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Manganese levels and hepatocellular carcinoma

A systematic review and meta-analysis based on Asian cohort

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Abstract

Several studies have investigated the relationship between Manganese (Mn) levels and hepatocellular carcinoma (HCC), but the results were inconsistent. Thus, we conducted a systematic review and meta-analysis to evaluate the association between Mn levels and HCC. Nine studies focusing on hair Mn levels, 6 studies on serum Mn levels and 6 studies on tissue Mn levels were identified in a systematic search of PubMed, CNKI, Wanfang and SinoMed databases. Standard mean differences (SMD) with the corresponding 95% confidence intervals (CI) were pooled to compare the Mn levels between HCC and controls. In serum, the Mn levels in HCC were significantly lower than in healthy controls (SMD (95% CI): −0.941 (−1.559, −0.323)). In hair, the Mn levels in HCC were slightly lower than in healthy controls, but not significant (SMD (95% CI): −0.168 (−0.766, 0.430)). In tissue, the Mn levels in tumors were significantly lower than in adjacent normal tissues (SMD (95% CI): −4.867 (−7.143, −2.592)). Subgroup analysis showed consistent results. In conclusion, this meta-analysis suggested an inverse association between Mn levels and HCC.

Abbreviations: AAS = atomic absorption spectrometry, CI = confidence interval, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, ICP-AES = inductively coupled plasma atomic emission spectrometry, Mn = Manganese, MnSOD = Manganese superoxide dismutase, NOS = Newcastle-Ottawa Scale, SMD = standard mean difference.

Keywords: hepatocellular carcinoma, Manganese, meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers around the world, and it is the second leading cause of cancer-related death among males.[1] Multiple factors were reported to be related with the pathogenesis of HCC, like chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), obesity and heavy alcohol consumption.[2,3] Trace elements also played a role in the development of HCC. In the meta-analysis of Zhang et al, HCC patients had lower selenium levels (serum/blood/toenail measurement) than healthy controls (SMD (95% CI): −1.08 (−0.136, −0.08)).[4] In the systematic review of Gurusamy, Iron, Zinc, and Copper content were lower in HCC than surrounding tissues.[5] Manganese (Mn) is an essential element that is required for many biological processes including bone health, macronutrient metabolism, and defense against reactive oxygen species (ROS).[6] The beneficial effects of Mn are due to the incorporation of the metal into metalloproteins, such as arginase (rate-limiting enzyme in urea synthesis), acetyl-CoA carboxylase (critical catalyst for endogenous fatty acid synthesis), phosphoenolpyruvate decarboxylase, pyruvate carboxylase (gluconeogenesis), Mn superoxide dismutase (mitochondrial antioxidant), glutamine synthetase (critical for brain ammonia metabolism), and glycosyltransferases (bone health).[7] Furthermore, several Mn metalloproteins had been reported in association with HCC.[8–10] However, no meta-analyses have focused on the Mn levels in HCC, although several studies reached inconsistent results.[11–29] Hence, we conducted a systematic review and meta-analysis to clarify these conflicting results and compare the Mn levels between HCC and controls.

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XBC, YHW, and XKC contributed equally to this study.

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2. Methods

2.1. Literature search

This meta-analysis was restricted to the studies which investigated the difference in hair, serum, and tissue Mn levels between HCC and controls. Two independent reviewers searched PubMed, China Knowledge Resource Integrated Database (CNKI), China Wanfang Database and China SinoMed Database from inception to September 2018, using the key words including: ("Manganese concentration" OR "Manganese content" OR "Manganese level" OR "Manganese" OR "trace element") AND ("hepatocellular" OR "hepatic" OR "liver")

