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Zinc level in hepatocellular carcinoma: a meta-analysis

Abstract

Background: Zinc exerts essential antioxidant, anti-inflammatory, and apoptotic effects and necessary in several regulatory proteins and hormone receptors. The role of zinc in the immune system and its contribution in preserving genome stability are all relevant to cancer. Hepatocellular carcinoma (HCC) is viewed as the fifth most common form of malignancy globally and it speaks to the third most common reason of cancer-related death. Many research studies have been done on zinc content in biological materials in liver cancer patients, but it did no longer provided consistent results. Therefore we investigated the prognostic relevance of zinc levels with hepatic carcinomas via meta-analysis.

Materials and methods: Meta-analysis was carried out on the findings of seven published studies that were related to zinc with Hepatocellular carcinoma patients. The pooled mean was estimated by using a random-effects model.

Results: Pooled mean for Zinc was 74.06µg/dL (95% CI: 61.0-87.06). There was a high degree of divergence among the studies, with the index of heterogeneity being more than 90%.

Conclusion: Zinc pooled mean reported lesser the then normal range. Pooled mean reported in this study can be useful in working out the quantum of development and progression of HCC.

Keywords: hepatocellular carcinoma, zinc, liver, antioxidant, serum zinc levels, meta-analysis

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Introduction

The biochemistry of zinc (Zn) deserves plenty more attention than it typically receives in textbooks of the medical sciences and also in some components of the scientific literature, as zinc is found in human body as a component of almost 300 enzymes as a catalytic co-factor, or as part of the enzyme's structure.[1,2] It is found to be second most widespread trace element in the body and is involved in many vital regulatory, catalytic, and defensive functions. It exerts essential antioxidant, anti-inflammatory, and apoptotic effects.[3,4] It is necessary in several regulatory proteins and hormone receptors, such as zinc-fingers, zinc-twists, or zinc-clusters, determinant in binding to DNA.[2]

Metallothionein (MT) is the principal protein accountable for cellular zinc homeostasis. Under regular physiological conditions, it serves as a zinc reservoir. Additionally it also acts as a zinc supplier by means of transferring zinc to Apo proteins to form useful zinc proteins. Zinc takes part in cell functions majorly through binding to numerous zinc proteins including metalloenzymes. However, zinc may additionally be released upon oxidation of the zinc-binding residues of cysteine, which can cause dysfunction of zinc proteins.[3–5]

As liver is a vital organ involved in zinc metabolism, it plays an essential role in retaining the systemic zinc homeostasis. Subsequently, liver ailments can alter zinc levels and, this in turn may be influenced by zinc deficiency. According to World Health Organization (WHO), zinc deficiency is the fifth most important risk element for morbidity and mortality in developing countries.[4,6] The role of zinc in the immune system and its contribution in preserving genome stability are all relevant to cancer. Additionally, the process of metastasis and angiogenesis also require zinc. Matrix metallo-proteinases enzymes are also involved in the process of metastasis. Cancer is often associated with low serum zinc, and with decreased or increased zinc in the malignant tissues.[7] Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the two main types of primary liver cancer, HCC being more common than the cholangiocarcinoma.[8] Hepatocellular carcinoma (HCC) is viewed as the fifth most common form of malignancy globally and it speaks to the third most common reason of cancer-related death.[4]

According to some clinical evidences of some studies, Zn concentrations in HCC tissues were found to be lower than those in the surrounding hepatic parenchyma cells.[9,10] Zn may additionally be involved in the regulation of apoptosis in HCC cells. Therefore, deficiency of Zn may contribute to the proliferation and rapid growth of HCC cells. In view of the perceptions of intracellular Zn concentrations level in various carcinomas, it has been hypothesized that these changes in Zn levels may contribute to the advancement of tumors by influencing a vast variety of molecular structures, such as receptors, kinases, caspases, phosphatases and various transcriptional factors.[11]

Many research studies have been done on zinc content in biological materials in liver cancer patients as shown in Table 1 of this study. These results mislead the clinician in decision of the actual measure of the respective parameters i.e., there is lack of systematic review of this major health issue. Hence, the present study was carried out to evaluate and determine the relationship between zinc levels with hepatic carcinomas.

Methods

This meta-analysis was designed and performed according PRISMA compliant.

