diagnostic markers and therapeutic targets [2].

The chromosomal region 11q13 is frequently amplified in several types of human cancer. This region harbors several established and identified oncogenes, including MEN1, CCND1, FGF3, EMS1, GARP, PAK1, and RSF1 [3]. Remodeling and spacing factor 1 (Rsf-1) protein or hepatitis B X-antigen-associated protein (HB-XAP) is encoded by the amplified RSF1 gene.

This protein is an ATP-dependent chromatin remodeling factor that binds to human sucrose non-fermenting protein 2 homolog (hSNF2H) to form a complex belonging to the ISWI chromatin remodeling family [4, 5]. The complex formed by Rsf-1 and hSNF2H in the cell nucleus participates in chromosomal recombination and changes chromosomal structure and nucleosome position. Nucleosome remodeling is indispensable for transcriptional regulation [6], DNA replication [7], and cell cycle progression [8]. This transversion under the energy supply of ATP hydrolysis changes growth-modifying signals and environmental cues, disrupts normal growth regulation and causes abnormal hyperplasia at the gene level, and responds to local tumor formation [9].

Recent studies have associated Rsf-1 with poor clinical outcome in several human solid tumors,

particularly ovarian cancer [10, 11], gallbladder carcinoma [12], gastric adenocarcinoma [13], oral squamous cell carcinoma [14], urothelial carcinoma of the urinary bladder (UCUB) [15], and colon cancer [16]. However, the findings of these studies are limited by retrospective design or a single tumor type. To the best of our knowledge, this meta-analysis is the first to investigate the relationship between Rsf-1 expression and solid tumor prognosis.

## Materials and methods

### Literature search

Studies were retrieved from electronic databases, including PubMed, Embase, and China National Knowledge Infrastructure (CNKI). The search terms were “rsf1”, “rsf-1”, “remodeling and spacing factor1”, or “HBXAP”, “hepatitis B virus x-associated protein”, “tumor (s)”, “cancer (s)”, “carcinoma (s)”, “malignant”, “neoplasm (s)”, “survival”, “prognostic”, and “prognosis”. The searching time ended on May 1, 2014, and no lower date time was used. The search was not restricted by language. Original articles that focused on this topic were manually reviewed and identified.

The meta-analysis was executed in accordance with the guidelines of Preferred Reporting Item for Systematic Reviews and Meta-analyses.

### Inclusion and exclusion criteria

The inclusion criteria used to select eligible studies were as follows: (1) the correlation between Rsf-1 expression and overall survival (OS), disease-specific survival (DSS), recurrent-free survival (RFS), or metastasis-free survival (MFS) was estimated from the date of operation or radiotherapy to the date of death; (2) Rsf-1 evaluation was performed through immunohistochemistry (IHC); (3) a cohort design was used; (4) the hazard ratio (HR) and 95% confidence interval (CI) were directly extracted from an original article or sufficient data were provided for the HR and 95% CI calculations; and (5) sample size was equal to or more than 50. Studies considered ineligible for the meta-analysis were reviews, conference abstracts, editorials, or letters, and articles with insufficient published data for estimating HR and 95% CI. If authors published multiple publications on the same institution with identical or overlapping patient cohorts, only studies with the largest number of patients were retained to avoid duplicate information.

