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Concentración de selenio, ingesta dietética y riesgo de carcinoma hepatocelular: revisión sistemática con metaanálisis

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Authors´s contribution: Yuanfeng Gong and Baohua Hou conceived and designed the study. Yan Geng and Kaihong Zhuang performed a literature search and identified eligible studies. Zuyi Ma, Zixuan Zhou, and Bowen Huang extracted data from retrieved studies. Yuanfeng Gong and Fengying Dong carried out the statistical analysis and interpreted the results. All drafts were written by Yuanfeng Gong and Baohua Hou. All authors read and approved the final paper.

ABSTRACT

Aim: this study was performed to investigate the association between selenium concentrations, dietary intake, and the risk of hepatocellular carcinoma (HCC).

Methods: we identified eligible studies in PubMed and EMBASE databases, in addition to the reference lists of original studies and review articles on this topic, up to 1 Feb 2019. A summary of standardized mean differences (SMD) with 95% confidence intervals (CI) was calculated using a random-effects model. Heterogeneity between studies was assessed using Cochran Q and I^2 statistics.

Results: finally, a meta-analysis showed that dietary intake of selenium and tissue selenium concentration were not associated with HCC risk (dietary SMD = -0.11, 95% CI: -0.26 to 0.03; tissue SMD = -0.12, 95% CI: -0.56 to 0.33). However, samples from

toenail, whole blood, and serum all showed an inverse association with HCC risk (toenail SMD = -0.53, 95% CI: -0.72 to -0.35; whole blood SMD = -2.21, 95% CI: -2.67 to -1.76; tissue SMD = -1.26, 95% CI: -1.71 to -0.81). Dose-response data from few studies showed that an extra increase in serum selenium was dramatically related with a lower risk of HCC (adjusted p-trend < 0.05). This study showed that selenium concentration in toenail, whole blood and serum was inversely associated with HCC risk.
Conclusion: increased concentration in serum selenium was related to a lower risk of HCC. However, these results based on dietary intake and tissue samples, which included few studies, did not reach statistical significance.

Key words: Selenium. Selenoprotein. Hepatocellular carcinoma. Morbidity. Meta-analysis.

RESUMEN

Objetivo: este estudio se realizó para investigar la asociación entre las concentraciones de selenio, la ingesta dietética y el riesgo de carcinoma hepatocelular (CHC).
Métodos: identificamos estudios elegibles en las bases de datos PubMed y EMBASE, además de las listas de referencias de los estudios originales y artículos de revisión sobre este tema hasta el 1 de febrero de 2019. Se realizó un resumen de las diferencias medias estandarizadas (SMD) con intervalos de confianza (CI) del 95% utilizando un modelo de efectos aleatorios. La heterogeneidad entre estudios se evaluó utilizando las estadísticas de Cochran Q e I^2.
Resultados: por último, el metaanálisis mostró que la concentración de selenio en la ingesta dietética y de selenio

tisular no estaban asociadas al riesgo de HCC (SMD dietética -0,11, IC 95%: -0,26 a 0,03; SMD tisular -0,12, IC 95%: -0,56 a 0,33). Sin embargo, las muestras de uña del pie, sangre entera y suero mostraron todas ellas una asociación inversa con el riesgo de CHC (SMD ungueal -0.53, IC 95%: -0.72 a -0.35; SMD de sangre entera -2.21, IC 95%: -2.67 a -1.76; SMD tisular -1.26, IC 95%: -1.71 a -0.81). Los datos de dosis-respuesta de pocos estudios mostraron que los incrementos del selenio sérico se relacionaban fuertemente con un menor riesgo de CHC (tendencia de p ajustada < 0.05). Este estudio demostró que la concentración de selenio en las uñas del pie, en sangre entera y en suero se asocian inversamente al riesgo de CHC.
Conclusión: El aumento de la concentración de selenio sérico se relacionó con menor riesgo de CHC. Sin embargo, los resultados de la ingesta dietética y los tejidos, que incluían pocos estudios, no alcanzaron la significación estadística.

Palabras clave: Selenio. Selenoproteína. Carcinoma hepatocelular. Morbilidad. Metaanálisis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major malignant tumor around the world, and particularly in China and Southeast Asia, with a poor 5-year survival rate. An estimated 782,500 new cases and 745,500 cancer-related deaths emerge every year, ranking HCC as the sixth cancer with more morbidity and the second in terms of cancer mortality (1). Hepatitis B virus (HBV) infection is the most important risk factor for HCC in Asia. (2). The only one exception in Asia is Japan, where the prevalence of HCC has been closely associated with hepatitis C virus (HCV) infection (3). In

western countries, however, HCV infection has been observed in about 60% of patients diagnosed with HCC (4,5).

Accompanied by infection with HBV or HCV, liver cirrhosis is also one of the most important risk factors in the development of HCC. Moreover, there are other confirmed risk factors, among which alcohol and aflatoxin stand out as most important (6,7). Food intake is also one of the most intensively studied risk factors closely related to HCC, most particularly coffee and tea (8), iron (9), red and white meats (10), some types of fat, and vitamin D (11). However, the results regarding the association of other dietary components with the risk of HCC are inconsistent.

Selenium has been shown to play important roles in multiple metabolic processes in the liver. Evidence from experimental studies suggested that dietary selenium intake might interact with selenoproteins and angiogenic cytokines in the hepatocarcinogenesis process, and high selenium concentrations could inhibit cancer progression (12-14). Low selenium intake was thought to increase susceptibility to HBV and HCV infection (15,16). Selenium deficiency has been observed in patients with liver cirrhosis and correlates well with severity of cirrhosis. This may create a vicious circle as deterioration in the homeostasis of selenium by severe cirrhosis may lead to greater oxidative stress and inflammation, which will aggravate the progression of cirrhosis. Selenium supplementation can suppress the progression of cirrhosis and the development of complications (17,18).

