Phosphatase of regenerating liver 3 as a prognostic marker for colorectal cancer: A meta-analysis of cohort studies

Na Yao[1 #] · Yan Chen[2 #] · Yan-Mei QIN[1] · Xiao-Yi Chen[1] · Li-Ren Hu[3] · Ming Shi[4] · Tai-Ping He[5 *]

[1]School of graduate, Guangdong Medical College, Zhanjiang, Guangdong 524023, China
[2]Center of Oncology, The Second Affiliated Hospital of Guangdong Medical College, Zhanjiang, Guangdong Province, China
[3]Department of Epidemiology and Health Statistics, School of Public Health, Guangdong Medical College, Zhanjiang, Guangdong 524023, China
[4]Department of Occupational and Environmental Health, School of Public Health, Guangdong Medical College, Dongguan, Guangdong 523808, China
[5]School of Public Health, Guangdong Medical College, Dongguan, Guangdong 523808, China
#Na Yao and Yan Chen contributed equally to this work
***Corresponding** author: E-mail: taipinghe@163.com

Abstract

The prognostic role of phosphatase of regenerating liver 3 (PRL-3) in colorectal cancer (CRC) remains inconclusive. We aimed to evaluate the association between the expression of PRL-3 and clinic outcomes in CRC patients by conducting a meta-analysis of cohort studies. Relevant studies were identified by electronic databases search through Feb 2014. We included cohort studies that reported hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of PRL-3 expression with overall survival (OS) or disease-free survival (DFS). A fixed- or random-effects model was used to calculate the pooled HR estimates. We identified 10 prospective cohort studies of PRL-3 expression and prognosis involving 1,462 CRC patients. Overall, the combined HR for OS and DFS in a random-effects model was 2.54 (95% CI, 1.70-3.80) and 2.47 (95% CI, 1.45-4.19), respectively. The association between PRL-3 expression and prognosis did not substantially modified by subgroup analysis. Omission of any single study had no significant effect on the combined HR estimate. No evidence of publication bias was observed. The present meta-analysis provides further evidence of a significant inverse association between PRL-3 overexpression and prognosis in CRC patients.

***Keywords*:** PRL-3 · colorectal cancer · prognosis · meta-analysis

{Citation: Na Yao, Yan Chen, Yan-Mei Qin, Xiao-Yi Chen, Li-Ren Hu, Ming Shi, Tai-Ping He. Phosphatase of regenerating liver 3 as a prognostic marker for colorectal cancer: A meta-analysis of cohort studies. American Journal of Research Communication, 2014, 2(7): 37-52} www.usa-journals.com, ISSN: 2325-4076.

Introduction

Colorectal cancer (CRC) is the third most common cancer in terms of incidence and mortality for the United States, with estimated 102,900 new cases in 2010 [1, 2] . The increase of CRC prevalence is also reported in Eastern Asia [3]. Although considerable advances have been made in understanding the pathogenesis, early diagnosis, and treatment of CRC, the survival rates have not been substantially improved over the past few years. Some independent prognostic factors for survival such as stage of disease at diagnosis, age, physical inactivity, and obesity have already been identified [4, 5]. Moreover, several biological factors involved in molecular carcinogenesis should be considered as potential prognostic and predictive molecular markers in individuals with CRC.

Protein tyrosine phosphatases (PTPs) are key regulatory enzymes in signal transduction pathways and are implicated in the tumorigenesis and metastasis of human cancers [6]. Phosphatase of regenerating liver (PRL) family, comprising three members, PRL-1, PRL-2, and PRL-3, belongs to the PTP superfamily [7]. PRL-3 (also known as PTP4A3) is an important metastasis gene firstly identified in CRC in 2001 [8]. PRL-3 gene has been observed to be consistently overexpressed in metastatic lesions derived from primary CRC versus the corresponding normal colorectal epithelium, adenomas, and primary tumors. Since then, numerous studies have suggested that PRL-3 expression is associated with various carcinogenic and metastatic processes by promoting cancer cell migration and invasion [9-11]. Therefore, PRL-3 is a promising prognostic marker and its enhanced expression

in cancer cells can be a significant biomarker for predicting poor survival in CRC [12, 13].

Several observational studies have evaluated whether PRL-3 expression can be a prognostic factor for survival in CRC patients. However, the results of these studies are conflicting or inconclusive because of limited sample size and genuine heterogeneity. We therefore designed this study to review all available reports that investigated the relationship between PRL-3 overexpression and clinical outcomes in CRC patients. A meta-analysis was conducted to derive a more precise estimate of the prognostic significance of PRL-3 expression.

Methods

Search strategy

The electronic databases PubMed, Embase, ISI Web of Science and China National Knowledge Infrastructure were searched for studies to be included in the present meta-analysis. An upper date limit of Feb 2, 2014 was applied; we used no lower date limit. Searches included the terms “PRL-3,” “PRL3,” “PTP4A3,” “phosphatase of regenerating liver 3,” or “protein tyrosine phosphatase type IVA member 3” and “colorectal tumor,”“colorectal tumour,” “colorectal cancer,” “colorectal carcinoma,” “colorectal neoplasms,” “rectal cancer,” “rectum cancer,” “colonic neoplasms,” “colon cancer,” “colonic cancer,” or “CRC.” and “survival,” “prognostic”, or “prognosis.” No language restrictions were imposed. We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search.