### Data extraction

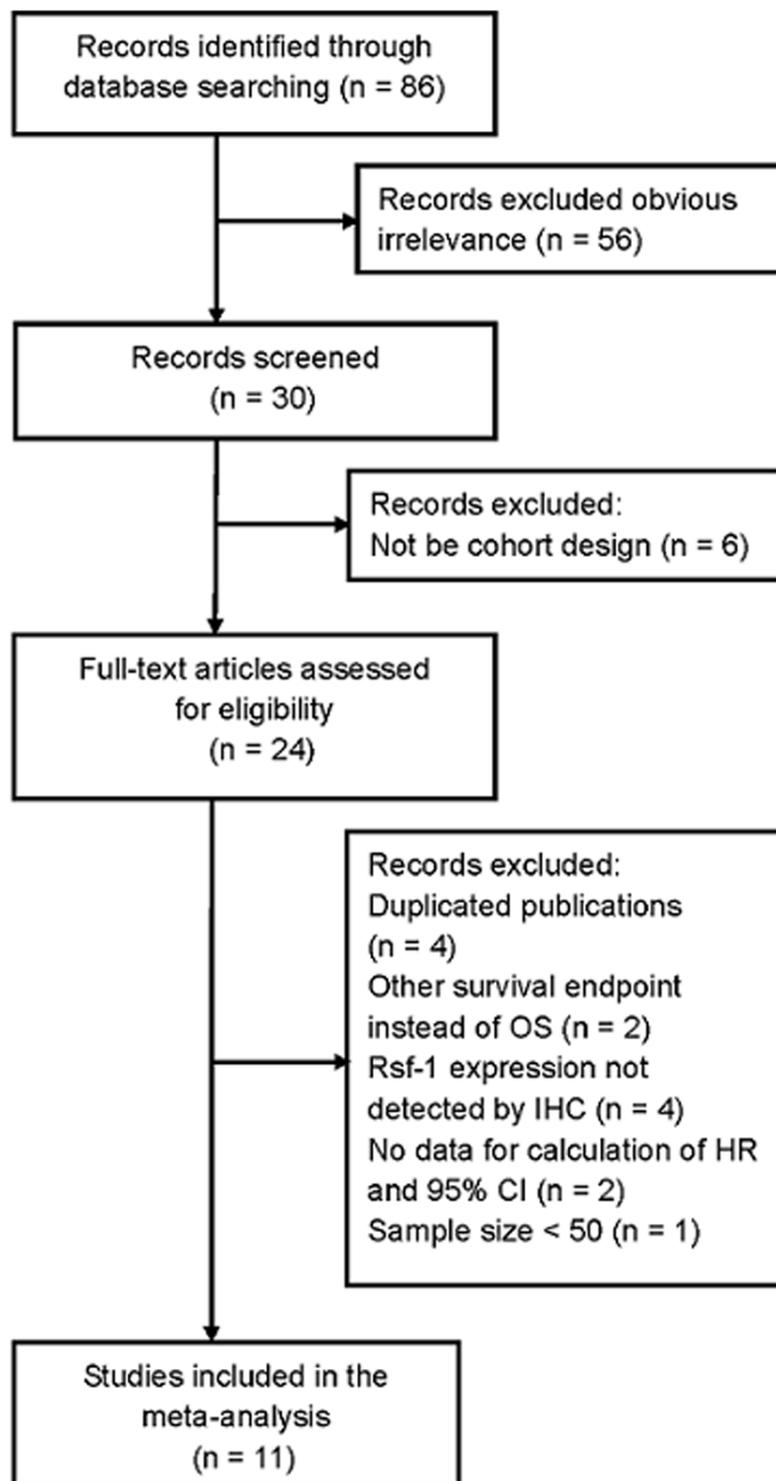
Information was carefully searched from all eligible publications by two authors (Wu JY and Hu LR) independently according to the inclusion criteria. For conflicting information, an agreement was reached through a discussion between the two reviewers. Data extracted from individual studies were recorded in standardized abstraction sheets. These data include the following: first author's name, year of publication, country of origin, recruitment time, number of analyzed patients, follow-up months, analysis method, blinding of Rsf-1 measurements, cut-off value, number of high/low Rsf-1 expression to the study outcomes, HR estimation, and quality scores. For each study, HR was estimated following the method described by Parmar et al. [17]. HR estimates and 95% CIs were either directly obtained from the original articles or calculated on the basis of parameters (*O-E* statistic and variance). For studies in which HRs were not given, the number of patients at risk in each group, the total number of events, and the *P*-value of the log-rank statistic were retrieved to estimate the HR and its variance. If the paper only reported data in the form of Kaplan-Meier curves, survival rates at certain times were extracted to reconstruct the HR estimate and its standard error. The rate of patients censored was constant during the follow-up [18].

### Quality assessment

Quality assessment of the cohort studies in this meta-analysis was performed using the Newcastle-Ottawa Scale (NOS) recommended by Cochrane Non-randomized Studies Methods Working Group [19, 20]. The studies were judged by three broad perspectives on the basis of the NOS: selection of study groups (four items, one star each), comparability of study groups (one item, up to two stars), and ascertainment of outcome of interest (three items, one star each). Considering the variable quality of observational studies found in our initial literature search, we considered studies as high quality if they met six or more of the NOS criteria [21].

### Statistical analysis

Odds ratios (ORs) and their corresponding 95% CIs were combined to estimate the correlation between Rsf-1 overexpression and clinicopath-



**Figure 1.** Flow diagram of the study selection process and specific reasons for exclusion in the meta-analysis.

ological features (age, sex, tumor stage, primary tumor, nodal status, histological grade, vascular invasion, and perineural invasion). HRs and their 95% CIs were also used to assess the strength of association between Rsf-1 expres-

sion and OS, DSS, RFS, or MFS. HR > 1 indicated worse prognosis for patients with Rsf-1 overexpression when 95% CI > 1. The statistical significance of the pooled HR was determined by a Z-test.  $P < 0.05$  was considered to indicate statistical significance. These studies were divided into four subgroups (OS, DSS, RFS, and MFS) to separately evaluate the effect of Rsf-1 overexpression and survival because of the different survival results. STATA version 11.0 (STATA Corporation, College Station, TX, USA) was used for all statistical analyses. All statistical tests were two sided.

The heterogeneity of each subgroup was quantified by the  $I^2$  metric, which is independent of the number of studies used in the meta-analysis ( $I^2 < 25\%$ , no heterogeneity;  $I^2 = 25\%$ - $50\%$ , moderate heterogeneity;  $I^2 > 50\%$ , extreme heterogeneity) [22]. Heterogeneity assumption was examined by the Q test and by visual inspection of forests plots. The Q value was defined as identical to the effect size of the  $I^2$  metric ( $P < 0.05$  was considered statistically significant). The pooled HR estimation of each study was calculated using a random-effect model (DerSimonian and Laird method) when  $P < 0.10$ ; otherwise,

a fixed-effect model was used (Mantel-Haenszel method) [23].