A previous meta-analysis including nine studies, performed by Zhang et al., suggested an inverse correlation between selenium concentration and risk of HCC (19). This study was limited by a small sample size and confined to two sample sources (blood and toenail). Recently, a large nested case-control study covering 132,765 people in China showed that no statistically significant association could be found between dietary intake of selenium

and HCC risk (20). Furthermore, two studies concerning selenium concentration in HCC tissues showed almost the same concentration among tumor tissues, nontumor tissues, and normal livers (21,22). Therefore, we performed this update meta-analysis and dose-response review of all available evidence from observational studies following the PRISMA guidelines to clarify the association between selenium concentrations, dietary intake, and risk of HCC.

METHODS

Data Sources and Search Strategy

Two of the authors (Y.G. and H.Z.) independently performed a literature search using PubMed and EMBASE databases for articles up to 1 Feb 2019. We searched the studies with the following text words and/or Medical Subject Heading (MeSH) terms: ("selenium") AND ("liver neoplasms" [MeSH] or "hepatocellular carcinoma" or "liver cancer").

Study Selection

We included studies that met all the following criteria: a) published as an original article; b) used a case-control, cross-sectional, nested case-control or cohort study design; c) explored selenium concentration in various samples including serum, whole blood, toenail, hair, tissue, and diet intake; d) a study endpoint was the morbidity or mortality of HCC; and e) the number of cases and controls, mean and standard deviation for both groups, estimated odds ratio (OR) or hazard rate (HR) with corresponding 95% confidence intervals (CIs) for cases versus controls, or the gradient concentrations versus lowest concentration were reported. Two authors (Y.G. and H.Z.) independently evaluated all the studies retrieved from the databases. We did not contact the authors for detailed information about the primary studies.

Data Extraction and Quality Assessment

Three authors (Z.M., Z.Z. and B.H.) independently evaluated all the studies retrieved according to the prespecified selection criteria. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article. The following information from each study was extracted using a standardized data collection form: the first author's last name, year of publication, geographic location, study design, number of cases, number of controls, quality of each study, types of samples, mean and standard deviation of selenium concentrations, the effect estimates with 95% CIs for cases versus controls, or the gradient concentrations versus lowest concentration. When crude or adjusted estimates were both presented in an individual study, we extracted the estimate adjusted for more confounding factors. The quality of each study was evaluated independently by three reviewers using the Newcastle-Ottawa Scale (NOS). The NOS consists of three parameters of quality: selection, comparability, and outcome (cohort studies) or exposure (case-control studies). The NOS assigns a maximum of four points for selection, a maximum of two points for comparability, and a maximum of three points for exposure or outcome. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article.

Statistical Analysis

We used the STATA 14.0 software (StataCorp, College Station, TX, USA) to conduct the meta-analysis of standardized mean differences (SMD) with 95% confidence intervals (CI), and to calculate the Cochran Q and I^2 statistics for heterogeneity across the studies. SMD was tested with an α level of 0.05, whereas an α level of 0.10 was used to examine Cochran's Q, as suggested by Higgins et al. To investigate the sources of

heterogeneity across these studies, we carried out heterogeneity tests and sensitivity analyses. In heterogeneity tests, we used the Cochran Q and I^2 statistics (23), which were used to test the differences obtained between studies due to chance. For the Q statistic, a p-value of less than 0.10 was considered representative of statistically significant heterogeneity. The I^2 statistic is the proportion of total variation contributed by between-study variation. It has been suggested that I^2 values of 25%, 50%, and 75% be assigned to low, moderate, and high heterogeneity, respectively ([24]). We conducted a sensitivity analysis to estimate the influence of each individual study on the summary results by repeating the random-effects meta-analysis after omitting one study at a time. We evaluated the role of several potential sources of heterogeneity by subgroup analyses according to study design, geographical locations, study quality, and sample sizes.

Dose-response data were reported in five studies (20,25-28). Data from different sources of selenium concentration varied from each other, and the baseline concentrations of selenium in the serum differed a lot between the studies performed by Yuan (26), by Hughes (25), and by Yu (28), so they could not be pooled together in one dose-response meta-analysis, and we could only report the dose-response data from a single study.

Funnel plots and Egger's test were performed to test for evidence of publication bias (29). In the presence of a publication bias, we used the "trim and fill" method to correct such bias (30).

RESULTS

Data Sources and Search Strategy

The detailed steps of our literature search are presented in figure 1. In brief, a total of 296 citations were obtained for a review of their titles and abstracts. Of these 296 citations, 279 were not relevant. The full texts of the remaining 17 studies were retrieved

for review. Two studies were retrieved by hand searching the references of included studies. These two studies were both indexed in ResearchGate, not in PubMed or Embase. Meanwhile, one study was excluded because of being reported as an abstract without any detailed data (31). One article (32) was duplicate with its updated one (33), and we included the latter. Two studies investigating tissue samples were excluded (22,34) due to lack of detailed data. Finally, 14 studies were included in the final meta-analysis (Fig. 1).

