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Serum Biomarkers of Iron Status and Risk of Primary Liver Cancer: A Systematic Review and Meta-Analysis

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Title: Serum biomarkers of iron status and risk of primary liver cancer: A systematic review and meta-analysis.

Short title: Serum iron status and liver cancer

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Authorship statement

KTT did the search strategy. CRC and KTT screened for the articles. KTT and CRC conducted statistical analysis. CRC acted as study supervisor. KTT wrote the manuscript. HGC, RSM, KTT, and CRC critically revised the manuscript for important intellectual content. All co-authors agreed the final manuscript.

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UNSTRUCTURED ABSTRACT

Hereditary hemochromatosis, a disease which causes iron overload, has been shown to increase liver cancer risk but the association between serum iron levels within non-hemochromatosis population and liver cancer risk is unclear. We investigated this association by conducting a systematic review and meta-analysis. Medline, Embase and Scopus were searched to identify articles published up to January 2019. The search incorporated terms for liver cancer (hepatocellular and cholangiocarcinoma) and for serum iron (iron, ferritin, and transferrin). Briefly, nested case-control or cohort studies were included if they recorded a measure of iron, prior to diagnosis, and contained liver cancer patients and controls. Meta-analysis techniques were used to calculate pooled hazard ratios (HRs) and investigate heterogeneity between studies. Nine relevant studies were identified. There was evidence of an association between high serum ferritin and primary liver cancer risk (6 studies, HR 1.49, 95% CI 1.13, 1.96) and high serum iron and primary liver cancer risk (3 studies, HR 2.47 95% CI 1.31, 4.63). However, these associations were subject to heterogeneity ($I^2=62\%$, $p=0.02$ and $I^2=80\%$, $p=0.007$ respectively). In conclusion, we found some evidence that increased iron levels was associated with primary liver cancer. The cause of this association merits additional research.

Keywords

Ferritin, hepatocellular carcinoma, iron, liver cancer, meta-analysis.

Introduction

Primary liver cancer (which includes hepatocellular carcinoma and intrahepatic cholangiocarcinoma) is the fifth most common cancer in men, and the ninth, in women(1). The prognosis for liver cancer is poor and it is the second leading cause of cancer death worldwide(1). Therefore investigating biomarkers that reflect liver health to allow early detection of liver cancer is of importance and recently the potential of iron biomarkers has received attention.

Iron is an essential element in the human body. It plays a pivotal role in hemoglobin and myoglobin formation, enzyme function, and is a key component in immune cell proliferation(2). Iron status is measured using serum ferritin, serum iron, serum transferrin, transferrin saturation, and total iron-binding capacity (TIBC). Iron deficiency is one of the most common nutritional deficiencies worldwide (3) but there have also been concerns about the potential adverse effects of excess iron. In 2016, a meta-analysis(4) of 24 studies showed that a common polymorphism (C282Y) of hemochromatosis, a genetic disease causing marked iron overload, was associated with a marked 55% increase in hepatocellular carcinoma (pooled HR=1.55, 95% CI 1.12, 2.14). Preclinical studies have shown that high iron levels enhance tumor cell growth in human liver cancer cell lines(5). Also, in liver cancer animal models, mice on an iron restricted diet (5 mg iron/kg diet) had reduced tumor size than mice on a normal iron diet (312 mg iron/kg diet), suggesting that tumor growth is promoted in iron-rich conditions(6).

Evidence from hemochromatosis and laboratory studies suggest that high iron levels could be associated with liver cancer risk in humans. However, few epidemiological studies investigating iron levels with liver cancer risk have been conducted in humans who are not

genetically predisposed to have abnormal iron status. The results of these studies have been inconsistent, with some studies reporting significant increased risks of liver cancer for high iron status(7), whilst others have not(8). Furthermore, there has not been any attempt to systematically review the evidence. Therefore, our aim was to determine the association between iron levels and liver cancer risk by conducting a systematic review and meta-analysis.