A sensitivity analysis was performed to identify “missing” studies and to assess the credibility

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**Table 1.** Main characteristics of 11 eligible studies in the meta-analysis

Study (authors-year)	Patients source	Recruitment time	No. of patients	Type of tumor	Follow-up (months)	Analysis method	Blinding evaluation	Cutoff scores (high/low)	Analysis of variance	HR estimation	Prognostic value	Language	Quality score
Davidson et al 2006	Norway	1998-2002	135	Ovarian Cancer	26 (1-85)	IHC	blinded	Score > 4 (68/67)	Univariate	OS:1.41 (1.01-1.97)*	Poor	English	7
Chen et al 2011	Taiwan	1986-2006	88	GC	29 (1-186)	IHC	NR	≥ 50% (61/27)	Multivariate	DSS:2.68 (1.18-6.12)	Poor	English	6
Fang et al 2011	Taiwan	NR	98	OSCC	40.12 (1-112)	IHC	blinded	Score ≥ 3 54/44	Multivariate	DSS: 33.97 (4.46-244.60)	Poor	English	7
Maeda et al 2011	Japan	NR	89	OCCC	50 (1-196)	IHC	blinded	Score ≥ 1 (73/16)	Univariate	OS: 1.25 (0.73-2.15)*	NS	English	7
Hu et al 2012	China	2003-2006	287	Gastric Adenocarcinoma	NR	IHC	blinded	Score ≥ 4 (151/136)	Multivariate	OS: 1.32 (0.68-1.72)	NS	English	6
Liang et al 2012	Taiwan	1998-2002	295	UCUB	NR	IHC	NR	Score ≥ 3 (101/194)	Multivariate	DSS: 2.00 (1.08-3.68) MFS: 1.62 (1.00-2.62)	Poor	English	6
Lin et al 2012	Taiwan	1998-2004	172	Rectal Cancer	NR	IHC	blinded	Score ≥ 3 (82/90)	Multivariate	DSS: 1.69 (0.76-3.80) RFS: 1.17 (0.49-2.83) MFS: 2.83 (1.17-6.88)	NS or Poor	English	7
Liu et al 2012	China	2006-2008	107	Colon Cancer	NR	IHC	blinded	Score ≥ 4 (54/53)	Multivariate	OS: 2.00 (1.08-3.72)	Poor	English	7
Tai et al 2012	Taiwan	1998-2002	108	NPC	64.8 (4-117)	IHC	blinded	Score ≥ 3 (49/59)	Multivariate	DSS: 4.44 (2.31-8.55) MFS: 3.19 (1.59-6.38) RFS: 5.29 (2.20-12.69)	Poor	English	7
Wu et al 2013	China	1997-2009	72	OSA	53.23 (3-163)	IHC	NR	Score ≥ 3 (58/14)	Univariate	OS : 1.99 (1.11-3.56)*	Poor	Chinese	6
Li et al 2014	China	2005-2007	169	Prostate Cancer	33.2	IHC	blinded	Score ≥ 4 (76/93)	Multivariate	RFS: 2.56 (1.23-5.34)	Poor	English	7

OS overall survival, DSS Disease-Specific Survival, RFS recurrence-free survival, MFS disease-free survival, NR data were not reported, NS not significant, GC gallbladder carcinoma, OSCC oral squamous cell cancer, OCCC ovarian clear cell carcinoma, UCUB urinary bladder urothelial carcinoma, NPC nasopharyngeal carcinoma, OSA ovarian serous adenocarcinoma, IHC immunohistochemistry, Score 2, 3, 4, 5, 6 different scores with combination of percentage of positives cells and intensity, \*Extrapolated from survival curve.

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**Table 2.** Meta-analysis of Rsf-1 overexpression and clinicopathological features in solid tumors patients

Categories	Studies (no. of patients)	OR (95% CI)	I <sup>2</sup> (%)	P <sub>h</sub>	Z	P
Age	9 (1387)	0.95 (0.75-1.19)	18.8	0.275	0.48	0.632
Sex	6 (1057)	0.92 (0.71-1.19)	15.4	0.315	0.66	0.511
Tumor stage	6 (751)	4.13 (2.84-6.00) <sup>R</sup>	65.2	0.013	7.45	< 0.001
Primary tumor	6 (939)	2.09 (1.58-2.75)	0.0	0.690	5.24	< 0.001
Nodal status	5 (851)	1.95 (1.40-2.72)	0.0	0.410	3.94	< 0.001
Histological grade	5 (946)	3.09 (2.10-4.54)	1.2	0.400	5.74	< 0.001
Vascular invasion	3 (555)	1.50 (0.95-2.39)	0.0	0.901	1.72	0.086
Perineural invasion	3 (555)	1.87 (0.91-3.83)	0.0	0.847	1.71	0.088

All pooled ORs were derived from fixed-effects model except for cells marked with (random<sup>R</sup>). P<sub>h</sub> denotes *P*-value for heterogeneity based on Q test; P denotes *P*-value for statistical significance based on Z test.

of meta-analysis outcomes. Begg's rank correlation and Egger's weighted regression method were used to evaluate the potential publication bias of each subgroup [24]. Standard error was plotted against log (HR) to form a simple scatterplot through visual inspection of funnel plots. The statistical significance of Egger's test results was defined as *P* < 0.10.