Study Characteristics

Fourteen articles that met our inclusion criteria for this meta-analysis were published between 1994 and 2017. There were three nested case-control studies (20,25,27) and eleven retrospective case-control studies (21,26,28,33,35-41). Nine articles described the association between serum selenium concentration and HCC risk (25,26,28,33,36,37,39-41), two described the association between whole blood selenium concentration and HCC risk (35,38), one reported the association between tissue selenium concentration and HCC risk (21), one reported the association between toenail selenium concentration and HCC risk (27), and the last one dealt with dietary intake selenium concentration (20). The average score for the quality assessment of included studies was 7.5. Dose-response data with the graded concentrations versus the lowest concentration were presented in five studies (20,25-28) (Table I).

Meta-Analysis

A well-designed case-control study conducted by Yuan et al. showed that no independent effect of serum selenium concentration on HCC risk was observed. However, only mean and p-value was provided, without standard deviation. A meta-analysis of 13 studies in a random-effects model found that the

selenium concentration of all samples was inversely associated with the risk of HCC (standardized mean difference (SMD) = -1.02, 95% CI: -1.34 to -0.70; test for heterogeneity $p < 0.001$, $I^2 = 94.0\%$) (Fig. 2A). Heterogeneity across studies was extremely high. A subgroup analysis of different samples showed that dietary intake selenium and tissue selenium concentrations were not associated with HCC risk (dietary intake SMD = -0.11, 95% CI: -0.26 to 0.03; tissue SMD = -0.12, 95% CI: -0.56 to 0.33). However, samples from toenail, whole blood and serum all showed an inverse association with HCC risk (toenail SMD = -0.53, 95% CI: -0.72 to -0.35; whole blood SMD = -2.21, 95% CI: -2.67 to -1.76; tissue SMD = -1.26, 95% CI: -1.71 to -0.81) (Fig. 2).

In a sensitivity analysis, the overall homogeneity and effect size was calculated by removing one study at a time. The direction of the effect did not change when any study was excluded, supporting the stability of low selenium concentration in all samples related to an increase in HCC risk (Fig. 2B).

We subsequently conducted a subgroup systematic review and meta-analysis according to geographical location, study quality, study design, and sample size. A statistically significant relation was observed in various regions – Asia, -0.77 (-1.11, -0.43); Europe, -1.52 (-2.52, -0.52); Africa, -2.07 (-3.01, -1.14). When assessing study quality, the inverse association was observed in both high- and low-quality groups – NOS ≥ 8, -0.38 (-0.61, -0.14); NOS < 8, -1.49 (-2.06, -0.93). As regards study design, both nested case-control studies and case-control studies showed a positive result – NCC, -0.34 (-0.60, -0.08); CC, -1.39 (-1.91, -0.86). Sample size for cases ranged from 10 to 536, and this might be an important confounder for risk of HCC. When we confined the meta-analysis to sample sizes with a cut-off point of 50, a positive association was also found in both groups – more than

50, -0.71 (-1.06, -0.37); less than 50, -1.42 (-2.10, -0.74) (Table II).

Publication Bias

The shape of the funnel plots for studies examining the association of selenium concentration, dietary intake, and HCC risk seemed asymmetrical [Begg's test (p = 0.155), Egger's test (p = 0.022)], indicating that there might be a potential publication bias (Fig. 2C). However, a trim-and-fill analysis with a linear estimator and random-effects model showed no trimming and unchanged data.

Dose-Response Data

Dose-response data were presented in five studies. The study by Ma et al. showed that dietary intake selenium was not associated with HCC risk. The study by Sakoda et al. revealed that toenail selenium was lower in HCC cases than in controls (p = 0.03); however, getting to a higher quartile of toenail selenium was not compatible with a significant trend in risk (p-trend = 0.06). Yuan's study showed a negative result (p-trend = 0.24, adjusted p-trend = 0.27). Hughes' study suggested that an extra increase in serum selenium (by 20 μg/L) was dramatically related to a lower risk of HCC (adjusted p-trend = 0.016, OR = 0.41, 95% CI: 0.23 to 0.72), whereas Yu's study showed that an increase in serum selenium by 12 μg/L was significantly related with a lower risk of HCC (adjusted p-trend = 0.036, OR = 0.937, 95% CI: 0.882 to 0.996).

DISCUSSION

In this collaborative meta-analysis, the results showed that samples obtained from toenail, whole blood, and serum were inversely associated with HCC risk (toenail SMD = -0.53, 95% CI: -0.72 to -0.35; whole blood SMD = -2.21, 95% CI: -2.67 to -1.76; tissue SMD = -1.26, 95% CI: -1.71 to -0.81); however, the results

from the analysis of dietary intake and tissues, which included few studies, did not reach statistical significance. Obvious heterogeneity was observed when all studies were included, but the omission of each one study made little or no difference, as seen in figure 3. Dose-response data including few studies revealed that an increased concentration in serum selenium was related with a lower risk of HCC (Hughes' study, by 20 μg/L, OR = 0.41; Yu's study, per 12 μg/L, OR = 0.937); however, no positive trend was observed in samples from dietary intake and toenail. Some marginal publication bias might have existed in this meta-analysis [Begg's test (p = 0.155), Egger's test (p = 0.022)], but the trim-and-fill analysis showed that the results remained unchanged.

It was surprising that the dietary intake of selenium was not associated with risk for HCC in the only study included; however, several confounding factors should be considered in the interpretation of Ma's study. First, food and trace element intakes were complicated, and they interacted with each other. It is impossible to adjust for all nutrition factors and trace elements in individual studies. Second, the commonly used Food Frequency Questionnaire (FFQ) was not accurate in assessing the actual amount of dietary intake, and it might be easily interfered with by recall bias. Third, Ma's study did not calculate the daily intake of any potential multi-mineral supplement (such as Centrum® produced by Pfizer), which represented a relevant source of the trace element.

