Hepcidin levels and gastric cancer risk in the EPIC-EurGast Study

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Abstract:

Hepcidin is the main regulator of iron homeostasis and dysregulation of proteins involved in iron metabolism has been associated with tumorogenesis. However, to date, no epidemiological study has researched the association between hepcidin levels and gastric cancer risk. To further investigate the relationship between hepcidin levels and gastric cancer risk, we conducted a nested case-control study (EURGAST) within the multicentric European Prospective Investigation into Cancer and Nutrition (EPIC) study. The study included 456 primary incident gastric adenocarcinoma cases and 900 matched controls that occurred during an average of 11 years of follow-up. We measured serum levels of hepcidin, serum iron, ferritin, transferrin and C-reactive protein. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of gastric cancer by hepcidin levels were estimated from multivariable conditional logistic regression models. Mediation effect of the ferritin levels on the hepcidin-gastric cancer pathway was also evaluated.

After adjusting for relevant confounders, we observed a statistically significant inverse association between gastric cancer and hepcidin levels (OR 5ng/l = 0.96, 95% CI = 0.93-0.99). No differences were found by tumor localization or histological type. In mediation analysis, we found that direct effect of hepcidin only represents a non-significant 38% (95% CI: -69%, 91%). In summary, these data suggest that the inverse association of hepcidin levels and gastric cancer risk was mostly accounted by ferritin levels. Further investigation including repeated measures of hepcidin is needed to clarify their role in gastric carcinogenesis.

INTRODUCTION

Hepcidin is a key regulator of the entry of iron into the circulation in mammals.[1]Production of hepcidin is decreased in situations demanding higher concentrations of circulating iron, such as hypoxia, anaemia, and iron deficiency, or conditions characterized by ineffective erythropoiesis such as thalassemia[1] . On the contrary, inflammation and infection cause an increase of hepcidin synthesis[2], reducing circulating iron availability by sequestration of iron in macrophages of the reticuloendothelial system, leading to hypoferremia, which is considered a defence mechanism of the human body against extracellularly proliferating pathogens[3]. Hypoferremia is a form of anaemia commonly associated with infectious and inflammatory conditions as well as cancer[4]. Subjects with high iron levels show increased levels of hepcidin, except when mutations are present in genes encoding hepcidin or in hepcidin's positive regulators[5]. Hepcidin deficiency also has been reported in patients suffering from hereditary hemochromatosis (HH), a group of genetic disorders defined by an excessive absorption of dietary iron which results in iron accumulation in the liver and other organs[6].

Cancers are frequently related to a disturbed /disrupted systemic iron homeostasis[7]. Tumour progression could be promoted through several signalling pathways, such as iron-induced cell growth and oxidative stress[8]. Following this hypothesis, one could expect to find a higher risk of developing cancer in subjects with elevated body iron stores. Disordered systemic iron homeostasis in cancer patients could be due to anomalous regulation of the hepcidin –ferroportin axis. However; the majority of the research in this field has shown inverse associations between iron stores and cancer risk[9]. In concordance with this, recently, we have found an inverse association between X and Gastric cancer risk in the EURGAST nested case control study[10].

The stomach plays a role in iron absorption and in defence against infections and recently was found that hepcidin is expressed in this organ[11]. Gastric hepcidin is located in parietal cells that are crucial for gastric acid secretion, and low hepcidin expression/secretion in the stomach is related to gastric bacterial overgrowth, and could contribute to development of peptic ulcers under stress conditions, as seen during

Helicobacter pylori infections[11]. However, to date, no epidemiological study has researched the association between hepcidin levels and cancer risk. Considering that iron dysregulation could contribute to increased cancer risk and that iron balance through the hepcidin-ferroportin complex could be involved in tumorigenesis, we aim to investigate the association between blood levels of hepcidin and risk of developing gastric cancer. Moreover, we have tested whether there is a potential mediator effect of ferritin by using mediation analysis.

MATERIAL AND METHODS

Study setting

The subjects of this nested case-control study are part of the EUR-GAST which is nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large multicentre prospective cohort including more than 500.000 men and women. Detailed information regarding EPIC methodology and rationale has been described elsewhere[12]. In summary, EPIC participants were recruited between 1992 and 2000 in 23 centres from 10 European countries. At time of recruitment each participant provided information on diet and lifestyle factors, and anthropometric data and blood samples were collected. This study was approved by the Ethical Committees at the International Agency for Research on Cancer (IARC) and in each of the EPIC centres.