### Results

#### Search results

The processes of identifying and selecting studies are presented in **Figure 1**. A total of 60 potentially relevant articles were obtained during the initial literature search. Upon further review of titles and abstracts, 45 were excluded because of lack of relevance [2, 25-27]. After reading the full texts of the remaining 15 articles, we further excluded one review [9] and three articles because of lacking data for HR and 95% CI calculation and because of inadequate contact with the investigators [28-30]. Overall, 11 articles were accepted for the meta-analysis [10-16, 31-34].

#### Characteristics of included studies

The main characteristics of the retained studies are listed in **Table 1**. The 11 cohort studies involved 1620 patients, with a sample size ranging from 72 to 295 patients per study (mean 147). These studies principally originated from Eastern Asia and were published between 2006 and 2014. Four articles [13, 15, 16, 31] did not report a follow-up period. The median follow-up period in the remaining seven

studies ranged from 26 months to 64.8 months. Among the 11 studies, three (with a total of 296 patients) investigated Rsf-1 expression in ovarian cancer [10, 11, 33], four (with 664 patients) in gastrointestinal tract tumors [13, 14, 16, 31], two (with 464 patients) in genitourinary system tumors [15, 34], and two (with 196 patients) in other types of human cancers [gallbladder carcinoma, nasopharyngeal

carcinoma (NPC)] [12, 32]. Ten studies were published in English, and only one study was published in Chinese [33]. Eight articles (1324 patients) reported multivariate-adjusted HRs, from which the HR estimations can be directly extracted. Three (296 patients) studies provided Kaplan-Meier curves [10, 11, 33]. Therefore, the HR calculations were extrapolated from the survival curves. Eight of the 11 eligible studies clearly stated that the blinding method was used in Rsf-1 determination. Information on the specified cutoff for Rsf-1 nuclear expression can be obtained from all included studies. Of the 11 studies, eight identified Rsf-1 as a significant indicator of poor prognosis, two showed negative results [11, 13], and the remaining one did not clearly state the exact value of Rsf-1 on prognosis [31]. According to the quality criteria, all cohort studies were of high quality (had scores of six or more). Clinical outcomes were assessed in each study. Five studies (including 690 patients) considered OS as the primary endpoint [10, 11, 13, 16, 33]. Another five studies (with 761 patients) reported data on DSS [12, 14, 15, 28, 32]. RFS was reported in three studies [31, 32, 34], and MFS was used as the terminal point in the three other articles [15, 31, 32].

#### Rsf-1 expression and clinicopathological parameters

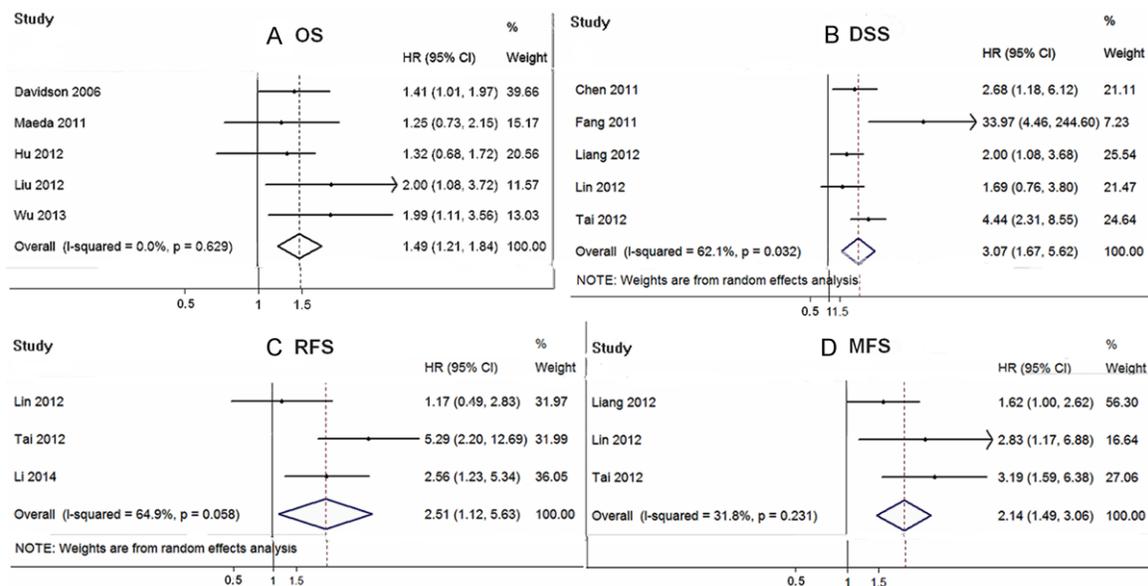
No association existed between Rsf-1 and certain clinicopathological parameters, such as age (pooled OR = 0.95; 95% CI = 0.75-1.19; *P* = 0.632; fixed effect), sex (pooled OR = 0.92; 95% CI = 0.71-1.19; *P* = 0.511; fixed effect),