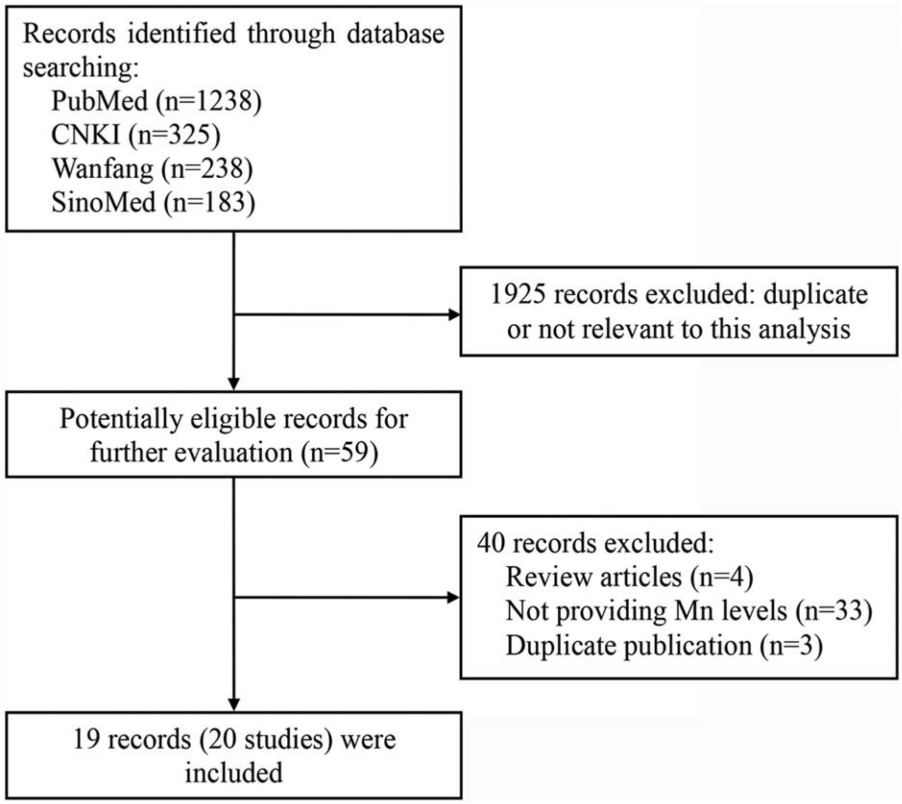

Figure 1. Flowchart of literature search.

AND ("cancer" OR "tumor" OR "carcinoma"). Moreover, we also reviewed the references of related studies and reviews for undetected studies. The study was approved by the ethnic committee of The First People's Hospital of Qinzhou.

2.2. Study selection and exclusion

The studies were included if meeting the following criteria:

1. all patients were diagnosed by pathology or other methods;
2. In the samples of hair and serum, the controls were from healthy individuals;
3. In tissue samples, the controls were adjacent normal tissues in HCC (obtained as far from the tumor as possible);
4. assessed the Mn levels in HCC and controls. The exclusion criteria were as follows: animal studies, reviews, or case reports.

2.3. Data extraction and quality assessment

Two authors extracted the data by a standardized collection form. All differences were resolved by discussion. In each study, the following information was extracted: first author, publication year, area, Mn measurement, type of samples, number of cases and controls, and Mn levels. The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of included studies.

2.4. Statistical analysis

Standard mean differences (SMD) and the corresponding 95% confidence intervals (CI) were pooled to compare hair, serum and tissue Mn levels between HCC and controls respectively. The heterogeneity among studies was estimated by Q test and I^2 statistic.[30] $I^2 > 50\%$ represented substantial heterogeneity, and the summary estimate was analyzed by a random-effects model. Otherwise, a fixed-effects model was applied. Sensitivity analysis was conducted to estimate the stability of the meta-analysis by omitting one study at a time during repeated analyses. Publication bias was assessed by using funnel plots and Egger test. All statistical analyses were performed using software STATA version 12.0 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of the included studies