Methods

Search strategy

The systematic review and meta-analysis was conducted following the PRISMA guidelines(9). We searched Medline, Embase, and Scopus for studies (cohort and case-control) investigating the association between serum biomarkers of iron status and liver cancer risk up to January 2019. The Embase search included terms for liver cancer (including hepatocellular cancer, biliary tract cancer, hepatoma and cholangiocarcinoma) and blood iron (including iron, ferritin, transferrin and total iron-binding capacity (TIBC)) and was limited to studies in human. There were no language restrictions. The full Embase search is shown in online Supplementary table A.1. Similar searches were conducted in Medline and Scopus. Finally, the reference lists of included articles were also screened.

Study selection

The inclusion criteria were: 1) cohort or case-control studies which identified hepatobiliary cancer (liver or bile duct cancer); 2) studies could compare hepatobiliary cancer to any of these controls: hepatobiliary cancer free, liver cirrhosis, hepatitis B or hepatitis C; 3) studies must record one of the following blood iron biomarkers: serum ferritin, serum iron, serum transferrin, transferrin saturation, or total iron-binding capacity. Studies were excluded if: 1) iron was measured solely in tissue or determined from dietary intake; 2) iron was measured in an anemic population; 3) studies included less than ten cases of hepatobiliary cancer; 4) studies solely assessed survival or recurrence of hepatobiliary cancer; 5) studies solely measured iron at time of liver cancer diagnosis (as liver cancer patients may have altered iron levels). Two reviewers (KT and CC) independently screened the articles identified by the searches. Initially, titles and abstracts were screened to remove obviously irrelevant articles.

Full texts of the remaining articles were then independently evaluated against the inclusion and exclusion criteria.

Data extraction and quality assessment

Two reviewers (KT and CC) independently extracted the following data from the included studies: the first author's name, year of publication, study design, country, source of cohort/controls (including years), source of cases (including ascertainment), duration of follow-up, exposure information (including type of iron recorded and timing of iron measurement), and confounders adjusted for in analysis used in the meta-analysis. The quality of included studies was evaluated using the Newcastle Ottawa scale (NOS)(10). A score was determined out of 9 for each study. This process was independently performed by two reviewers (KT and CC).

Statistical analysis

An estimate (and standard error) of the association between blood iron measures (in categories used in the original studies) and hepatobiliary cancer risk was extracted from the included studies where possible. By necessity, odds ratios (ORs, 3 studies)(11)(7)(12) and hazard ratios (HRs, 6 studies)(13)(14)(15)(8)(16)(17) were combined to allow a pooled estimate to be determined, however ORs should approximate HRs as liver cancer was relatively rare(18). Random effects models(19) were used to pool the overall estimate as heterogeneity between studies was anticipated. Statistical heterogeneity among studies was evaluated by χ^2 test and I^2 statistics(20). One study(7) reported the estimate and p value for the association but not the 95% CI, so we determined the standard error based upon the p value. In another study(12) an OR and standard error was determined from the number of cases and controls in the low and high iron levels groups. In one study(14), the HRs presented

separately for males and females were combined using a fixed effects model before entry into the meta-analysis. In most studies, the lowest blood iron level category was the reference category but two studies used the second lowest category as their reference level(11)(15). In one study(13) a HR was calculated directly from the regression coefficients of a cox regression model based upon a hypothetical comparison of 200ng/ml to 20ng/ml of serum ferritin. Subgroup analysis was further performed to check whether associations differed by study characteristics such as study design, ethnicity, NOS score or background risk. A sensitivity analysis was conducted using an estimate of the association between iron and liver cancer based upon average iron, over the study period, rather than baseline iron as used in the main analysis(7). Funnel plots were produced to investigate the potential for publication bias.