Study eligibility

The studies included in this meta-analysis are prospective cohort studies that evaluated the association between PRL-3 expression and overall survival (OS; i.e., date of surgery to date of death as a result of any cause) and disease-free survival (DFS; i.e., date of surgery to date of second cancer, local or regional recurrence, or distant metastases). Studies considered ineligible for the

meta-analysis were as follows: reviews, conference abstracts, editorials, or letters; studies in which OS or DFS was not used as clinical endpoints index; and articles with insufficient published data for determining an estimate of hazard ratio (HR) and 95% confidence interval (CI). In the case of multiple publications from the same institution with identical or overlapping patient cohorts, only the largest study was included to avoid duplication of information.

Data extraction

Two authors (N. Yao and Y. Chen) independently extracted data from eligible studies and disagreements were resolved through consensus in all items. Standardized abstraction sheets were used to record data from individual studies. Data retrieved from the studies included: first author, year of publication, country of origin, number of patients analyzed, follow-up months, analysis method, blinding of PRL-3 measurements, cutoff scores, number of high/low PRL-3 expression to the study outcomes, and HR estimation. For each study, HR was estimated using methods reported by Parmar et al [14]. The most accurate approach is to obtain the HR estimate and 95% CI from the paper directly, or by calculation using the parameters such as statistics of observed minus expected events and variance provided in the papers. Otherwise, the number of patients at risk in each group, the number of events and *P*-value of the log-rank statistic were retrieved to permit an approximate calculation of the HR estimate and its variance. If the study did not show the HR while the survival curve was reported, survival rates at certain specified times were extracted from them for the reconstruction of the HR estimate and its variance, with the assumption that the rate of patients censored was constant during the follow-up [15].

Quality assessment

Quality assessment of the cohort studies in this meta-analysis was performed using the Newcastle Ottawa scale (NOS) recommended by the Cochrane Non-randomized Studies Methods Working Group [16, 17]. Based on the NOS, studies were judged based on three broad perspectives: selection (four items, one star each), comparability (one item, up to two stars), and outcome (three items, one star each). A ‘‘star’’ represents a ‘‘high-quality” choice of an individual study. Given the variability in

quality of cohort studies found in our initial literature search, we considered studies as of high quality if they achieved a score of five or more.

Statistical analysis

STATA version 11.0 (STATA Corporation, College Station, TX, USA) was used for all statistical analyses. The combined HR with 95% CI was used to calculate and assess the strength of the association of PRL-3 expression with OS or DFS, and HR > 1 indicated poor prognosis in patients with PRL-3 expression if the 95% CI did not overlap 1. The significance of the pooled HR was determined using a *Z*-test, and $P < 0.05$ was considered statistically significant.

Heterogeneity assumption was examined by the chi-squared test based on the *Q* statistic [18] and was considered statistically significant when $P < 0.10$. Heterogeneity 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). The pooled HR estimation of each study was calculated using a random-effects model (DerSimonian and Laird method) when $P < 0.10$; otherwise, a fixed-effects model was used (Mantel–Haenszel method) [19].

To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of each individual study using the “metaninf” STATA command. Potential publication bias was evaluated through Begg’s and Egger’s Asymmetry tests [20], as well as through visual inspection of funnel plots, in which the standard error was plotted against log (HR) to form a simple scatterplot. Statistical significance for the interpretation of the Egger’s test was defined as $P < 0.10$.

Results

Study characteristics

The literature search identified a total of 73 potentially relevant articles. Among them, 60 were

excluded after reading the title and abstract because of obvious lack of relevance. These other articles were also excluded: one review-type article [13], one duplicated publication [21], and one study in which other survival endpoint was used instead of OS or DFS [22]. Finally, 10 prospective cohort studies were eligible for the meta-analysis [23-32]. A flow chart summarizing the process of study inclusion or exclusion is shown in Figure 1. The main characteristics of the selected studies are reported in Table 1.