Study participants

Identification of incident cancer diagnoses were based on population cancer registries (Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom). In France, Germany, Greece and Naples, a combination of methods was used and included health insurance records, cancer and pathology hospital registries, and active follow-up through study subjects. Eligible incident gastric cancer cases (C16) included cancers coded as C16 according to the 10th Revision of the International Classification of Diseases (ICD-10). Case subjects had no previous cancer, and were newly diagnosed with primary gastric cancer after their recruitment into the EPIC study through 2010 depending on the study centre. Cancer cases were also classified according to both anatomic location cardia (GCC) and non-cardia (GNCC) and

Lauren histological type (intestinal and diffuse). For each case, two randomly controls, alive and free of cancer at the time of diagnosis of the index case, and matched by centre, sex, age at baseline (±2.5 years) and date of blood collection (±45 days), were selected. From the 471 cases and 942 controls there were available biological samples for 460 cases and 905 controls. We then proceeded to exclude 4 cases and 5 controls because of biomarkers' implausible values, lipidemic samples. After all exclusions we had 456 cases and 900 controls for the analyses.

Laboratory procedures and measurements of biomarkers of iron homeostasis

Hepcidin was measured using liquid chromatography coupled to mass spectrometry. Hepcidin was extracted from the serum by liquid-liquid extraction by using an acidified organic solvent mixture, and quantified in a 1290 UHPLC Series Liquid Chromatograph coupled to a 6490 QqQ-MS/MS (Agilent Technologies). A reverse phase (RP) liquid chromatography column was used for the separation. Ionization was performed by jet stream electrospray (ESI), while QqQ operated in positive mode, working in multiple reaction monitoring (MRM) conditions. The technique uses 50 µl of serum and was performed in the Center for Omic Sciences (COS) (Tarragona, Spain). In this nested case control study the following biomarkers ere previously measured and reported (serum iron, ferritin, total iron binding capacity (TIBC) and transferrin saturation), high sensitivity C-reactive protein (hsCRP), pepsinogen 1, *Helicobacter pylori*[10]. Data from the cohort baseline questionnaire (social demographics, anthropometrics and diet), can be found elsewhere[10].

Statistical Analysis

Conditional logistic regression modelling was used to estimate the odds ratio (OR) and its corresponding 95% confidence intervals (CI) of hepcidin levels and GC, by histological subtype (intestinal and diffuse). Unconditional regression models, including the matching variables, were used to explored effect-measure modification by sex, age group, smoking status (never, ever), alcohol intake, body mass index (BMI;<25, 25-30, >30kg/m2), plasma vitamin C, hip circumference, dietary iron, dietary heme iron, serum ferritin (WHO ranges: deficiency, normal, excess), serum iron (WHO ranges: deficiency, normal, excess), and mutations for HFE gene (H63D and/or C282Y) and polymorphisms (yes, no). Likelihood ratio test (LRT)

was use to evaluate these interactions. Age groups were defined using tertiles of the age at recruitment. Cut points for alcohol intake, plasma vitamin C, dietary iron and heme iron were based on control's median. Sex-specific median cut points based on controls were used for hip circumference variable. Deficiency of ferritin referred to values under 15ng/ml, excess of ferritin represented values of ferritin higher that 200ng/ml for men and 150ng/ml for women. Values within this range were considered to be normal. Iron levels below 50µg/dl and above 120µg/dl were considered as deficiency and excess of iron respectively. Furthermore, we assessed the effect of biomarkers of iron status on GC risk according to the time elapsed from the date of blood drawing to date of incidence.

Finally, we studied the role of ferritin as a potential mediator in the pathway between hepcidin and GC. To consider ferritin as a potential mediator, the following criteria should be met: a) Hepcidin should be statistically significant associated with GC; b) Ferritin should be statistically significantly associated with hepcidin; c) the relation between ferritin and GC should be statistically significant[10] (Figure 1). Structural equation modeling was used to calculate the direct and indirect effect of hepcidin with GC controlling for the possible confounders[13]. Bootstrapping with 10,000 interactions was used to calculate the 95% CIs for all the estimated parameters. To obtain the normal distribution of hepcidin and ferritin, both variables were log2 transformed. All analyses were performed using SAS v. 9.4 (Cary, North Carolina, USA).