Results

Description of selected studies

From the search strategy we identified 3482 articles from Medline, Embase, and Scopus database (Figure 1). After removing duplicates, 2435 articles remained for title and abstract screening, of which 91 articles were selected for full text assessment. We excluded 81 articles for reasons outlined in Figure 1. Finally, the meta-analysis included 10 publications however only 9 independent studies (14)(15)(8)(16)(7)(12)(13)(11)(17) were reported, because two studies Aleksandrova et al.(21) and Jenab et al. (11) were based upon the same cohort and therefore only one(11) could be included, though study characteristics were was extracted from both.

The included studies contained seven cohort studies, and two nested-case control studies capturing 1589 incident liver cancer cases (Table 1). Five of the studies were from Asian countries. Four of studies were based upon patients with liver diseases. In six studies the main outcome was primary hepatocellular carcinoma whilst the rest captured any primary liver cancer. In all but two studies, cancer was confirmed by active follow-up or national cancer registration data. Among these studies, serum ferritin was explored in six studies; serum iron was explored in three; serum transferrin was explored in two; transferrin saturation and TIBC for each was explored in one study. Half of the studies had a NOS quality score of 6 or less out of 9 (Table 1). Details of the NOS assessment for individual studies are presented in Supplementary table A.2.

Overall analysis of serum ferritin and liver cancer

The forest plot of the association between serum ferritin and liver cancer risk is presented in Figure 2. The HR of liver cancer in the high serum ferritin category was 1.49 compared with the low serum ferritin category (combined HR 1.49, 95% CI 1.13, 1.96) but there was marked heterogeneity between studies ($I^2 = 62\%$, $p = 0.02$). In addition two studies reported the mean serum ferritin prior to diagnosis in a liver cancer and control group. Aleksandrova et al.(21) observed a difference in mean ($p < 0.001$) in the liver cancer compared with the control group (mean = 323.8 $\mu\text{mol/L}$, standard deviation (sd) = 56.0, and mean = 156.2 $\mu\text{mol/L}$, sd = 166.8, respectively). Stevens et al.(13) also observed a difference in mean ($p < 0.05$) in the liver cancer compared with the control group (mean = 121.4 ng/ml, range 8 to 381 and mean = 99.5 ng/ml, range 5 to 342, respectively). The study by Uchino et al.(14) reported the association by sex and showed little evidence of a difference in the association between high versus low serum ferritin and liver cancer in women (HR = 1.64, 95% CI 0.70, 3.84) or men (HR = 1.48, 95% CI 0.67, 3.30). Stevens et al.(13) only included males and found little evidence of an association between high serum ferritin and liver cancer (HR = 1.41, 95% CI 1.00, 1.99).

Subgroup analysis for ferritin and liver cancer

The main findings were little altered in various subgroup analyses (see Table 2). For instance, similar estimates were observed when restricting the analysis to cohort studies, studies based upon liver disease populations, sex, and studies conducted in Asia.

Other measures of iron biomarkers

Three studies investigated serum iron and risk of liver cancer, see Figure 2. The pooled HR of liver cancer in the high serum iron category was 2.47 compared with the low serum iron

category (95% CI 1.31, 4.63). There was a high and significant heterogeneity among studies ($I^2 = 80\%$, $p < 0.05$) (Figure 2). Aleksandrova et al.(21) reported the difference in mean serum iron ($p < 0.0001$) prior to diagnosis in the liver cancer group compared with the control group (mean=21.5 $\mu\text{mol/L}$, sd= 8.9, and mean=18.4 $\mu\text{mol/L}$, sd=5.8, respectively). Wen et al.(15) reported similar associations between high versus low serum iron and liver cancer risk in women (HR=3.39, 95% CI 2.22, 5.18) and men (HR=3.24, 95% CI 2.31, 4.53).

One study (Gaur et al.)(8) investigated TIBC, in which the HR was 1.23 (95% CI 0.75-2.01) in the liver cancer group compared with the control group. Another study (Ellervik et al.)(16) investigated transferrin saturation and observed a HR of 5.9 (95% CI 1.8, 20) in the liver cancer group compared with the control group. Ellervik et al.(16) also reported associations by sex, observing a HR for high versus low transferrin saturation of 9.6 in women (95% CI 1.3, 73) and 4.4 in men (95% CI 1.1, 20).