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**Table 3.** Meta-analysis of Rsf-1 overexpression and survivals in cancers

Categories	Studies (no. of patients)	HR (95% CI)	I <sup>2</sup> (%)	P <sub>h</sub>	Z	P
overall survival (OS)	5 (690)	1.49 (1.01-1.97)	0.0	0.629	3.70	< 0.001
disease-specific survival (DSS)	5 (761)	3.07 (1.67-5.62) <sup>R</sup>	62.1	0.032	3.63	< 0.001
recurrent-free survival (RFS)	3 (449)	2.52 (1.57-4.04) <sup>R</sup>	64.9	0.058	2.24	0.025
metastasis-free survival (MFS)	3 (575)	2.14 (1.49-3.07)	31.8	0.231	4.11	< 0.001

All pooled HRs were derived from fixed-effects model except for cells marked with (random<sup>R</sup>). P<sub>h</sub> denotes P-value for heterogeneity based on Q test; P denotes P-value for statistical significance based on Z test.



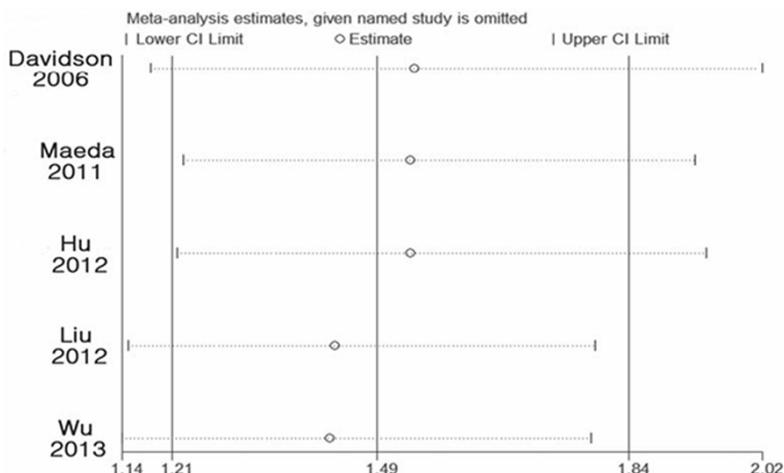
**Figure 2.** Forest plot of the overall association between Rsf-1 expression and survival in patients with human solid tumors. A. Forrest plot to assess the prognostic effect of Rsf-1 on OS in solid tumors. B. Forrest plot to assess the prognostic effect of Rsf-1 on DSS in solid tumors. C. Forrest plot to assess the prognostic effect of Rsf-1 on RFS in solid tumors. D. Forrest plot to assess the prognostic effect of Rsf-1 on MFS in solid tumors.

vascular invasion (pooled OR = 1.50; 95% CI = 0.95-2.39;  $P = 0.086$ ; fixed effect), and peri-neural invasion (pooled OR = 1.87; 95% CI = 0.91-3.83;  $P = 0.088$ ; fixed effect). However, Rsf-1 was significantly related to tumor stage (pooled OR = 4.13; 95% CI = 2.84-6.00;  $P < 0.001$ ; random effect), primary tumor (pooled OR = 2.09; 95% CI = 1.58-2.75;  $P < 0.001$ ; fixed effect), nodal status (pooled OR = 1.95; 95% CI = 1.40-2.72;  $P < 0.001$ ; fixed effect), and histological grade (pooled OR = 3.09; 95% CI = 2.10-4.54;  $P < 0.001$ ; fixed effect). These findings suggest that Rsf-1 overexpression is obviously associated with tumor stage, primary tumor, nodal status, and histological grade. Additional results for the associations between Rsf-1 and clinicopathological characteristics are listed in **Table 2**.

### Rsf-1 expression and survival

We conducted a meta-analysis on the association between Rsf-1 overexpression and OS, DSS, RFS, or MFS in patients with human solid tumors. The pooled HRs and their 95% CI are listed in **Table 3**. In the five studies that used OS as the primary endpoint, poor prognosis was demonstrated in the pooled HR estimate (HR = 1.49; 95% CI = 1.01-1.97;  $P < 0.001$ ). In the other five articles, a significant association was observed between Rsf-1 and DSS (HR = 3.07; 95% CI = 1.67-5.62;  $P < 0.001$ ). The negative prognostic role of high Rsf-1 expression was also observed in RFS (including three studies, HR = 2.52; 95% CI = 1.57-4.04;  $P < 0.001$ ) and MFS (contained three articles, HR = 2.14; 95% CI = 1.49-3.07;  $P < 0.001$ ). A forest plot for

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**Figure 3.** Effect of individual studies on pooled hazard ratios (HR) for Rsf-1 expression and overall survival (OS) in patients with human solid tumors.

the overall association between Rsf-1 overexpression and survival is shown in **Figure 2**.