RESULTS

Table 1 presents the results of the logistic regression models for hepcidin and gastric adenocarcinoma overall, and by site (cardia and non-cardia) and histology (diffuse and intestinal) of the tumour. Our study included 456 gastric adenocarcinoma cases, 116 of which were GCC (25%), 236 were GNCC (52%) and for 104 cases the site was unknown (23%). We observed a statistically significant inverse association with gastric adenocarcinoma risk (OR for Q4 vs Q1 0.41, 95% CI=0.28-0.61; p for trend<0.0001). On the continuous scale, the risk decreased by 4% (95% CI =.93-0.99) for each 5ng/ml increment in hepcidin levels.

Similar results were seen for gastric subtypes associations when comparing the highest to the lowest tertiles (GCC OR=0.43, 95% CI=0.19-0.96; GNCC OR=0.47, 95% CI=0.28-0.76) and histology (intestinal OR=0.51, 95% CI=0.27-0.96; diffuse OR=0.47, 95% CI=0.25-0.89) of the tumour. None interactions between age, sex, tobacco smoking status, vitamin C levels were observed alcohol intake, body mass index (BMI <25, 25-30, >30kg/m2), plasma vitamin C, hip circumference, dietary iron, dietary heme iron, serum ferritin serum iron and mutations for HFE gene (H63D and/or C282Y) and polymorphisms (yes, no) (data not shown).

After researching the possible role of ferritin as a mediator of the effect of hepcidin on GC risk, we found that the direct effect of hepcidin represents approximately 38% (95%CI: -69%, 91%) of the total hepcidin effect although it did not reach statistical significance. The other 62% (95%CI: 9%, 169%) is obtained by the pathway hepcidin>ferritin>GC (Figure 1).

Most of our study subjects (n=289) were diagnosed with gastric adenocarcinoma after five years from blood collection, 111 subjects were diagnosed between 2 and 5 years and 56 were diagnosed within the first two years of follow-up. Associations between hepcidin levels and gastric cancer risk were only significant for cases diagnosed within the first two years (n=56) (OR 5ng/l=0.68, 95% CI=0.53-0.87) (figure 2).

DISCUSSION

In recent years, hepcidin has become the subject of great interest among the scientific community due to its pivotal role in iron homeostasis. We report for the first time the association of hepcidin with GC risk using the large prospective EPIC cohort .We have found that levels of hepcidin were inversely associated with gastric adenocarcinoma risk.

One of the possible explanations regarding the inverse association between hepcidin and gastric adenocarcinoma could be due to bleeding from early un-detected lesions, leading to depleted iron stores. Hepcidin is strongly correlated with ferritin, as they are physiologically affected by iron availability in a similar way[14]. We previously reported a weak association between serum ferritin and gastric cancer over time[32]. Our results of lag-time analysis show that the inverse association between hepcidin and gastric adenocarcinoma disappears after five years of diagnosis and it is stronger within the first two years of follow-up, which suggests reversed causation with lower levels of hepcidin induced by the cancer.

Adjustment for ferritin levels revealed that the hepcidin – inverse associated gastric cancer risk was largely dependent on the serum concentrations of ferritin, which supported the results of previous studies that demonstrate that increased stored iron stimulates hepcidin production.

Hypoferremia is a common response to systemic infections or generalized inflammatory disorders[2], since most pathogens require iron for proliferation and full virulence[15]. Hypoferremia represents a major host defense strategy and promotes a form of anaemia generally associated with infectious and inflammatory conditions as well as cancer[4,16]. Hepcidin's expression is significantly upregulated in inflammatory states, possibly due (among other factors) to the excessive production of interleukin-6[11], a known stimulus for hepcidin synthesis[21]. In our study, subjects with higher hsCRP levels, indicating higher levels of inflammation, showed increased values of hepcidin, although differences between high and low hsCRP levels were not statistically significant; furthermore, we found stronger inverse associations between hepcidin and gastric cancer in subjects with above the median hsCRP levels, although the differences were not statistically significant.

Recent research has shown hepcidin to be expressed in gastric parietal cells[11]. What is more, that hepcidin regulates acid secretion and is induced by *Helicobacter pylori* infection. Hepcidin deficiency in the stomach is related with gastric bacterial overgrowth and altered factors involved in acid secretion. Hepcidin's impact on gastric acid production suggests it might contribute to development of gastric ulcers[11]. Although gastric ulcers are probably not a cause of gastric cancer, the positive association

between the two diseases suggests common etiologic factors[17], such as atrophic gastritis induced by *Helicobacter pylori* infection. We found lower values of hepcidin in subjects with chronic atrophic gastritis, both among cases and controls. Nonetheless, assessing a potential interaction between chronic atrophic gastritis and hepcidin was hampered by small sample size of subjects suffering from this condition. We indirectly evaluated the potential effect of gastritis and atrophy using pepsinogen 1 as a proxy, but adjusting for pepsinogen 1 level did not modify the association of hepcidin with gastric adenocarcinoma (data not shown).