The liver is commonly known as an important organ in the metabolism of trace elements. However, selenium concentration was shown to be almost the same among tumor tissues, non-tumor tissues, and normal livers. The result might not be robust and stable. First, important confounding factors (dietary intake, HBV and/or HCV infection, cirrhosis, diabetes status, and BMI) were not controlled for between case and control groups. Second,

sample size was too small, and further study was still needed to address this problem.

High selenium concentrations in toenail, whole blood, and serum samples were related to a lower risk of HCC, and the protective effect seemed to be strengthened by increasing levels in serum concentration. The biological functions of selenium are mainly mediated by selenium-containing proteins (selenoproteins), which contain at least one selenocysteine (Sec). Although the identification and functions of many selenoproteins remain unknown, there has been significant progress in characterizing some selenoproteins and in understanding their physiological functions. Single-nucleotide polymorphisms (SNPs) in selenoprotein genes can alter the concentration and function of selenoproteins. SNPs in selenoprotein genes have been reported to be associated with risk for various cancers. Polymorphisms of the glutathione peroxidase 1 (GPx-1) gene, which codes for a selenium-containing protein, have been implicated in the development of head and neck, lung, and breast cancers (42,43). Polymorphisms in the GPx2, GPx4 and selenoprotein P (SePP) genes have been found to be associated with colorectal cancer (44,45), whereas 15 kDa selenoprotein (Sep15) gene polymorphisms may increase lung cancer risk in smoking individuals (46). Selenoprotein S (SEPS) polymorphisms might influence susceptibility to gastric cancer (47). Polymorphisms in the genes coding for SEPP and mitochondrial superoxide dismutase have synergic effects in the development of prostate cancer (48). A novel study investigating the underlying pathway showed that decreased selenium concentrations resulted in accumulation of lipid peroxides. This led to enhanced activator protein 1 (AP-1) activation, and consequently to elevated expression of vascular endothelial growth factor (VEGF) and interleukin 8 (IL-8), which accelerated the growth of HCC (49).

Based on a compelling preclinical rationale, selenium supplementation might be considered as a promising treatment for cancer patients with low selenium concentrations. A multicenter, double-blind cancer prevention trial (Nutritional Prevention of Cancer Study Group, NPC trial) showed that selenium treatment (200 micrograms daily) significantly reduced total cancer incidence and the incidences of lung, colorectal, and prostate cancers (50). A follow-up study continued to show a significant protective effect on the overall incidence of prostate cancer; however, the effect was restricted to those with low serum levels of selenium (51). In another randomized, placebo-controlled trial, selenium supplementation (200 μg daily) did not prevent colorectal adenomas. However, the recurrence of adenoma can be reduced by 18% with selenium supplementation (52). The above results were inconsistent with two novel phase-III trials (ECOG 5597 and the SELECT study). Selenium supplementation (200 μg daily) in patients with resected stage-I non-small-cell lung carcinoma had no benefit over placebo in the prevention of second primary tumors (ECOG 5597) (53). Similarly, neither selenium (200 micrograms daily from L-selenomethionine) nor vitamin E, alone or in combination, could reduce the risk of prostate cancer (54). Scientists and clinicians should reconfirm the role of selenium supplementation in more individualized trials before new public health recommendations can be made.

There are several strengths to the present study – a) only nine studies covering toenail and blood samples were included in previous meta-analyses. The present study included 14 studies after a comprehensive and systematic search of the literature, which covered selenium concentrations in dietary intake, tissue, toenail, and blood samples. With the available evidence and an enlarged number of studies to date, we have enhanced statistical power to detect any associations between selenium

concentration and the risk of HCC; b) although few studies were included, we presented the dose-response data showing that an increase in serum selenium concentrations was significantly related with lower risk of HCC (3). The analysis process was normative. We performed sensitivity analyses and subgroup analyses to investigate heterogeneity across studies, and a further trim-and-fill analysis to verify the results concerning publication bias.

This meta-analysis has limitations that affect interpretation of the true results. First, all studies in this meta-analysis used a nested case-control study or case-control study design, which is more susceptible to recall and selection biases. Second, there is substantial heterogeneity across studies. Heterogeneity was likely due to unmeasured confounding factors and to misclassified exposure to selenium and/or selenium species, including HBV and HCV infection, cirrhosis, alcohol consumption, smoking, DM, and BMI. Individual studies were adjusted for these potential confounders in an inconsistent way. Third, we did not have sufficient information to perform a subgroup analysis, which might affect the stability of the results due to heterogeneity across studies. Dose-response data were reported in only five studies. Data from different sources of selenium concentration varied from each other, so they could not be present without being pooled together in one dose-response meta-analysis.

CONCLUSIONS

Our meta-analysis of observational studies provided evidence that selenium concentration in toenail, whole blood, and serum was inversely associated with HCC risk. Increasing concentrations in serum selenium were related with a lower risk of HCC. However, the results obtained for dietary intake and tissues, which included few studies, did not reach statistical significance. Given the small number of studies included in this meta-analysis,

its limited details, and the non-randomized or controlled study designs, further prospective cohort studies with a larger sample size and a more accurate assessment of baseline characteristics, in addition to being well-controlled for confounders, are needed to confirm the effect of selenium concentration on HCC risk.