The search strategy identified 1984 records: 1238 from PubMed, 325 from CNKI, 238 from Wanfang, and 183 from SinoMed (Fig. 1). After excluding duplicated and irrelevant records, 19 records (20 studies) were included into this meta-analysis (Table 1).[11–29] The research by Wang et al was based on 2 cohorts, which were regarded as 2 individual studies. Nineteen studies were from China, and one was from Japan. Nine studies investigated the hair Mn levels in 235 HCC cases and healthy controls. Six studies investigated the serum Mn levels in 272 HCC cases and 248 healthy controls. Six studies investigated the tissue Mn levels in the tumors and adjacent normal tissues of 201 HCC cases. Most studies used the method of atomic absorption spectrometry (AAS) to measure Mn levels, followed by inductively coupled plasma atomic emission spectrometry (ICP-AES). In quality assessment, all included studies had an NOS score of 6.

Table 1

Characteristics of included studies.

				Hepatocellular carcinoma		Controls*	
First author, year	Area	Measurement	Sample	N	Manganese levels	N	Manganese levels
Wang XL 1983 (11)	China	AAS	Hair	26	6.62±4.05 r/g	48	3.34±2.39 r/g
Wang XL 1983 (11)	China	AAS	Hair	20	4.43±2.13 r/g	25	2.38±1.74 r/g
Li ZX 1985 (12)	China	ICP-AES	Hair	37	4.05±3.27 ppm	41	9.18±7.79 ppm
Miyata G 1986 (13)	Japan	AAS	Tissue	19	0.63±0.57 ppm	19	1.77±0.72 ppm
Zhang LS 1987 (14)	China	AAS	Hair	37	1.62±1.352 ppm	32†	3.01±1.873 ppm
						31‡	2.349±1.389 ppm
Lv MH 1989 (15)	China	AAS	Serum	20	14.89±6.80 ug/L	98	29.35±16.55 ug/L
Ye RM 1991 (16)	China	AAS	Hair	26	20.642±26.675 ug/g	152	11.965±11.617 ug/g
Tao WZ 1991 (17)	China	AAS	Tissue	52	0.78±0.72 ug/g	52	2.12±1.35 ug/g
Gu GW 1991 (18)	China	AAS	Hair	33	2.80±0.96 ppm	127	4.44±1.70 ppm
Luo YH 1993 (19)	China	AAS	Serum	26	8.44±6.36 ug%	20	16.36±5.74 ug%
Wang JY 1994 (20)	China	ICP-AES	Serum	33	0.473±0.582 umol/L	17	0.49±0.182 umol/L
Lv CP 1999 (21)	China	ICP-AES	Hair	26	2.23±1.46 mg/L	27	1.12±1.67 mg/L
He Q 2000 (22)	China	AAS	Serum	62	0.0046±0.006 ug/L	42	0.016±0.002 ug/L
Cai KR 2003 (23)	China	AES	Tissue	30	3.52±0.75 ug/g	30	1.43±0.48 ug/g
Yu RZ 2004 (24)	China	AAS	Serum	38§	0.67±0.17 mol/L	56	1.44±0.84 mol/L
			Serum	38¶	0.76±0.15 mol/L		
Yang HJ 2008 (25)	China	ICP-MS	Tissue	25	0.92±0.079 ug/g	25	3.85±0.12 ug/g
Xie YD 2008 (26)	China	AAS	Hair	20	0.33±0.21 ug/g	20	0.78±0.23 ug/g
Zhou XZ 2010 (27)	China	ICP-AES	Tissue	20	1.37±0.15 ug/g	20	4.16±0.14 ug/g
Li Y 2013 (28)	China	ICP-AES	Hair	10	4.40±5.58 ug/g	24	3.05±10.34 ug/g
Liu ZH 2016 (29)	China	AAS	Serum	55	27.48±14.39 ug/L	15	23.29±8.89 ug/L
			Tissue	55	580.61±227.55 ng/L	55	761.42±179.70 ng/L

AAS=atomic absorption spectrometry, AES=atomic emission spectrometry, ICP-AES=inductively coupled plasma atomic emission spectrometry, ICP-MS=inductively coupled plasma mass spectrometry.
* Hair and serum samples were from healthy controls, and tissue samples were from adjacent normal tissues in hepatocellular carcinoma (HCC).
† Healthy controls from the area with low HCC incidence.
‡ Healthy controls from the area with high HCC incidence.
§ Before treatment.
¶ After treatment.