### Evaluation of heterogeneity

Heterogeneity testing was performed among the selected studies to evaluate the influence of individual studies on the survival rates according to the  $P$  value for heterogeneity. **Table 3** shows that a moderate degree of heterogeneity was found in five studies that used DSS as the endpoint ( $I^2 = 62.1\%$ ,  $P_h = 0.032$ ) and three studies that reported data on RFS ( $I^2 = 64.9\%$ ,  $P_h = 0.058$ ). A random-effect model was used to estimate the overall HR. Heterogeneity was not found in the other subgroups that evaluated OS and MFS (OS:  $I^2 = 0.0\%$ ,  $P_h = 0.629$ ; MFS:  $I^2 = 31.8\%$ ,  $P_h = 0.231$ ). Thus, a fixed-effect model was applied to calculate the pooled HR.

### Sensitivity analysis and cumulative meta-analysis

A sensitivity analysis was conducted by omitting one study each time and analyzing the effects on the remaining studies to validate the stability of the HR estimates. Results indicated that no point estimate of the omitted individual study was beyond the 95% CI of the combined analysis based on the overall HR estimated by OS (**Figure 3**). Similarly, no significant effects were observed when DSS, RFS, and MFS were considered. These results suggested that no individual study affected the meta-analysis results and that the outcomes were robust and credible.

We conducted a cumulative meta-analysis of the eligible studies to evaluate the cumulative HR estimate over time. In the OS subgroup, Davidson et al. [10] reported an effect estimate of 1.41 (95% CI = 1.01-1.97) in 2006. Four other studies with a cumulative HR of 1.49 (95% CI = 1.21-1.84) were published between 2011 and 2013 (**Figure 4A**). In the DSS subgroup, five publications reported a cumulative HR of 3.07 (95% CI = 1.67-5.62) from 2011 to 2012 (**Figure 4B**). In the subgroup that evaluated RFS in 2012 to 2014, three studies with a cumulative HR of 2.51 (95% CI = 1.12-5.63) were delivered (**Figure 4C**). In 2012, three articles estimated MFS with a cumulative HR of 2.14 (95% CI = 1.49-3.06) (**Figure 4D**).

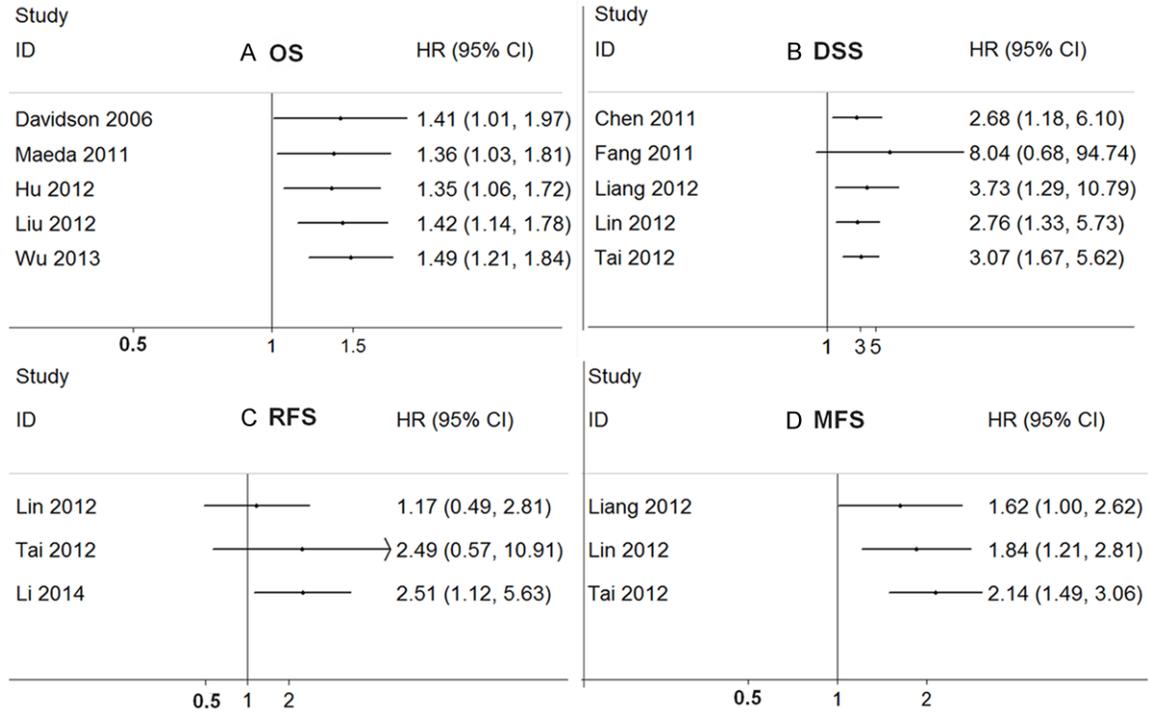
### Publication bias

Both Begg's and Egger's tests provided no evidence of publication bias in the overall HR estimate after validating that the  $P$  values were all more than 0.1. The funnel plot shapes did not show obvious evidence of asymmetry for OS (**Figure 5**), DSS, RFS, or MFS. This result indicated that our findings in the subgroup analysis were statistically steady. The funnel plots for publication bias in studies that estimated HR via survival stratification are shown in **Table 4**.