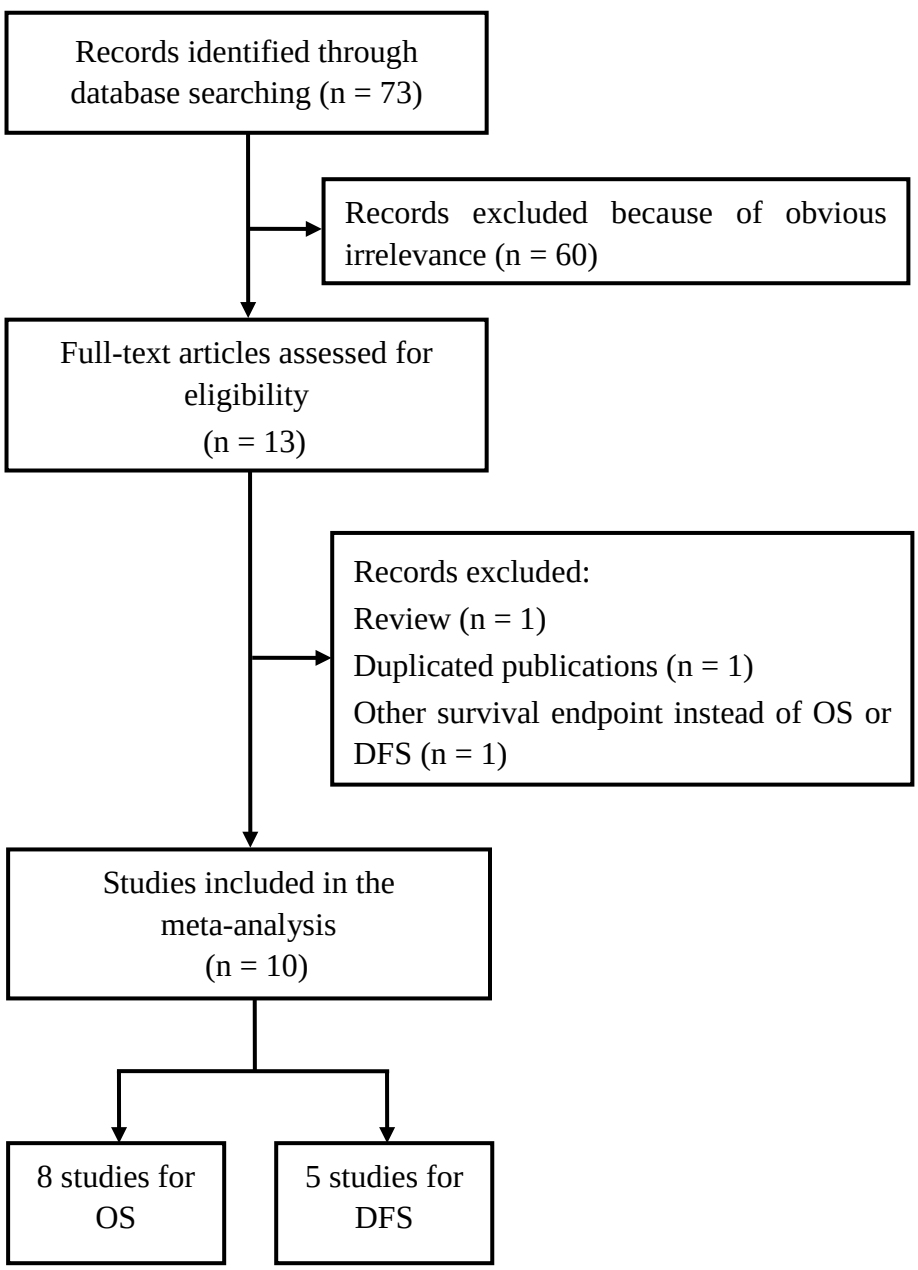

Fig. 1 Flow diagram for study selection and specific reasons for exclusion in the meta- analysis.

The 10 prospective cohort studies with a total of 1462 CRC patients ranging from 46 to 273 patients per study were conducted in three countries (China, Japan, and Spain) and published between 2004 and 2012. The follow-up period ranged from 34.0 to 107.3 m. Among the 10 studies, nine studies (1382 patients, 94.5 %) were performed in Asian populations, and the remaining one study (80 patients) followed up non-Asian patients. Six studies were published in English and four studies were published in Chinese. Eight studies (with a total of 1070 CRC patients) reported the effect of PRL-3 expression on OS, among which two reported multivariate adjusted HRs and six provided Kaplan–Meier curves. Five studies (with a total of 871 CRC patients) reported the effect of PRL-3 expression on DFS, among which only one reported multivariate adjusted HR and four provided Kaplan–Meier curves. For each single endpoint, 5 of 8 studies used OS to identify PRL-3 overexpression as an indicator of poor prognosis, whereas 3 of 5 studies used DFS. All other studies showed no statistically significant effect of PRL-3 overexpression on the survival period. According to the quality criteria, all prospective cohort studies were high quality with five scores or higher.

Table 1 Main characteristics of 10 eligible studies in this meta–analysis

Study (authors–year)	Patients source	Analysis method	Blinding evaluation	PRL–3 expression (High/Low)	Cutoff scores	Outcomes	Analysis of variance	HR (95% CI)	Language
Kato H (2004)	Japan	ISH	NR	79/98	> 10%	DFS	Univariate	5.53 (0.86–35.4) [b]	English
Peng LR (2004)	China	IHC	NR	21/67	NR	OS	Univariate	3.45 (1.60–7.48) [b]	English
Lian P (2006)	China	IHC	NR	97/99	Score≥ 6	OS	Univariate	8.06 (3.11–20.90) [b]	Chinese
Mollevi DG (2008)	Spain	IHC	blinded	38/42	NR	OS	Multivariate	3.32 (1.41–7.85) [a]	English
						DFS	Univariate	5.93 (2.54–13.81) [a]	
Zhao GP (2008)	China	IHC	NR	32/14	> 5%	OS	Univariate	1.14 (0.17–7.754) [b]	Chinese
Xing XF (2009)	China	IHC	blinded	64/209	> 10%	OS	Univariate	1.46 (0.97–2.19) [b]	English
						DFS	Univariate	2.30 (1.41–3.76) [b]	
Wu YY (2009)	China	IHC	NR	33/36	Score> 4	OS	Univariate	1.66 (0.28–9.82) [b]	Chinese
Liu CY (2010)	China	IHC	blinded	38./78	Score≥ 2	OS	Univariate	2.28 (1.21–4.31) [b]	Chinese
						DFS	Univariate	2.27 (1.12–4.61) [b]	
Liu CY (2012)	China	IHC	blinded	56/169	Score≥ 3	DFS	Multivariate	1.30 (0.80–1.90) [a]	English
Tamagawa H (2012)	Japan	QRT-PCR	NR	101/101	NR	OS	Multivariate	2.36 (1.21–4.60) [a]	English

OS overall survival, *DFS* disease–free survival, *NR* data were not reported, *NS* not significant, *CRC* colorectal cancer, *ISH* in situ hybridization, *IHC* immunohistochemistry, *QRT‐PCR* quantitative real–time polymerase chain reaction, *Sur. Curves* survival curves, *Score* 2, 3, 4, 5, 6 different scores with combination of percentage of positives cells and intensity, [a] Directly extracted from original data, [b] Calculated from Kaplan–Meier curve.