Our study presents several important strengths. It is the first cohort-nested case-control study on prediagnostic hepcidin concentrations in the blood and subsequent gastric adenocarcinoma risk. Also, it is the first study to report hepcidin levels in a large sample of control subjects residing in European countries.

One of the limitations of our study is that the measurement of hepcidin was based on a single blood sample. Another limitation was the information available concerning pepsinogen 1, which was only available on a small subset of participants; therefore, further analysis on the possible relation between gastric atrophy and gastric adenocarcinoma risk was restricted.

In summary, we found pre-diagnostic hepcidin concentrations to be inversely associated with subsequent gastric adenocarcinoma risk. Considering the dominant mediating effect of ferritin and the previous findings we reported on biomarkers of iron status and adenocarcinoma risk[10], reverse causation cannot be ruled out, as the inverse associations found in this study could be due to bleeding from early gastric cancer lesions. More prospective studies are needed to better elucidate the possible direct and indirect effect of hepcidin in gastric cancer risk, preferably including repeated measures.

Table 1: ORs and 95% CI for the association between gastric cancer and hepcidin (ng/ml) concentrations in the EURGAST nested-case control study

		Controls	Cases	OR (95%CI)[3]	p[4]
Gastric adenocarcinoma					
Hepcidin, ng/ml[1]	Q1	200	139	reference	<0.0001
	Q2	222	117	0.72(0.51- 1.00)	
	Q3	234	105	0.57(0.40- 0.81)	
	Q4	244	95	0.41(0.28- 0.61)	
Hepcidin, 5ng/ml		900	456	0.96(0.93- 0.99)	0.01
Tumour site					
Cardia					
Hepcidin, ng/ml[2]	T1	71	44	reference	0.03
	T2	68	41	0.91(0.43- 1.93)	
	T3	89	31	0.43(0.19- 0.96)	
Hepcidin, 5ng/ml		228	116	0.96(0.91- 1.01)	0.15
Non-cardia					
Hepcidin, ng/ml[2]	T1	143	91	reference	<0.05
	T2	161	85	0.82(0.54- 1.24)	
	T3	163	60	0.47(0.28- 0.76)	
log2(hep)		467	236	0.86(0.78- 0.94)	<0.05
Hepcidin, 5ng/ml		467	236	0.95(0.90- 0.99)	0.03
Tumour Histology					
Intestinal					
Hepcidin, ng/ml[2]	T1	96	57	reference	0.04
	T2	89	56	1.13(0.64- 1.98)	
	T3	107	36	0.51(0.27- 0.96)	
Hepcidin, 5ng/ml		292	149	0.97(0.91- 1.03)	0.33
Diffuse					
Hepcidin, ng/ml[2]	T1	99	65	reference	0.01
	T2	112	49	0.55(0.32- 0.94)	
	T3	96	40	0.47(0.25- 0.89)	
Hepcidin, 5ng/ml		307	154	0.94(0.88- 1.00)	0.04

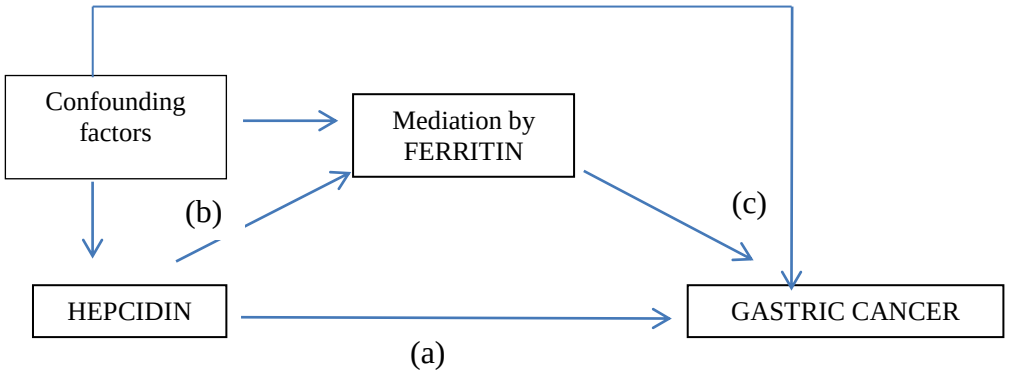
[1]♀: Q1: 0.35-4.48; Q2: 0.49-10.66; Q3: 10.67-21.71; Q4: 21.72-482.77 // ♂: Q1: 0.35-7.11; Q2: 7.12-14.40; Q3: 14.41-27.29; Q4: 27.30-324.07