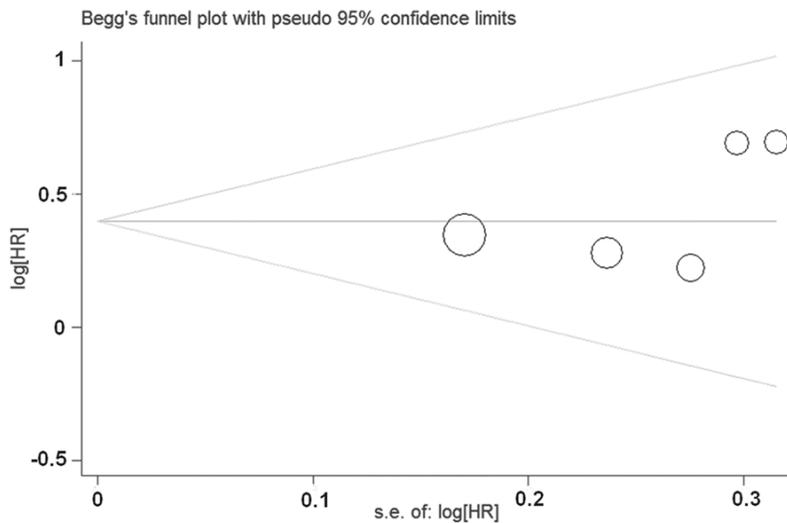
### Discussion

Chromatin remodeling is a common mechanism underlying oncogenic activation in human cancers [26]. The chromatin 11q13.5 amplicon, which is present in a fraction of ovarian, breast, and head and neck carcinomas, contains many potential candidate drivers. These drivers include those (CCND1, FGF4/3, EMS1, GARP, PAK1, and EMSY) that are centromeric to Rsf-1 and those (CLNS1A, ALG8, and GAB2) that are near Rsf-1 [35]. Identifying the "drivers" of genomic aberrations is important to improve our understanding of solid tumors and to develop new diagnostic markers and therapeutic targets. Rsf-1 is a potential prognostic factor in different types of human solid can-

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**Figure 4.** Cumulative meta-analysis of Rsf-1 expression and survival in patients with human solid tumors. A. Cumulative HR estimate for OS in solid tumors. B. Cumulative HR estimate for DSS in solid tumors. C. Cumulative HR estimate for RFS in solid tumors. D. Cumulative HR estimate for MFS in solid tumors.



**Figure 5.** Funnel plot of Rsf-1 expression and overall survival (OS) in patients with solid tumors.

However, individual studies were based on various recruitment procedures of the study populations and on differences in the environmental backgrounds. Considering that meta-analyses are useful to integrate results from independent studies for a specified outcome, we conducted a meta-analysis of published studies.

Recent studies have identified that Rsf-1 overexpression contributes to tumor development. Rsf-1 correlates with the malignant growth and invasive ability of several cancer cell lines [14, 16]. These phenomena can be attributed to two possible mechanisms. First, RSF complexes change the structures of chromatin or the functions of oncogenes and tumor suppressors that interact with the complexes [36]. These changes lead to the alteration of gene expression. Second, Rsf-1 overexpression can alter cellular distribution and hSNF2H partnership. hSNF2H, which is encoded by the SMARCA5 gene at 4q31, interacts with several proteins to form different hSNF2H-containing proteins with diverse cellular functions. In the RSF/hSNF2H complex, Rsf-1 functions as a histone chaperone to accommodate DNA binding activity, whereas hSNF2H possesses nucleosome-dependent ATPase and helicase activi-

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**Table 4.** Results of Egger's test and Begg's test

Comparison	Egger's test			Begg's test	
	t	P	95% CI	Z	P
overall survival (OS)	1.15	0.332	-2.999-6.406	0.24	0.806
disease-specific survival (DSS)	1.52	0.227	-3.419-9.632	0.73	0.462
recurrent-free survival (RFS)	-0.03	0.983	-204.956-204.072	0.00	1.000
metastasis-free survival (MFS)	1.71	0.338	-22.289-29.201	0.00	1.000

ties for DNA unwinding [25]. Thus, excessive Rsf-1 molecules may separate hSNF2H from other hSNF2H-containing complexes, such as hSNF2H/BAZ1A and hSNF2H/BAZ1B, making them decrease in number. Several SNF family members inhibit tumor growth and are down-regulated or inactivated in cancer tissues [37, 38]. Thus, a decrease in the hSNF2H complexes that act as tumor suppressors caused by Rsf-1 overexpression may contribute to the observed growth-stimulating effects in cancer cells [25]. In addition, the Rsf-1 protein contains the plant homology domain zinc finger to mediate protein-protein interaction and transcriptional regulation in response to different growth signals and environmental cues [25, 26]. However, the mechanism by which Rsf-1 affects tumor progression remains unclear. Further investigations must be conducted to demonstrate the detailed molecular mechanisms by which Rsf-1 regulates solid cancer malignancy.