Main results of meta-analysis

We conducted meta-analysis on the association of PRL-3 overexpression in CRC patients with OS or DFS. The pooled HRs, along with their 95% CIs, are presented in detail in Table 2. Among the eight studies on OS, a poor prognosis was demonstrated in the pooled HR estimate (HR = 2.54; 95% CI, 1.70–3.80). When the results of HR obtained from the Kaplan–Meier curves by univariate analysis were pooled, combined HR was 2.51 (95 % CI, 1.44–4.39). Furthermore, when we pooled the studies of HR derived from multivariate analysis, a significant association was observed with HR of 2.68 (95 % CI, 1.59–4.54). We also observed statistically significant effect of PRL-3 expression on OS from the studies published in English and Chinese with the HR of 2.01 (95% CI, 1.50–2.71) and 2.90 (95 % CI, 1.25–6.72), respectively. After exclusion of the study [26] from Spain, the pooled HR in Asian populations was 2.46 (95% CI, 1.57–3.85); and omission of the study [32] with quantitative real-time PCR not immunohistochemistry analysis yielded a pooled result of 2.61 (95% CI, 1.61–4.24). When the blinding evaluation in three studies [26, 28, 30] was considered, the results did not change (HR = 1.83; 95% CI, 1.33–2.51). The forest plot for the overall association between PRL-3 overexpression in CRC patients and OS is shown in Figure 2. Similar results were found among the five studies on DFS, as presented in detail in Table 2. The pooled HR estimate for DFS in CRC patients with PRL-3 expression was 2.47 (95% CI, 1.45–4.19), and poor prognosis was also observed in subgroup analyses, such as Kaplan–Meier curves (HR = 2.80; 95% CI, 1.96–4.00), published in English (HR = 2.62; 95% CI, 1.31–5.22), IHC analysis, and blinding evaluation (HR = 2.33; 95% CI, 1.34–4.06). The forest plot for the overall association between PRL-3 overexpression in CRC patients and DFS is shown in Figure 3.

Table 2 Results of meta-analysis of PRL-3 overexpression and prognosis in colorectal cancer patients

Categories	Studies (no. of patients)	HR (95% CI)	I^2 (%)	P_h	Z	P_Z
Overall survival						
Total	8(1070)	2.54(1.70–3.80)	49.4	0.054	4.55	<0.001
Multivariate analyses	2(282)	2.68(1.59–4.54) [F]	0.00	0.539	3.67	<0.001
Univariate analyses	6(788)	2.51(1.44–4.39)	61.1	0.025	3.24	0.001
Asian populations	7(990)	2.46(1.57–3.85)	53.6	0.044	3.94	<0.001
Published in English	4(643)	2.01(1.50–2.71) [F]	48.2	0.122	4.62	<0.001
Published in Chinese	4(427)	2.90(1.25–6.72)	52.2	0.099	2.49	0.013
IHC analysis	7(868)	2.61(1.61–4.24)	56.5	0.032	3.88	<0.001
Stated blinding	3(469)	1.83(1.33–2.51) [F]	42.6	0.175	3.71	<0.001
Disease-free survival						
Total	5(871)	2.47(1.45–4.19)	65.8	0.020	3.33	0.001
Univariate analyses	4(669)	2.80(1.96–4.00) [F]	33.1	0.214	5.66	<0.001
Published in English	4(755)	2.62(1.31–5.22)	74.1	0.009	2.73	0.006
IHC analysis	4(694)	2.33(1.34–4.06)	71.6	0.014	2.99	0.003
Stated blinding	4(694)	2.33(1.34–4.06)	71.6	0.014	2.99	0.003

All pooled *HRs* were derived from random-effects model except for cells marked with (fixed [F])
P_h denotes *P*- value for heterogeneity based on ***Q*** test
P_Z denotes *P*- value for statistical significance based on ***Z*** test