Two studies reported the mean serum transferrin prior to diagnosis in the liver cancer group and the control group. Stevens et al.(13) observed a difference in mean ($p > 0.05$) in the liver cancer compared with the control group (mean=286.2 mg/dL, range 129 to 579, and mean=268.9 mg/dL, range 74 to 579, respectively). Aleksandrova et al.(21) reported a difference in mean ($p = 0.74$) in the liver cancer and the control group (mean=242 mg/dL, sd=42 and mean=240, sd=30, respectively).

Publication bias

A visual inspection of the funnel plot for ferritin levels and liver cancer revealed some asymmetry, which could reflect publication bias (see Figure 3).

Discussion

Our systematic review and meta-analysis demonstrated some evidence of an increased risk of primary liver cancer with high iron levels as measured by serum ferritin or serum iron, based upon cohort studies and nested case-control studies.

A strength of our study is that this is the first systematic review and meta-analysis of the association between serum iron and liver cancer risk. Secondly, the study included some large cohort and nested case-control studies, with long follow-up ranging from 5 to 17 years. Thirdly, as we excluded studies which recorded iron at the time of liver cancer diagnosis the risk of reverse causation, caused by changes in iron levels following liver cancer diagnosis, will be reduced.

The systematic review has a number of weaknesses. All the included studies were observational and therefore the causal relationship between high iron levels and risk of liver cancer cannot be confirmed. There were relatively small numbers of studies and therefore even in pooled analyses the estimate of the associations had relatively wide confidence intervals. The reporting of the studies made it difficult to extract estimates which were consistently adjusted for confounding factors. Furthermore, the quality score of many of the included studies was low mainly because the original studies did not adjust for a number of potential confounders including infection, chronic kidney disease, or alcoholism(22) but also because some studies had limited generalizability for instance because they were restricted to specific hospitals rather than being population-based. A further weakness is that we had limited data on cholangiocarcinoma. For instance, all six studies included in the analysis of serum ferritin were based upon

hepatocellular carcinoma. Finally, the funnel plot of the association between serum ferritin and liver cancer risk was asymmetrical which could reflect publication bias and we therefore could have over estimated the association between serum ferritin and liver cancer risk. However, this funnel plot is difficult to interpret because there were fewer than 10 studies, recommendations suggest greater numbers are required(23), and there are other reasons for funnel plot asymmetry(24) besides publication bias.

Our review findings provide insight into potential etiology, however the cause of the increased risk of liver cancer with high circulating iron levels is unknown. It is accepted that accumulation of iron within tissue is carcinogenic, and high levels have been noted in hepatocellular carcinoma(25). The most commonly cited mechanism by which excess iron may promote carcinogenesis is through DNA damage from the production of reactive oxygen species, particularly hydroxyl radical(26). Excessive oxidative stress is also fundamental to alcohol-related hepatocarcinogenesis(27). Iron overload is a proposed mechanism by which alcohol-related liver cancer may develop(27), and so alcohol intake is an important confounder to consider in the interpretation of our review results. Cirrhosis can be a consequence of both iron overload and excessive alcohol consumption, and in itself promotes carcinogenesis by fibrogenesis, cell damage, and mutagenesis(28). Only three studies(15)(16)(17) in this review adjusted for alcohol intake in the association between iron status and liver cancer risk, however it is notable that two of them(15)(16) continued to see significant direct associations. This suggests that additional mechanisms independent of alcohol could explain any potential association between iron status and liver cancer risk. Recent evidence indicates a role for the tumor suppressor gene, p53, in iron homeostasis (including serum iron levels) to

influence liver cancer risk(29). p53 mutation was also significantly associated with reduced expression of ISCU (iron-sulfur cluster assembly enzyme), which in turn was highly prevalent in tissue microarrays from several hundred human hepatocellular carcinoma samples evaluated as part of The Cancer Genome Atlas(29), pointing to a new p53-ICSU pathway in the development of this tumor.