3.2. Hair Mn levels and HCC

Nine studies investigated the difference of hair Mn levels between HCC and healthy controls. The research by Zhang et al included 2 groups of healthy controls from the areas with low and high incidence of HCC. It was found that hair Mn levels in HCC were lower than in controls, but not significant (SMD (95% CI): −0.168 (−0.766, 0.430); $I^2=92.4\%$, $P_{heterogeneity}<.001$) (Fig. 2). Sensitivity analysis showed the result was robust. Egger test detected no significant publication bias ($P=.850$).

Subgroup analysis was conducted on measurement and publication year. No substantial changes of the primary result were found between subgroups (Table 2).

3.3. Serum Mn levels and HCC

Six studies investigated the difference of serum Mn levels between HCC and healthy controls. The study by Yu et al also investigated the serum Mn levels of HCC cases before and after treatment. It was found that serum Mn levels in HCC were significantly lower than in controls (SMD (95% CI): −0.941 (-1.559, −0.323); $I^2=90.0\%$, $P_{heterogeneity}<.001$) (Fig. 3). Sensitivity analysis showed the result was robust. Egger test detected no significant publication bias ($P=.483$).

Subgroup analysis was conducted on measurement and publication year. No substantial changes of the primary result were found between subgroups (Table 2).

3.4. Tissue Mn levels and HCC

Six studies investigated the difference of tissue Mn levels between the tumors and adjacent normal tissues in HCC. It was found that tissue Mn levels in tumors were significantly lower than in adjacent normal tissues (SMD (95% CI): −4.867 (−7.143, −2.592); $I^2=98.2\%$, $P_{heterogeneity}<.001$) (Fig. 4). Sensitivity analysis showed the result was robust. Egger test detected no significant publication bias ($P=.268$).

Subgroup analysis was conducted on measurement and publication year. No substantial changes of the primary result were found between subgroups (Table 2).

4. Discussion

As an essential trace element, Mn played an important role in a wide range of biological processes. It is a cofactor of some important enzymes, like Mn superoxide dismutase (MnSOD). MnSOD is a mitochondrial antioxidant enzyme which is down-regulated in a majority of cancers and suggested as a tumor suppressor due to potent antioxidant activity.[31] Thus, Mn was thought to be associated with multiple diseases. In the meta-analysis of Du et al, patients with Alzheimer's disease and mild cognition impairment had significantly reduced serum Mn levels compared to healthy controls (SMD (95% CI): −0.39 (−0.71, −0.08); −0.37 (−0.60, −0.13)).[32] In the meta-analysis of Shen et al, a significant association was found between deficient Mn levels and breast cancer (SMD (95% CI): −1.51 (−2.47, −0.56)), and different sample specimens showed consistent results (serum: −1.24 (−2.31, −0.16); hair: −1.99 (−3.91, −0.06)).[33] Furthermore, in the recent study by Ma et al, a population-based epidemiological research was conducted to investigate the relationship between dietary trace element intake and liver cancer risk.[34] It was found that dietary intake of Mn was inversely