[2]♀: T1: 0.35-6.63; T2: 6.64-14.85; T3: 15.86-482.77 // ♂: T1: 0.35-9.20; T2: 9.21-21.61; T3: 21.62-324.07

[3] OR matched for age at recruitment, sex, center, date of blood extraction and further adjusted for smoking status (never, former, current and unknown),
alcohol (≤5.59g/d, >5.59g/d), educational level (none, primary school completed, technical/professional school, secondary school, longer education and not specified),
fruits, and vegetables.

[4]p-trend for categorical variables / LRT p-value for continuous

Figure 1. Model used in the mediation analysis of the association between hepcidin and gastric cancer.



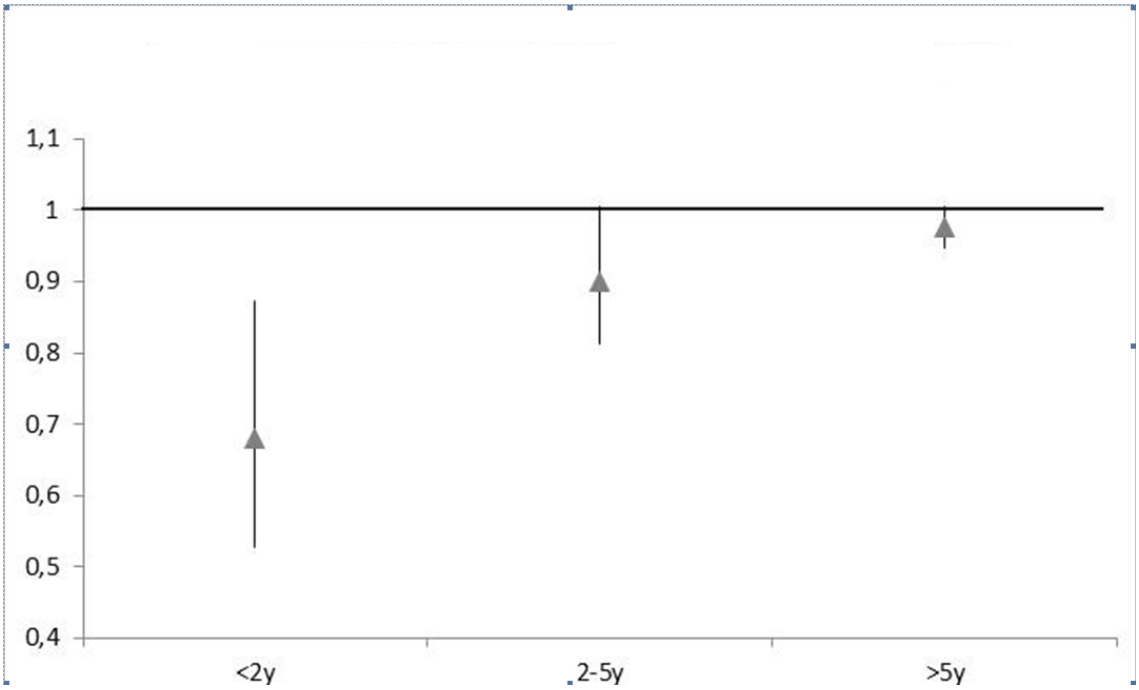
a) Relation of Hepcidin to Gastric Cancer

b) Relation of Ferritin to Hepcidin

c) Relation of Ferritin to Gastric Cancer

a+b+c: Hepcidin total effect; a: Hepcidin direct effect; b+c: Hepcidin indirect effect

Figure 2. OR and 95%CI for gastric cancer and hepcidin levels by time between blood draw and gastric cancer diagnosis.



OR matched for age at recruitment, sex, center, date of blood extraction and further adjusted for smoking status (never, former, current and unknown), alcohol (≤5.59g/d, >5.59g/d), educational level (none, primary school completed, technical/professional school, secondary school, longer education and not specified), fruits, and vegetables.

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