Clarifying the association between iron and liver cancer risk is of importance because, if high levels of iron were shown to increase liver cancer risk, it would be possible to intervene to reduce iron levels and therefore decrease cancer risk. The most common cause of iron overload is hereditary hemochromatosis. Other causes include iron-loading anemia such as thalassemia, blood transfusions, chronic hepatic disorders such as alcoholic liver disease and chronic viral hepatitis(30), and excessive iron replacement through both the enteral or parenteral route(31). Intervention is generally in the form of phlebotomy in hemochromatosis patients(32), although chelating agents are an option in the management of iron-loading anemia(30). Furthermore, iron supplementation for anemia is common, but should high levels of iron be shown to increase liver cancer risk, this would underline the importance of assessing iron status prior to replacement therapy, adhering to guidelines(33) and stopping iron supplementation once anemia is resolved.

Further prospective studies, which are population-based, with long term follow-up and collecting information on a wide range of confounders are required to further investigate the association between iron and liver cancer risk.

In conclusion, our review demonstrated some evidence that high iron levels are associated with primary liver cancer risk. Further high quality studies are required to confirm this association.

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Figure 1: Flow diagram for studies selecting progress

Figure 2: Forest plot of iron biomarkers and risk of liver cancer

*Also included additional confounders: systolic blood pressure, total cholesterol, hemoglobin level, physical activity.

Figure 3: Funnel plot of serum ferritin and liver cancer

Table 1. Characteristics of included studies investigating the association between serum iron and liver cancer risk.

First author, Year	Design	Country	Cohort			Cases					Exposure		NOS score
			Source	Years	N*	Cancer type	N*	Ascertainment	End of f- up	Mean f-up	Timing	Types of iron	
Bian, 2018 (17)	Cohort	USA	Liver Disease Prevention Center at Thomas Jefferson University Hospital	88-08	1,152	HCC	96	Clinical diagnosis, imaging techniques, blood markers.	08	Not stated	Baseline	Ferritin	8
Uchino, 2016 (14)	Cohort	Japan	Chronic hepatitis C patients from University of Tokyo Hosp.	05-06	487	HCC	72	Active follow-up of including ultrasonography and CT.	12	Mean 5 yrs	Baseline	Ferritin	6
Aleksandrova,2 015 (21) & Jenab,2013 (11)	Nested CC	Europe	EPIC study	92-00	250	HCC	125	Not stated.	06	Mean 8 (6-9) yrs	Baseline	Iron, Ferritin, Transferrin	8
Wen, 2014 (15)	Cohort	Taiwan	MJ Health Management Institution	97-08	309,443	Liver cancer	989	National cancer registry	08	Median 7 yrs	Baseline	Iron	9
Gaur, 2012 (8)	Cohort	Sweden	General population laboratory test database	85-96	220,503	Liver cancer	139	Swedish National Cancer Registry	02	Mean 11 yrs	Baseline	Iron, TIBC	9
Ellervik, 2011 (16)	Cohort	Denmar k	The Copenhagen City Heart Study	91-94	8039	Liver/ biliary tract cancer	47	National cancer registry	07	14 (13- 15) years	Not stated	Transferrin saturation	8
Kato 2007 (7)	Cohort	Japan	Chronic hepatitis C from Sapporo Medical University Hospital	94-96	75	HCC	17	Active follow-up of including ultrasonography and CT.	06	Up to 12 yrs	Baseline	Ferritin	6
Hann, 1989 (12)	Cohort	Korea	Chronic liver diseases from Seoul National University Hosp.	67-78	162	HCC	34	Active follow-up of including ultrasonography and CT.	84	2-17 yrs	First 8 months	Ferritin	6
Stevens, 1986 (13)	Nested CC	China	Male government workers	75-78	128	PHC	70	Not stated	83	3-79 months	Baseline	Ferritin, Transferrin	4

Abbreviations: CC, case control; CT, computed tomography scan; f-up, follow-up; HCC, Hepatocellular carcinoma; PHC, Primary hepatocellular carcinoma; NOS score, Newcastle Ottawa Scale score; TIBC, total iron binding capacity; yrs, years.