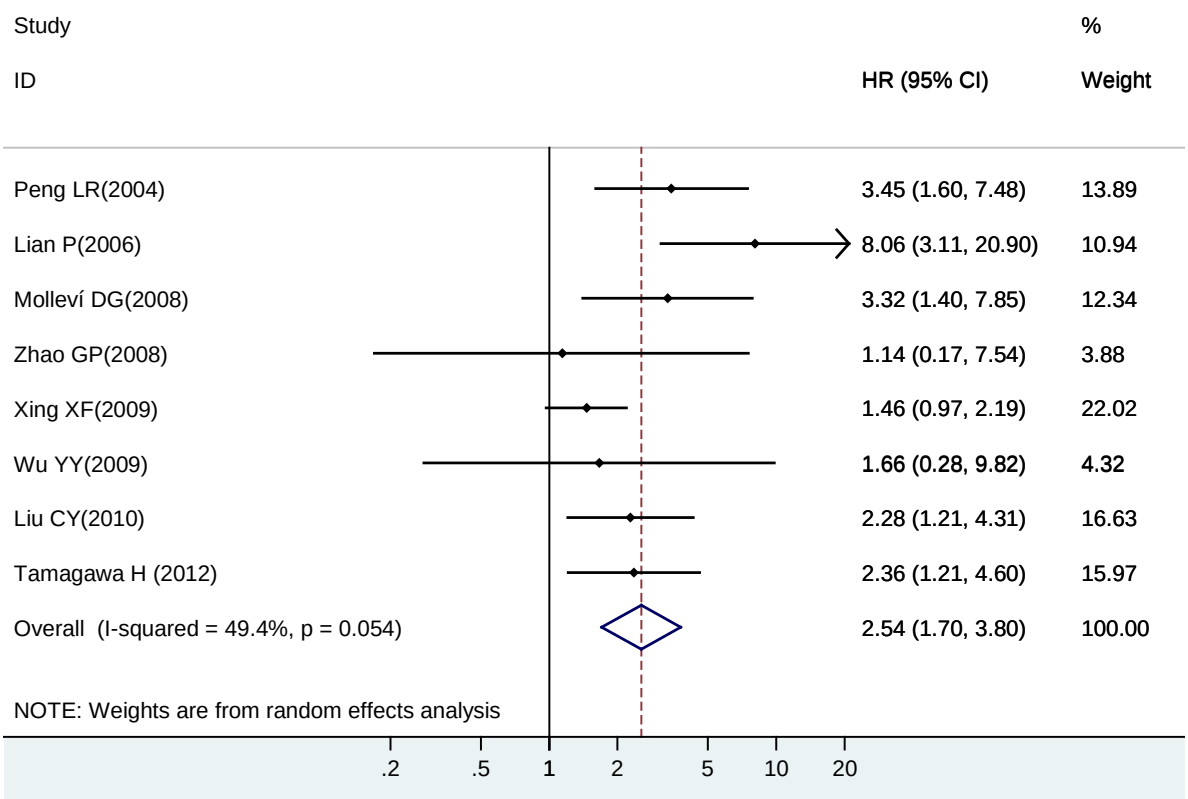

Fig. 2 The forest plot for the overall association between PRL-3 overexpression and OS of CRC patients.

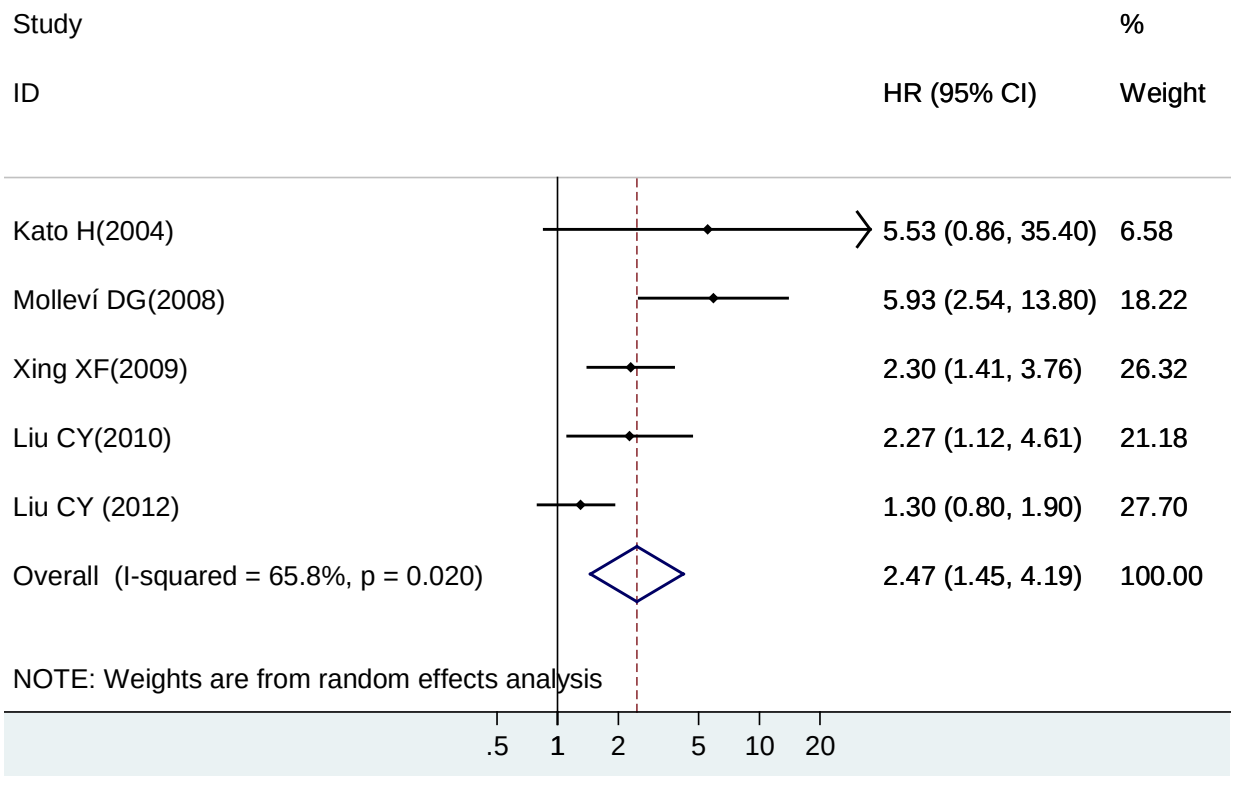

Fig. 3 The forest plot for the overall association between PRL-3 overexpression and DFS of CRC patients.