Table 1 Study characteristics for zinc in hepatic carcinoma patients with mean, 95% confidence interval (CI)

Author	Population (n)	Mean	95% confidence interval	
			LL	UL
Shigefuku R et al.[17]	299	60.80	55.72	65.88
Hosui A et al.[14]	196	61.70	59.58	63.82
Ito T et al.[15]	179	78.00	71.49	84.51
Fang A et al.[12]	986	84.82	37.64	132.00
Stepien M et al.[16]	106	104.60	100.56	108.64
Katayama K et al.[18]	31	60.10	56.30	63.90
Imai K et al.[13]	310	75.80	74.23	77.37

Data sources and searches

A comprehensive, computerized literature search was conducted in PubMed databases regarding the association between serum zinc levels and hepatic cancer risk, from 1 January 2014 to April 2020 with the help of keywords "zinc levels" OR "zinc concentration" OR "zinc" in combination with "hepatic cancer" OR "hepatic tumor". We also accessed references of retrieved publications additional supports.

Study selection criteria

Eligibility criteria for our the studies were : (1) epidemiological studies; (2) the aim was to evaluate the associations between serum zinc levels and hepatic cancer risk; (3) the numbers, mean, and standard deviation (SD) of serum zinc levels were available. It is noticed that duplicated outcomes might be published in more than one research paper, so we choose the latest or most instructive paper in our investigation. A flow chart of a process in the selection of study along with numbers selected and excluded at different levels appears in Figure 1.

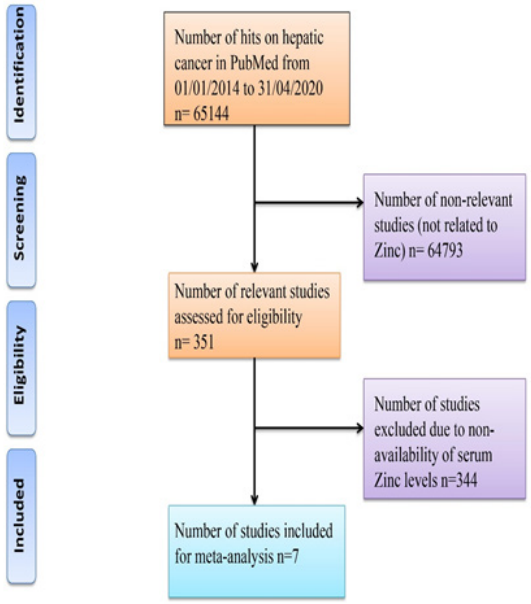

Figure 1 Flow chart in the process of study selection.

There were 65144 articles on hepatic cancer published between 01/01/2014 to 31/04/2020 ut we include only 7 papers in our study as per our inclusion criteria.

Data extraction and quality assessment

Data was extracted independently by two of the authors, confirming to the determination standards above. A standardized data assortment convention was as per the following: the last name of the first author, year of publication, range mean and SD of serum zinc levels for hepatic cancer.

Statistical analysis

The overall mean and 95% confident interval (CI) by adopting random effects models that taking into account for our study. The analysis assessed the heterogeneity among researches with the help of the Cochran's Q test and I2 (inconsistency index) statistic. STATA-16 statistical software was used to prepare forest plot and funnel plot and to describe individual studies and pooled mean. Heterogeneity between studies was detected by I2 value. Less than of 50% I2 statistics were considered as low and indicating a greater degree of similarity between studies. P-value less than 5% was fixed as Statistical significance because meta-analysis is a kind of observational study; errors can happen in the method of study inclusion and analysis, resultant in incorrect results. The funnel graph can be used to evaluate the bias of the study as shown in Figure 2.

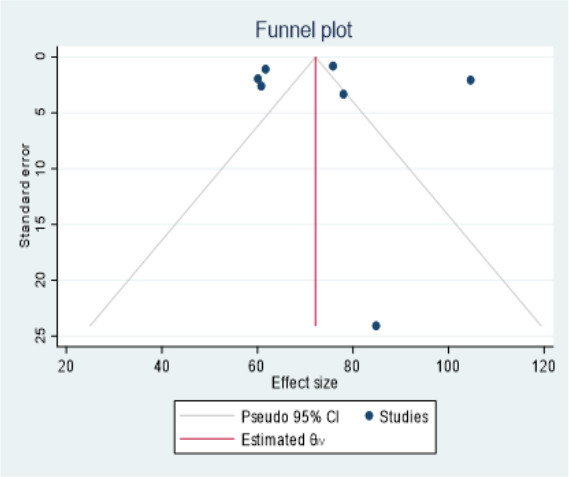

Figure 2 Funnel plot with Pseudo 95% Confidence Interval for zinc in hepatic carcinoma.