*Numbers used in analysis of iron and liver cancer risk.

Table 2: Subgroup analysis for the association of serum ferritin and liver cancer

Subgroup	Number of studies	Pooled estimate HR (95%CI)	P value	Heterogeneity p value (I ²)
Main analysis	6	1.49 (1.13, 1.96)	0.004	0.02 (62%)
Study design				
Cohort studies	4	1.28 (1.01, 1.62)	0.04	0.21 (34%)
Nested case-control studies	2	2.05 (0.89, 4.75)	0.09	0.03 (79%)
Source of population				
Liver diseases population	4	1.28 (1.01, 1.62)	0.04	0.21 (34%)
Healthy population	2	2.05 (0.89, 4.75)	0.09	0.03 (79%)
Sex				
Male	3	1.43 (1.11, 1.85)	0.006	0.99 (0%)
Female	2	1.53 (0.73, 3.19)	0.26	0.75 (0%)
Time point of iron assessment				
Using Kato average iron	5	1.98 (1.36, 2.87)	0.003	0.12 (46%)
Ethnicity				
European	1	3.34 (1.67, 6.68)	<0.001	Not applicable
Asian	5	1.28 (1.06, 1.55)	0.009	0.25 (26%)
NOS assessment				
≥ 8 (higher quality)	2	2.10 (0.93, 4.72)	0.07	0.04 (76%)
< 8 lower quality	4	1.27 (1.02, 1.59)	0.03	0.20 (35%)

Supplementary table A.2: Newcastle Ottawa Scale assessment for individual studies

Study	Selection				Comparability		Outcome		NOS score
	Representativeness	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at baseline	Confounders adjustment*	Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Bian, 2018	0	1	1	1	2	1	1	1	8
Uchino, 2016	0	1	1	1	0	1	1	1	6
Jenab, 2013	1	1	1	1	1	1	1	1	8
Wen, 2014	1	1	1	1	2	1	1	1	9
Gaur, 2013	1	1	1	1	2	1	1	1	9
Ellervik, 2011	1	1	1	0	2	1	1	1	8
Kato, 2007	0	1	1	1	0	1	1	1	6
Hann, 1989	0	1	1	1	0	1	1	1	6
Stevens, 1986	0	1	1	0	1	0	1	0	4

*Refers to confounders used in extracted estimate of iron and liver cancer.

Supplementary table A.1: The search strategy

Embase

1. exp liver cancer/
2. exp liver tumor/
3. exp liver cell carcinoma/
4. exp bile duct cancer/
5. exp bile duct tumor/
6. exp bile duct carcinoma/
7. exp biliary tract cancer/
8. exp biliary tract tumor/
9. exp gallbladder cancer/
10. exp gallbladder tumor/
11. exp gallbladder carcinoma/
12. exp hepatobiliary system cancer/
13. exp hepatobiliary system carcinoma/
14. exp hepatobiliary system tumor/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. ((liver or hepatocellular or "bile duct" or "biliary tract" or "gall bladder" or hepatobiliary) adj5 (cancer or carcinoma or tumor or neoplasm*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
17. hepatoma.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18. cholangiocarcinoma.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
19. 15 or 16 or 17 or 18
20. exp iron/
21. exp iron blood level/
22. exp iron binding capacity/
23. exp ferritin/
24. exp ferritin blood level/
25. exp transferrin/
26. exp transferrin blood level/
27. exp heme/
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. ((iron or ferritin* or transferrin or TIBC) adj5 (serum or plasma or blood)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
30. 28 or 29
31. 19 and 30
32. limit 31 to human
33. review.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
34. 32 not 33
35. limit 34 to updatetrange="oemez(20170610-20190122]"

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