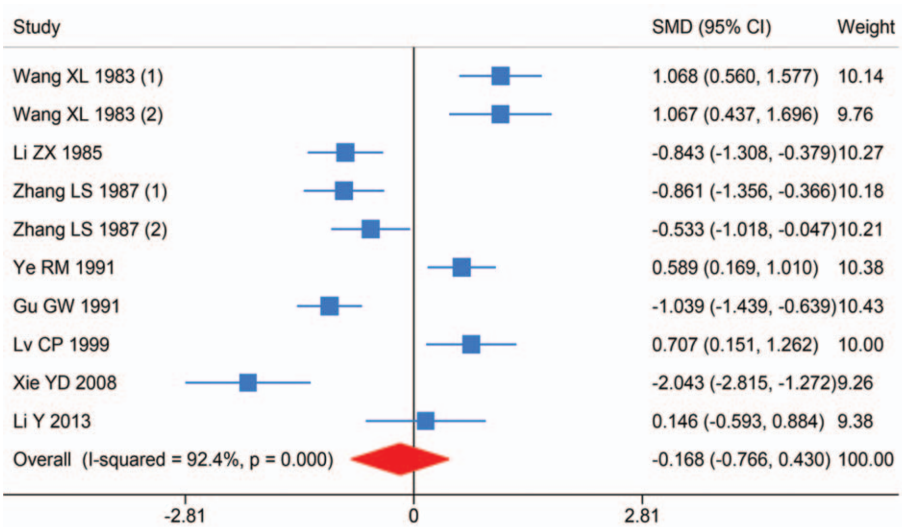

Figure 2. Forest plot of meta-analysis on hair Manganese levels and hepatocellular carcinoma.

Table 2

Subgroup analysis of Manganese levels and hepatocellular carcinoma.

	Hair			Serum			Tissue		
Variable	**N**	**SMD (95% CI)**	**I^2 (%)**	**N**	**SMD (95% CI)**	**I^2 (%)**	**N**	**SMD (95% CI)**	**I^2 (%)**
Measurement									
AAS	7	−0.238 (−1.020, 0.544)	94.0	6	−1.088 (−1.732, −0.444)	89.6	3	−1.202 (−1.627, −0.778)	54.9
ICP-AES	3	−0.010 (−1.016, 0.997)	89.1	1	−0.035 (−0.620, 0.550)	–	1	−19.230 (−23.597, −14.862)	–
Publication year									
Before 2000	8	0.008 (−0.624, 0.640)	92.6	3	−0.754 (−1.459, −0.049)	78.0	2	−1.398 (−1.867, −0.930)	27.4
After 2000	2	−0.946 (−3.091, 1.200)	93.8	4	−1.072 (−2.039, −0.106)	93.7	3	−9.759 (−14.863, −4.656)	98.8

AAS = atomic absorption spectrometry, ICP-AES = inductively coupled plasma atomic emission spectrometry, N = number of included studies.

associated with liver cancer risk (highest vs lowest quintile, hazard ratio (95% CI): 0.51 (0.35–0.73), $P_{trend} < .001$). However, no meta-analyses have focused on the Mn levels in HCC, although several studies reached inconsistent results.

In this meta-analysis, we also suggested a significant association between Mn levels and HCC. In serum, the Mn levels in HCC were significantly lower than in healthy controls. In tissue, the Mn levels in tumors were significantly lower than in adjacent normal tissues. Furthermore, in the study by Yu et al, the serum Mn levels in HCC increased significantly after treatment (SMD (95% CI): −0.561 (−1.020, −0.103)), which also indicated an inverse association between Mn levels and HCC. In hair, the Mn levels in HCC were slightly lower than in healthy controls, but not significant, which might contribute to tissue specificity. Similarly, breast cancer patients had a higher nickel (Ni) level in serum (SMD: 1.76, 95% CI: 0.82–2.70), but it was not significant