Result

Seven articles that met the eligibility criteria for this study and dealt with the association of Hepatic Carcinoma with serum Zinc levels were included in the study.[12–18] Table 1 summarizes the results of our study in the form of mean, lower limit, upper limit of each study. Figure 3 shows the results of the meta-analysis for each study and studies combination based on the random-effects model. There was a high degree of divergence among the studies, with the index of heterogeneity being more than 90% as shown in Figure 3.

Serum zinc levels and hepatic carcinoma

All seven studies dealing with zinc levels reported its association with Hepatic carcinoma, reveals a statistically significant association. Pooled mean for all seven studies was 74.06µg/dL (95% CI: 61.0-87.06) with I^2=98.97% as shown in Figure 3. Most studies were located at the outside of the funnel figure, which means that the research publication bias was large. The Egger test showed that the publication bias, as shown in Figure 2.

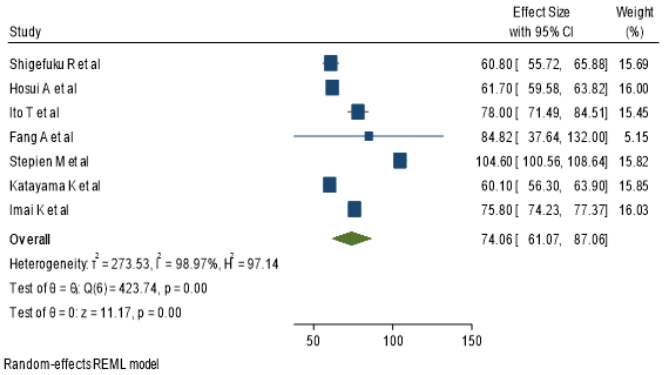

Figure 3 Forest plot of random-effects meta-analysis for zinc in hepatic carcinoma.

Discussion

The current meta-analysis, to our knowledge, is the first meta-analysis evaluating the role zinc in the development and progression of hepatic cancer, giving insights to comprehend if this action should exert a strategic function also in other cancers. The pooled estimates of 7 studies of hepatic cancer studies having serum zinc levels were taken in this study. A random effect model was used in present study, with the hypothesis that every study selected samples for analysis randomly. The studies were carried out in the different periods and the diversity of cultures, locations and economic status so high heterogeneity was observed.

As reported in previous studies, for zinc metabolism liver was an important organ, it plays an important role in maintaining the systemic zinc homeostasis. Subsequently, zinc levels may be altered in many liver diseases or influenced by zinc deficiency.[4]

Zinc helps in immune system and provides genome stability which were useful in cancer. In addition the process of metastasis and angiogenesis also require zinc. Cancer is often associated with low serum zinc, and with increased or decreased zinc in the malignant tissue.[7]

Our meta-analysis study observes pooled mean Zinc level was lesser than the normal range (78.48 to 130.8µg/dl 19) in hepatic carcinomas patients. The possible mechanism was explained that in hepatic carcinoma patient; diminished hepatic zinc extraction occurs which leads to hypozincemia although Zinc have an important role in development and progression of chronic liver diseases.[16] Similar results shown by studies done by Shigefuku R et al.[17] Hosui A et al.[14] Katayama K et al.[18] Ito T et al.[15] Imai K et al.[13] showed hypozincemia. However, studies done by Fang A et al.[12] and Stepien M et al.[16] showed normal zinc levels in hepatic carcinomas patients.[19]

Conclusion

This study has reported pooled mean of Zinc levels, which is the second most prevalent trace element in the body to evaluate the prognosis of liver carcinomas patients. Pooled mean reported in this study will be useful in working out the quantum of liver cancer. Zinc pooled mean reported lesser the then normal range. So, it could be useful for the determination of risk association liver carcinomas and development and progression of chronic liver diseases.

Acknowledgments

Not applicable.

Conflicts of interest

The authors declare there are no conflicts of interest.

Availability of supporting data

This study is based on Secondary data, which is available online at different Website as mention in materials and methods sections.

Funding source

Not applicable.

Ethical clearance

Not applicable.

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