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PRISMA 2009 Flow Diagram

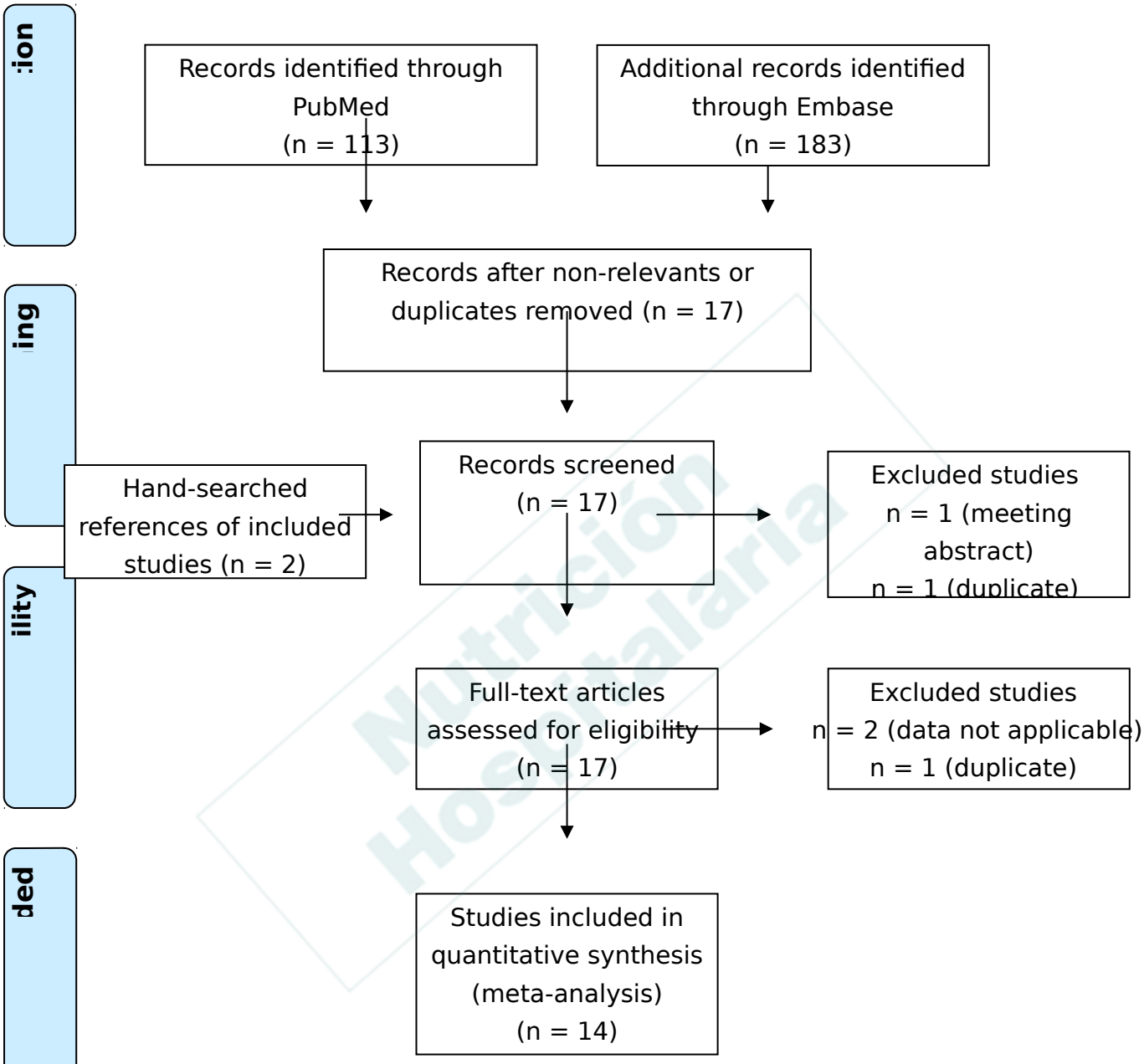
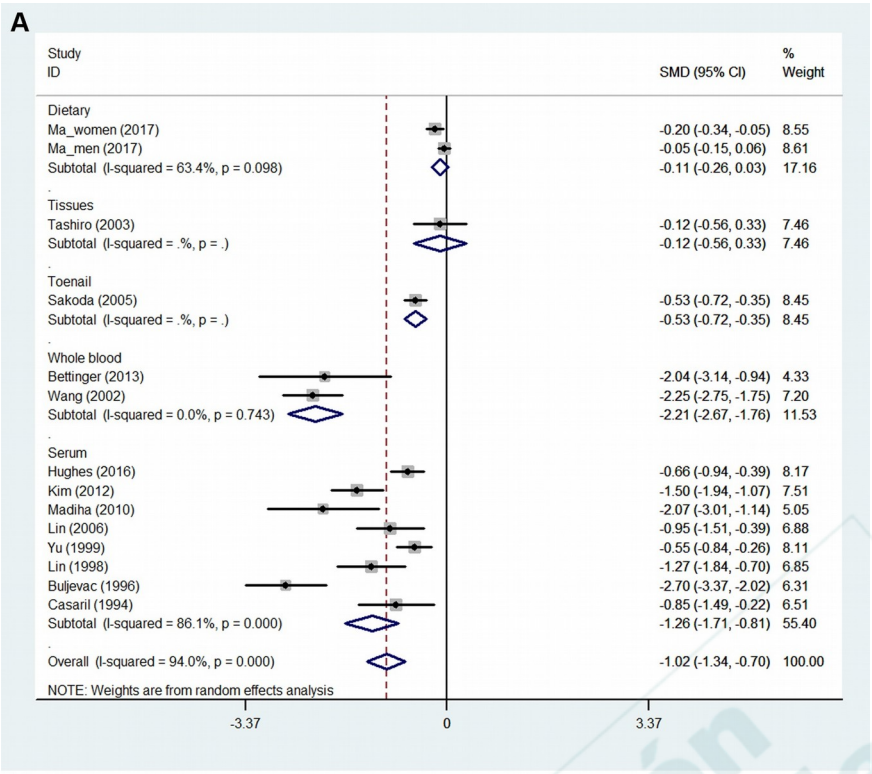
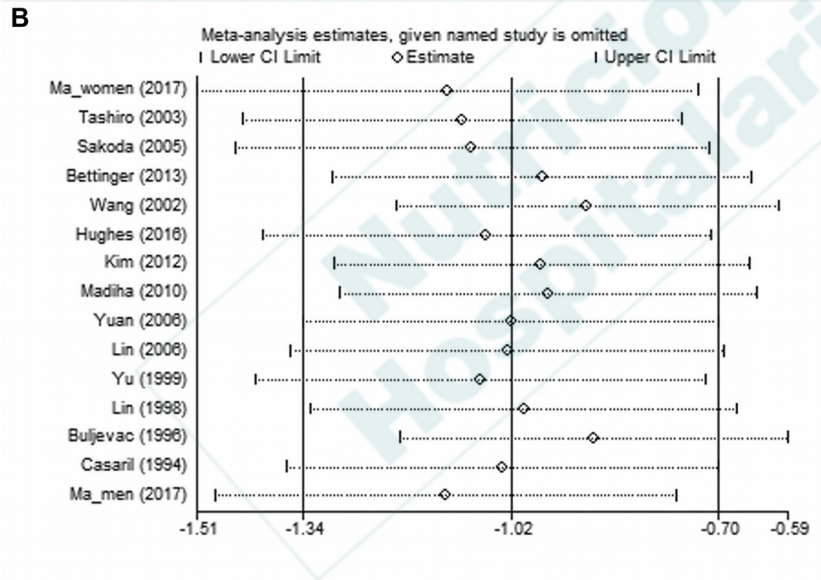
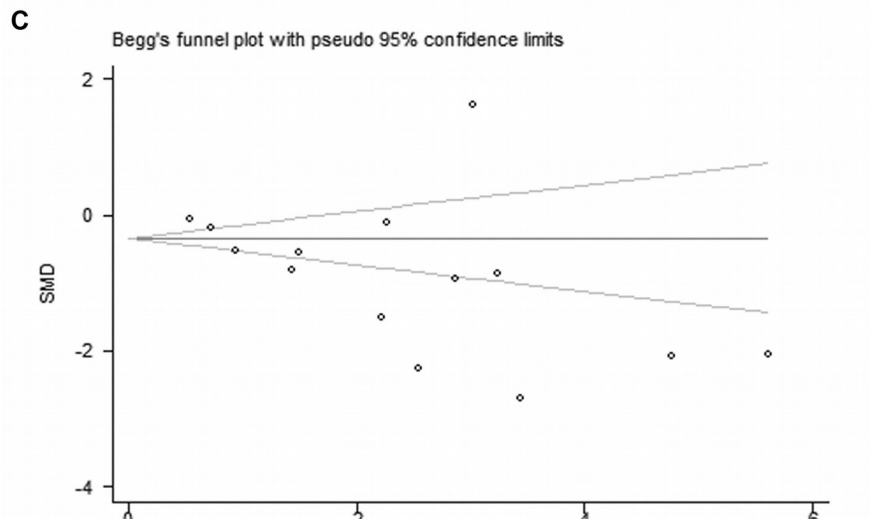