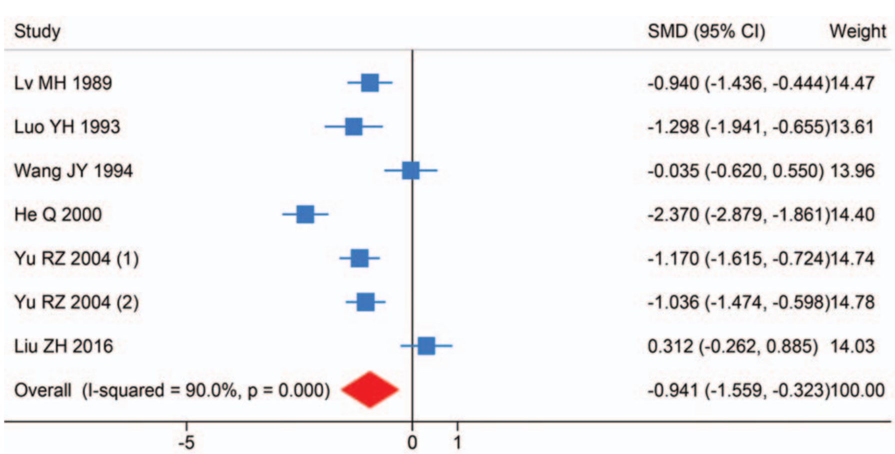

Figure 3. Forest plot of meta-analysis on serum Manganese levels and hepatocellular carcinoma.

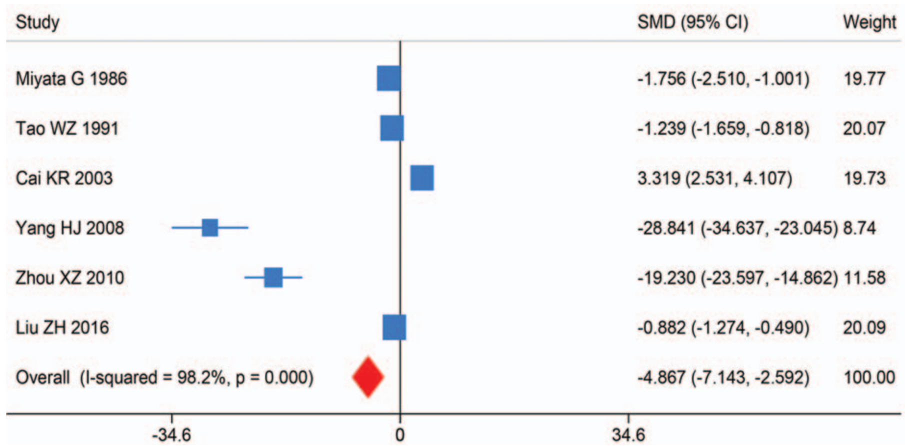

Figure 4. Forest plot of meta-analysis on tissue Manganese levels and hepatocellular carcinoma.

in hair (SMD: 0.16, 95% CI: −1.08 to 1.40).[35] Breast cancer patients had a lower Zinc (Zn) level in hair (SMD: −1.99, 95% CI: −3.46 to −0.52), but it was not significant in serum (SMD: −0.65, 95% CI: −1.42 to 0.13).[36] Nevertheless, Zinc supplementation could significantly increase natural killer T (NKT) cells, which were involved in the direct killing of target cells and thus provided anti-tumor protection.[37]

This meta-analysis had several strengths. First, to the best of our knowledge, this is the first meta-analysis to evaluate the association between Mn levels and HCC. Second, the conditions in hair, serum, and tissue were considered respectively. Third, sensitivity analysis and Egger test were conducted to estimate the stability of pooled results and potential publication bias. However, several limitations in this study should be considered. First, the number of cases and controls in each study was relatively small. Second, the obvious heterogeneity between studies was observed. For this, we conducted a sensitivity analysis to evaluate the stability of pooled results.

In conclusion, this meta-analysis suggested an inverse association between Mn levels and HCC.

Author contributions

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Methodology: Xiubing Chen, Yuehui Wei, Xiu-Ke Chen, Jia-Yan Nie.
Software: Xiubing Chen, Jian Zhong.
Supervision: Jian Zhong, Jia-Yan Nie.
Validation: Jian Zhong.
Visualization: Xiubing Chen.
Writing – original draft: Xiubing Chen, Youbao Zou.
Writing – review & editing: Xiu-Ke Chen, Youbao Zou, Jia-Yan Nie.

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