Sensitivity analysis and publication bias

In the sensitivity analysis, the influence of each study on the pooled HR was examined by omission while repeating the meta-analysis. Figure 4 demonstrates that no point estimate of the omitted individual study lied outside the 95% CI of the combined analysis on the summary OS. Similarly, no significant influence was observed when the overall DFS was analyzed. These analyses suggested that no individual study dominated the meta-analysis results, which validated the credibility of outcomes.

Publication bias was analyzed in the included literature involving the overall HR estimation of OS or DFS. Neither Begg's nor Egger's tests provided any obvious evidences of publication bias ($P > 0.10$; Table 3). In addition, the shapes of the funnel plots showed that the included studies did not have apparent asymmetry, indicating that our results were statistically robust.

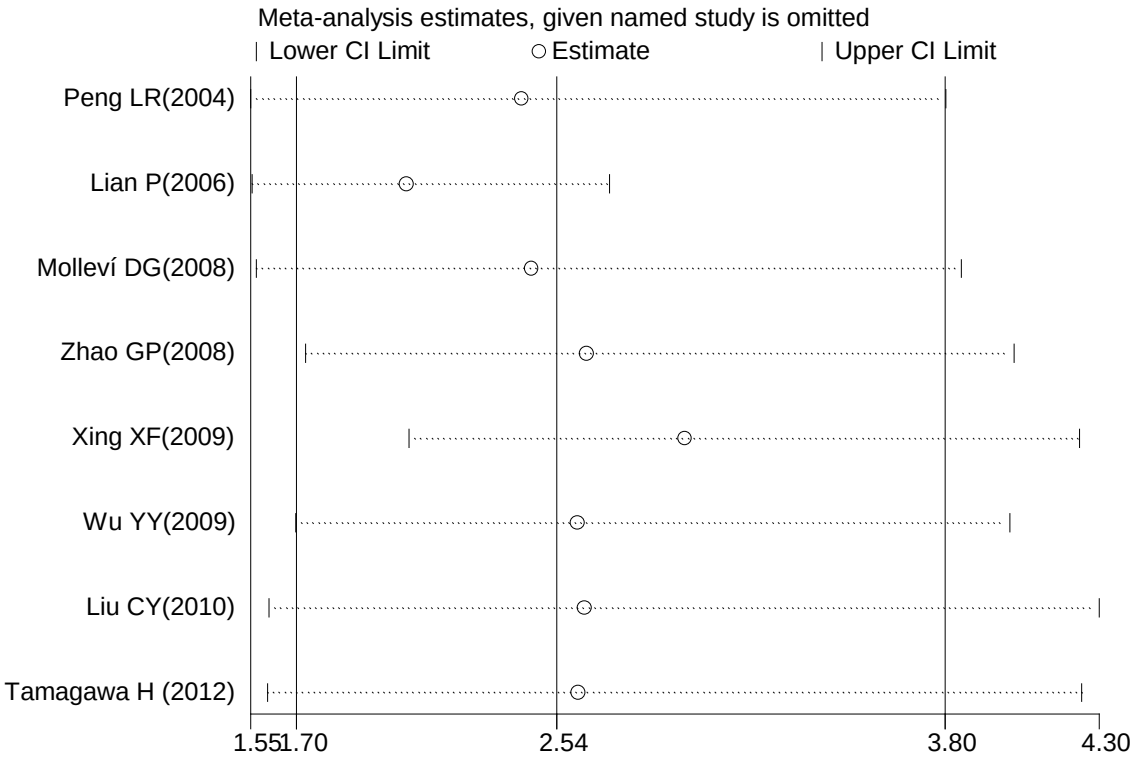

Fig. 4 Effect of individual studies on the pooled HR for PRL-3 overexpression and OS of CRC patients.

Table 3 Results of Egger's test and Begg's test for overexpression of PRL-3 and prognosis in colorectal cancer patients

Categories	Egger's test			Begg's test	
	t	*P*	95% CI	*Z*	*P*
Overall survival	1.10	0.312	–1.584 to 4.188	0.37	0.711
Disease-free survival	1.85	0.161	–2.073 to 7.836	1.22	0.221

Discussion

The relationship between CRC prognosis and predictive molecular markers is attracting considerable attention. Since PRL-3 protein was firstly determined to play a key role in tumor metastatic process, the biological functions of this protein have been extensively studied by in vitro experiments and in

vivo analyses. For example, stably expressing PRL-3 facilitated the lung and liver metastasis of B16F10 cells in an animal model [33]. Similarly, migration and invasion have been shown to be enhanced by PRL-3 expression in Chinese hamster ovary cells, and overexpression of the protein induces metastatic tumor formation in mice [34]. Furthermore, PRL-3 expression is reported to be a potential prognostic factor in different types of cancer, including gastric [35], nasopharyngeal [36], hepatocellular [37], ovarian [38], and breast [39] cancers.