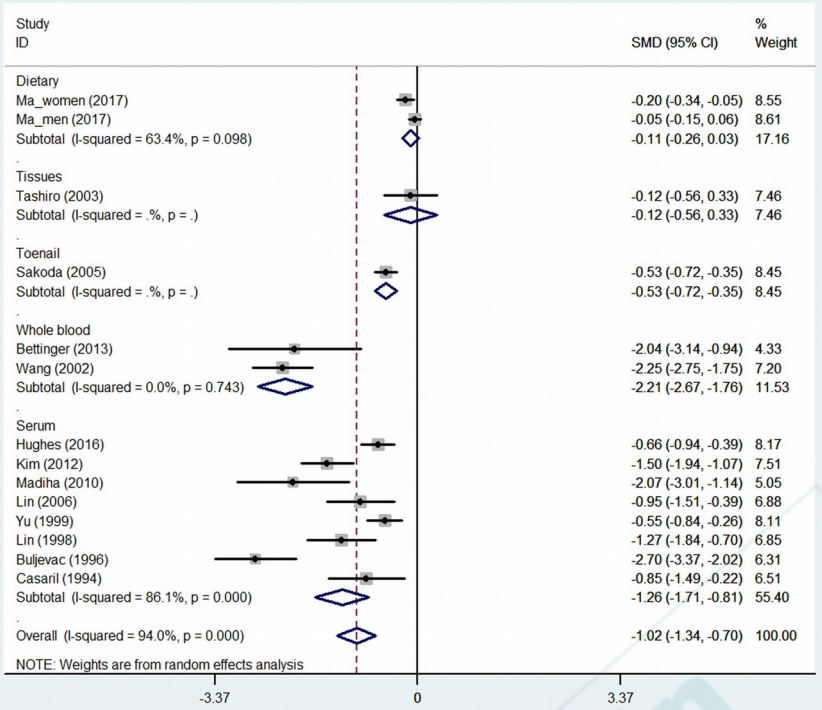
Fig. 1. Flow chart showing the selection process of the studies included in the meta-analysis.