To the best of our knowledge, this meta-analysis is the first to analyze the high expression of Rsf-1 as an independent prognostic factor for short survival in patients with solid tumors. We divided the 11 cohort studies into four subgroups. Each subgroup represented one subtype of the survival endpoints. In the OS subgroup, high Rsf-1 expression was related to unfavorable OS. This condition was obvious for all tumors combined and for all subtypes of cancers, except for ovarian clear cell carcinoma (OCCC) and gastric adenocarcinoma. These contradictions may be attributed to several reasons. First, the number of Rsf-1 negative cases in the study of OCCC was relatively small (16 patients), and the cutoff score was set to 1, which was significantly smaller compared with others (i.e., 3 or 4). Second, a study on gastric adenocarcinoma calculated the HR and 95% CI by multivariate analysis, which was adjusted by ki67 index and other factors. Rsf-1 overexpression also correlated with poor DSS and RFS. Ho-

wever, the HR and 95% CI of rectal cancer were not statistically significant in these two subgroups. With the recent advances in treatment, the recurrence rate of rectal cancer decreased. However, the incidence of distant metastasis

was still high. Hence, Rsf-1 level was not associated with RFS, which may attenuate its influence on DSS. By contrast, Rsf-1 level significantly correlated with MFS. Although the result of UCUB in the MFS subgroup was critical with a 95% CI of 1.00 to 2.62, many meta-analyses would consider this result statistically significant [39, 40]. Therefore, the pooled HR estimates indicated that high Rsf-1 expression corresponded to poor MFS. The major results of the current meta-analysis show that high Rsf-1 expression leads to poor prognosis and is related to short survival. Therefore, Rsf-1 may be an independent, adverse prognostic factor for patient survival in solid tumors.

Rsf-1 overexpression is also significantly correlated with tumor stage, primary tumor, nodal status, and histological grade. This finding indicates that Rsf-1 possibly promotes tumor progression and aggressiveness. Liang et al. [15] found that Rsf-1 expression is abundant in UCUB cells but not in normal urothelial cells, and Lin et al. [31] discovered that Rsf-1 can promote resistance to radiotherapy or chemotherapy in rectal cancers. Rsf-1 can significantly promote resistance to radiotherapy in NPC [32] and reduce the sensitivity of ovarian cancer cells to paclitaxel [26]. These results indicate that Rsf-1 influences the prognosis of patients with solid tumors by promoting cancer progression and increasing cancer resistance to oncotherapy. Therefore, detecting Rsf-1 in tumor biopsy tissues before treatment may be useful to predict distant metastasis. However, further validation is necessary [31]. Meanwhile, Begg's test, Egger's test, and funnel plots showed no evidence of publication bias in the subgroup analysis. The sensitivity analysis also clarified the robustness of the meta-analysis findings.

Despite the robustness of our results, the findings should be interpreted with caution. In this review, the heterogeneity of all survival subgroups, except for the OS group, was moderate.

Each subgroup with an endpoint contains insufficient studies to conduct subgroup analyses based on variable analysis, cancer type, blinded evaluation, and sample size. Consequently, we were unable to identify the source of heterogeneity. In the future, we will conduct a new meta-analysis that includes more studies and larger scale to reduce heterogeneity.

Our meta-analysis has the following limitations. First, the number of included studies was relatively small, with only approximately 1620 patients. The patients had various features in treatment options, tumor location, preoperative TNM category, and histological types. Nevertheless, we were unable to assess these potential confounders in individual studies. Second, the included studies were mainly published patients in Eastern Asia. Only one study (135 patients) originated in Western Europe. Thus, the studies lacked racial representation. Third, the studies in our meta-analysis used different techniques to detect Rsf-1 expression alterations and to dilute the antibodies. In addition, the studies had different sources of Rsf-1 antibody. Thus, experimental factors might have confounded the results. Fourth, we only included studies from which we could extract HR or estimate HR; thus, some useful data were lost. Fifth, the HRs in some studies in our meta-analysis were calculated from the survival curves. According to Tierney's method, some minor differences existed between the exact and extrapolated HR [41]. Finally, the cutoff definition of Rsf-1 overexpression and the experimental processes were different. Such differences may partly affect the significance of the clinicopathological outcome in survival analysis and partially account for the inter-study heterogeneity.

In conclusion, Rsf-1 overexpression, as measured by IHC, is associated with poor prognosis in different tumor types. Moreover, Rsf-1 may be a predicative factor of poor prognosis and aggressive tumor behavior in solid tumors. Therefore, further data are required, and developing strategies against this receptor could be a reasonable therapeutic approach.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Taiping He, School of Public Health, Guangdong Medical College, Dongguan, Guangdong Province, China. Tel: 86-759-2388590; Fax: 86-759-2284104; E-mail: taiping-he@163.com

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