Meanwhile, several studies have investigated the effect of PRL-3 overexpression on the clinical outcomes of CRC. Mollevi et al. [26] reported that individuals with highly expressed PRL-3 have a significantly shorter survival than individuals with no or low expression genotype. However, some researchers such as Xing et al. [28] and Liu et al. [31] failed to demonstrate any relationship between PRL-3 overexpression and survival in CRC patients. These controversies in the predictive significance of the PRL-3 expression in CRC warrant a quantitative meta-analysis of the studies' outcomes.

To our knowledge, the present meta-analysis is the first study to systematically elucidate the association between PRL-3 expression and CRC survival. Our results showed that PRL-3 overexpression was significantly associated with OS and DFS, indicating that PRL-3 may be a marker for poor prognosis of CRC. Furthermore, all subgroup analyses and sensitivity analyses identified the prognostic role of PRL-3 overexpression in CRC patients. Notably, when the analysis was restricted to multivariate analyses adjusting for clinicopathological factors such as age, sex, tumor size and tumor differentiation, heterogeneity was not detected and a statistically significant unfavorable effect of PRL-3 overexpression on OS was observed, indicating PRL-3 expression to be an independent factor for OS. In addition, using Begg’s, Egger’s test, and funnel plot, we found no publication bias in our analysis. Regarding quality assessment, all included prospective cohort studies in the meta-analysis were high quality with five scores or higher. These results are thus encouraging and may provide further basis for the development of a new marker for CRC prognosis and of PRL-3 inhibitors for CRC therapy.

Our study had several important strengths. Because individual studies had insufficient statistical power, our meta-analysis of 10 studies involving a large number of CRC patients enhanced the power to detect a significant association and provided more reliable estimates. All the original studies used a prospective cohort study design, which greatly reduced the likelihood of recall and selection biases.

Potential limitations of the present meta-analysis should be considered. The first was our inability to explore the potential confounding factors such as disease stage and different treatment regimes, because of insufficient information in these included studies. Second, the studies included in this meta-analysis were from different sources of PRL-3 antibody, indicating a possibility that the antibody factor can confound the results. Third, differences in definition of PRL-3 overexpression and experimental process may partly influence the significance of the clinic outcome in survival analyses. Fourth, patient cohorts in our meta-analysis were mainly from Eastern Asian countries (1 382 patients, 94.5 %); only one study was from Spain. The pooled HRs only represented the Eastern Asian population in our meta-analysis; however, the results of western countries remained unclear. The last limitation is related to the method of HR and 95% CI estimations. In the meta-analysis, the majority of HRs and 95% CI were calculated from Kaplan–Meier curves and not directly extracted from original data in these included studies. Thus, the estimated HR may be less reliable than that directly obtained from published statistics. Meanwhile, we compared our estimated HRs and their statistical significance with the results reported in papers and did not identify any major deviation.

We hereby make the following recommendations to future studies: 1) usage of anti-PRL-3 monoclonal antibody instead of polyclonal antibody for immunostaining, 2) uniform standard for assessment the overexpression of PRL-3, 3) presentation of results as a comparison of survival curves and as a multivariate Cox proportional hazard model, and 4) complete description of survival events to allow calculations. Moreover, future studies should include more homogeneous populations.

In conclusion, this meta-analysis of prospective cohort studies indicated that PRL-3

overexpression may be a poor prognostic factor of survival in CRC patients. Further studies using additional putative prognostic markers in combination with PRL-3 are required to evaluate their potential in predicting patient outcomes.

Acknowledgments

This study was funded by Scientific and Technological Innovation Project of Educational Commission of Guangdong Province (Grant No. 2013KJCX0092). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest: The authors have declared that no competing interests exist.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
2. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg 2009;22:191-7.
3. Yee YK, Tan VP, Chan P, Hung IF, Pang R, Wong BC. Epidemiology of colorectal cancer in Asia. J Gastroenterol Hepatol 2009;24:1810-6.
4. Lieberman DA. Clinical practice. Screening for colorectal cancer. N Engl J Med 2009;361:1179-87.
5. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B et al. Colorectal cancer. Lancet 2010;375:1030-47.
6. Scott LM, Lawrence HR, Sebti SM, Lawrence NJ, Wu J. Targeting protein tyrosine phosphatases for anticancer drug discovery. Curr Pharm Des 2010;16:1843-62.
7. Kozlov G, Cheng J, Ziomek E, Banville D, Gehring K, Ekiel I. Structural insights into molecular function of the metastasis-associated phosphatase PRL-3. J Biol Chem 2004;279:11882-9.
8. Saha S, Bardelli A, Buckhaults P, Velculescu VE, Rago C, St Croix B et al. A phosphatase associated with metastasis of colorectal cancer. Science 2001;294:1343-6.
9. Wang H, Vardy LA, Tan CP, Loo JM, Guo K, Li J et al. PCBP1 suppresses the translation of metastasis-associated PRL-3 phosphatase. Cancer Cell 2010;18:52-62.
10. Bardelli A, Saha S, Sager JA, Romans KE, Xin B, Markowitz SD et al. PRL-3 expression in metastatic cancers. Clin Cancer Res 2003;9:5607-15.
11. Al-Aidaroos AQ, Zeng Q. PRL-3 phosphatase and cancer metastasis. J Cell Biochem 2010;111:1087-98.