A
Study
ID
SMD (95% CI)
%
Weight
Dietary
Ma_women (2017) -0.20 (-0.34, -0.05) 8.55
Ma_men (2017) -0.05 (-0.15, 0.06) 8.61
Subtotal (I-squared = 63.4%, p = 0.098) -0.11 (-0.26, 0.03) 17.16
Tissues
Tashiro (2003) -0.12 (-0.56, 0.33) 7.46
Subtotal (I-squared = .%, p = .) -0.12 (-0.56, 0.33) 7.46
Toenail
Sakoda (2005) -0.53 (-0.72, -0.35) 8.45
Subtotal (I-squared = .%, p = .) -0.53 (-0.72, -0.35) 8.45
Whole blood
Bettinger (2013) -2.04 (-3.14, -0.94) 4.33
Wang (2002) -2.25 (-2.75, -1.75) 7.20
Subtotal (I-squared = 0.0%, p = 0.743) -2.21 (-2.67, -1.76) 11.53
Serum
Hughes (2016) -0.66 (-0.94, -0.39) 8.17
Kim (2012) -1.50 (-1.94, -1.07) 7.51
Madiha (2010) -2.07 (-3.01, -1.14) 5.05
Lin (2006) -0.95 (-1.51, -0.39) 6.88
Yu (1999) -0.55 (-0.84, -0.26) 8.11
Lin (1998) -1.27 (-1.84, -0.70) 6.85
Buljevac (1996) -2.70 (-3.37, -2.02) 6.31
Casaril (1994) -0.85 (-1.49, -0.22) 6.51
Subtotal (I-squared = 86.1%, p = 0.000) -1.26 (-1.71, -0.81) 55.40
Overall (I-squared = 94.0%, p = 0.000) -1.02 (-1.34, -0.70) 100.00
NOTE: Weights are from random effects analysis
-3.37
0
3.37


B
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Ma_women (2017)
Tashiro (2003)
Sakoda (2005)
Bettinger (2013)
Wang (2002)
Hughes (2016)
Kim (2012)
Madiha (2010)
Yuan (2006)
Lin (2006)
Yu (1999)
Lin (1998)
Buljevac (1996)
Casaril (1994)
Ma_men (2017)
-1.51
-1.34
-1.02
-0.70
-0.59


C
Begg's funnel plot with pseudo 95% confidence limits
SMD
2
0
-2
-4

A


Study ID
SMD (95% CI)
% Weight
Dietary
Ma_women (2017) -0.20 (-0.34, -0.05) 8.55
Ma_men (2017) -0.05 (-0.15, 0.06) 8.61
Subtotal (I-squared = 63.4%, p = 0.098) -0.11 (-0.26, 0.03) 17.16
Tissues
Tashiro (2003) -0.12 (-0.56, 0.33) 7.46
Subtotal (I-squared = .%, p = .) -0.12 (-0.56, 0.33) 7.46
Toenail
Sakoda (2005) -0.53 (-0.72, -0.35) 8.45
Subtotal (I-squared = .%, p = .) -0.53 (-0.72, -0.35) 8.45
Whole blood
Bettinger (2013) -2.04 (-3.14, -0.94) 4.33
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Serum
Hughes (2016) -0.66 (-0.94, -0.39) 8.17
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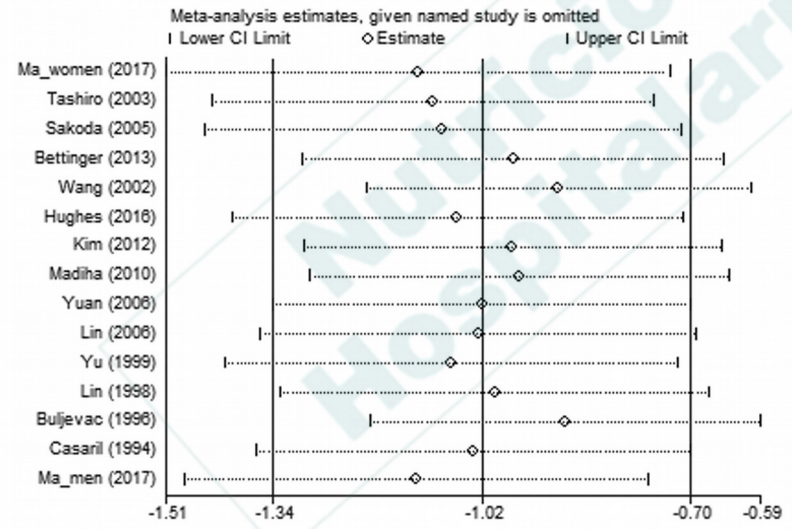
Casaril (1994) -0.85 (-1.49, -0.22) 6.51
Subtotal (I-squared = 86.1%, p = 0.000) -1.26 (-1.71, -0.81) 55.40
Overall (I-squared = 94.0%, p = 0.000) -1.02 (-1.34, -0.70) 100.00
NOTE: Weights are from random effects analysis
-3.37
0
3.37

B


Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Ma_women (2017)
Tashiro (2003)
Sakoda (2005)
Bettinger (2013)
Wang (2002)
Hughes (2016)
Kim (2012)
Madiha (2010)
Yuan (2006)
Lin (2006)
Yu (1999)
Lin (1998)
Buljevac (1996)
Casaril (1994)
Ma_men (2017)
-1.51
-1.34
-1.02
-0.70
-0.59

C

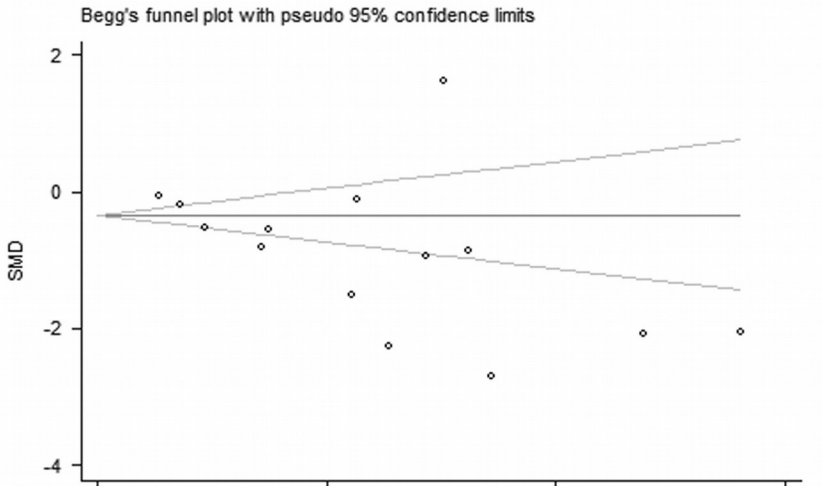

Begg's funnel plot with pseudo 95% confidence limits
SMD
2
0
-2
-4

Fig. 2. A. Forest plot examining the association of selenium levels in various samples and hepatocellular carcinoma risk. SMD: standardized mean deviation. B. Sensitivity analysis by removing one study at a time and calculating the overall homogeneity and effect size. C. Funnel plots examining the association of selenium levels in various samples and hepatocellular carcinoma risk. Begg’s test (p = 0.155), Egger’s test (p = 0.022). SMD: standardized mean deviation.

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Table I. Characteristics of the 14 studies included

Author (Refs.)	Year/ Location	Study design	Cases (n)	Controls (n)	Sample source	Selenium level (X ± SD) Case	Control	NOS
Ma (20)	2017/China	NCC (women)	192	72,593	Dietary μg/d	40.8 ± 14.5	44.2 ± 17.3	9
		NCC (men)	344	59,636		49.1 ± 17.2	50.0 ± 19.0	
Tashiro (21)	2003/Japan	CC	23	123	Tissues μg/g	1.51 ± 1.26	1.66 ± 1.26	7
Sakoda (27)	2005/China	NCC	166	394	Toenail ppm	3.1 (1.5-3.6)	3.5 (1.7-4.4)	8
Bettinger (35)	2013/Germany	CC	10	10	Whole blood μg/L	84.7 ± 16.4	117.5 ± 15.7	6
Wang (38)	2002/China	CC	51	50	Whole blood μg/L	180 ± 20	280 ± 60	7
Hughes (25)	2016/Europe	NCC	106	106	Serum μg/L	71.3 (41.3-105.9)	85.2 (55.3-117.5)	9
						73.6 ± 19.64 †	86.4 ± 18.91 †	
Kim (36)	2012/Korea	CC	30	120	Serum ug/L	67.47 ± 14.30	108.38 ± 29.5	7
Madiha (41)	2010/Egypt	CC	20	10	Serum μg/L	47.3 ± 10.5	67.3 ± 7.55	7
Yuan (26)	2006/China	CC	213	1087	Serum μg/dL	10.9 (p = 0.58) ‡	10.9	9
Lin (37)	2006/China	CC	18	50	Serum μg/L	108.5 ± 21.8	129.0 ± 21.5	7
Yu (28)	1999/China	CC	69	138	Serum μg/L	131.6 ± 30.9	150.2 ± 35.2	8
Lin (39)	1998/China	CC	51	19	Serum μg/L	106.0 ± 17.7	126.4 ± 10.1	7
Buljevac (40)	1996/Croatia	CC	10	248	Serum g/L	42.00 ± 10.59	66.79 ± 9.13	7

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Table II. Subgroup analysis of selenium levels in various samples and hepatocellular carcinoma risk

Subgroup	References	SMD (95% CI)	Tests for heterogeneity	
			I^2 (%)	p-value
Geographical region				
Asia	20, 21, 27, 28, 36-39	-0.77 (-1.11, -0.43)	94.2	< 0.001
Europe	25, 33, 35, 40	-1.52 (-2.52, -0.52)	91.1	< 0.001
Africa	41	-2.07 (-3.01, -1.14)	NA	NA
Study quality				
NOS ≥ 8	20, 25, 27, 28	-0.38 (-0.61, -0.14)	88.9	< 0.001
NOS < 8	21, 33, 35-41	-1.49 (-2.06, -0.93)	87.8	< 0.001
Study design				
NCC	20, 25, 27	-0.34 (-0.60, -0.08)	90.4	< 0.001
CC	21, 28, 33, 35-41	-1.39 (-1.91, -0.86)	89.5	< 0.001
Sample size				
More than 50	20, 25, 27, 28, 38, 39	-0.71 (-1.06, -0.37)	94.5	< 0.001
Less than 50	21, 33, 35-37, 40, 41	-1.42 (-2.10, -0.74)	88.2	< 0.001
Overall	20, 21, 25, 27, 28, 33, 35-41	-1.02 (-1.34, -0.70)	94.0	< 0.001

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