12. Bessette DC, Qiu D, Pallen CJ. PRL PTPs: mediators and markers of cancer progression. Cancer Metastasis Rev 2008;27:231-52.
13. Guzinska-Ustymowicz K, Pryczynicz A. PRL-3, an emerging marker of carcinogenesis, is strongly associated with poor prognosis. Anticancer Agents Med Chem 2011;11:99-108.
14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.
15. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
16. Maxwell L, Santesso N, Tugwell PS, Wells GA, Judd M, Buchbinder R. Method guidelines for Cochrane Musculoskeletal Group systematic reviews. J Rheumatol 2006;33:2304-11.
17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, Ottawa Health Research Institute Web site. 2012.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
19. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
20. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
21. Zhao GP, Zhou ZG, Lei WZ, Yu YY, Zheng XL, Gao HK. Expression of phosphatase of regenerating liver-3 mRNA and its clinical implictions in human colorectal carcinoma. Clin J Gastrointest Surg 2005;8:237-40.
22. Hatate K, Yamashita K, Hirai K, Kumamoto H, Sato T, Ozawa H et al. Liver metastasis of colorectal cancer by protein-tyrosine phosphatase type 4A, 3 (PRL-3) is mediated through lymph node metastasis and elevated serum tumor markers such as CEA and CA19-9. Oncol Rep 2008;20:737-43.
23. Kato H, Semba S, Miskad UA, Seo Y, Kasuga M, Yokozaki H. High expression of PRL-3 promotes cancer cell motility and liver metastasis in human colorectal cancer: a predictive molecular marker of metachronous liver and lung metastases. Clin Cancer Res 2004;10:7318-28.
24. Peng L, Ning J, Meng L, Shou C. The association of the expression level of protein tyrosine phosphatase PRL-3 protein with liver metastasis and prognosis of patients with colorectal cancer. J Cancer Res Clin Oncol 2004;130:521-6.
25. Lian P, Cai GX, Xu Y, Cai SJ, Shi YQ. Expression of PRL-3 gene in colorectal cancer and its clinical significance. Chin Oncology 2006;16:823-7.
26. Mollevi DG, Aytes A, Padulles L, Martinez-Iniesta M, Baixeras N, Salazar R et al. PRL-3 is essentially overexpressed in primary colorectal tumours and associates with tumour aggressiveness. Br J Cancer 2008;99:1718-25.
27. Zhao GP, Zhou ZG, Lei WZ, Wang C, Zheng XL, Zheng YC. Expression of phosphatase of regeneration liver-3 in human colorectal carcinoma and its prognosis value. Chin J Gastrointestinal Surgery 2008;11:487-91.
28. Xing X, Peng L, Qu L, Ren T, Dong B, Su X et al. Prognostic value of PRL-3 overexpression in early stages of colonic cancer. Histopathology 2009;54:309-18.
29. Wu YY. The expression of PRL-3 and VEGF in colorectal cancer andthe analysis of hepatic metastases multiple factors [D]. Ningxia Medical University 2009.

30. Liu CY. Expression of PRL-3 protein in patients with Duke's C colorectal cancer and its association with liver metastasis and prognosis [D]. Guangxi Medical University 2010.
31. Liu C, Qu L, Dong B, Xing X, Ren T, Zeng Y et al. Combined phenotype of 4 markers improves prognostic value of patients with colon cancer. Am J Med Sci 2012;343:295-302.
32. Tamagawa H, Oshima T, Yoshihara K, Watanabe T, Numata M, Yamamoto N et al. The Expression of the Phosphatase Regenerating Liver 3 Gene is Associated with Outcome in Patients with Colorectal Cancer. Hepatogastroenterology 2012;59.
33. Song R, Qian F, Li YP, Sheng X, Cao SX, Xu Q. Phosphatase of regenerating liver-3 localizes to cyto-membrane and is required for B16F1 melanoma cell metastasis in vitro and in vivo. PLoS One 2009;4:e4450.
34. Zeng Q, Dong JM, Guo K, Li J, Tan HX, Koh V et al. PRL-3 and PRL-1 promote cell migration, invasion, and metastasis. Cancer Res 2003;63:2716-22.
35. Wang Z, He YL, Cai SR, Zhan WH, Li ZR, Zhu BH et al. Expression and prognostic impact of PRL-3 in lymph node metastasis of gastric cancer: its molecular mechanism was investigated using artificial microRNA interference. Int J Cancer 2008;123:1439-47.
36. Zhou J, Wang S, Lu J, Li J, Ding Y. Over-expression of phosphatase of regenerating liver-3 correlates with tumor progression and poor prognosis in nasopharyngeal carcinoma. Int J Cancer 2009;124:1879-86.
37. Mayinuer A, Yasen M, Mogushi K, Obulhasim G, Xieraili M, Aihara A et al. Upregulation of protein tyrosine phosphatase type IVA member 3 (PTP4A3/PRL-3) is associated with tumor differentiation and a poor prognosis in human hepatocellular carcinoma. Ann Surg Oncol 2013;20:305-17.
38. Reich R, Hadar S, Davidson B. Expression and clinical role of protein of regenerating liver (PRL) phosphatases in ovarian carcinoma. Int J Mol Sci 2011;12:1133-45.
39. Wang L, Peng L, Dong B, Kong L, Meng L, Yan L et al. Overexpression of phosphatase of regenerating liver-3 in breast cancer: association with a poor clinical outcome. Ann Oncol 2006;17:1517-22.