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Reliability of serum iron, ferritin, nitrite, and association with risk of renal cancer in women

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Abstract

Reliability of serum levels of iron, ferritin and nitrite (NO_2^-) over a 2-year period were evaluated in 40 healthy women (20 pre-menopausal and 20 post-menopausal), ages 39–65 years, from the New York University Women's Health Study (NYUWHS). Three blood samples per woman collected at yearly intervals were analyzed. Reliability coefficients (RCs) of serum iron, ferritin, and nitrite were 0.03 (95% confidence interval (CI), 0–0.33), 0.90 (95% CI, 0.79–0.95), and 0.72 (95% CI, 0.50–0.86), respectively, for pre-menopausal women, and 0.26 (95% CI, 0–0.56), 0.77 (95% CI, 0.59–0.89), and 0.55 (95% CI, 0.30–0.77), respectively, for post-menopausal women. In a case–control study nested within NYUWHS cohort, serum levels of nitrite, ferritin, and iron were measured in women apparently healthy at the time of blood donation but diagnosed with renal cancer 1.8–12.2 years later ($n = 24$) and in individually matched controls (two per case). The results suggest that high serum levels of ferritin and nitrite may be associated with a decreased risk of renal cancer (odds ratio (OR), 0.55, 95% CI, 0.15–2.01 for ferritin, and OR, 0.52, 95% CI, 0.17–1.60 for nitrite in women with above median level as compared to women with below median level). The possible role of ferritin and nitrite in renal cancer is discussed.

Keywords

Renal cancer; Ferritin; Nitrite; Serum iron; Reliability

1. Introduction

Kidney cancer accounts for 2.1% of all cancer in men and 1.6% in women. A steady increase in the number of patients with renal cancer has recently been noted, such that the rates for both men and women were 50% higher in the mid-1990s than the comparable rates in the early 1970s [1,2]. The American Cancer Society estimates that there should be about 30,800 new cases of renal cancer (18,700 in men and 12,100 in women) in the US in the year 2001, and about 12,100 people (7500 men and 4600 women) will die from this disease [3]. Renal cell carcinoma (RCC) accounts for 80–85% of all kidney cancers in the US. The remaining 15–20% of renal cancer are mostly cancers of the renal pelvis, which are anatomically and histologically distinct from RCC.

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Cigarette smoking and obesity are established risk factors for RCC [4–6]. Hypertension as well as occupational exposure to substances such as asbestos, cadmium, and solvents have been linked to an increased risk of RCC [7–10]. Among dietary factors, an inverse relationship between risk and consumption of vegetables and fruits has been found [11]. After accounting for the exposure to these risk factors, about half of RCC cases still remain unexplained [4].

The goal of the present study was to identify endogenous risk factors that may be involved in RCC development. Since kidney is one of the main organs for iron metabolism, we explored the hypothesis that high serum levels of iron, ferritin, and nitrite in the body may contribute to the etiology of RCC. It is well accepted that iron serves as a nutrient for cancer cell proliferation and that it causes oxidative DNA damage through its interaction with oxygen and hydrogen peroxide [12,13]. Several prospective studies have shown a positive association between high body iron stores and increased risk of cancer in general [14–16]. Although other studies reported either no association or an inverse association [17,18], this discrepancy may be due to the fact that the iron measured in these studies represents only a small fraction (<1%) of the total iron in the body [19]. Serum iron, which is the iron stored in transferrin, total iron-binding capacity, which is the total level of transferrin when 100% saturated with iron, and percentage saturation of transferrin were used as biological indices of body iron storage in these studies [15–18,20,21]. In contrast, ferritin, an iron storage protein, has rarely been measured. Because of its ability to sequester up to 4500 molecules of iron per molecule ferritin, ferritin was postulated to have antioxidant properties, which may play a protective role in cancer development [22,23]. Nitrite is one of the end-products of nitric oxide, a messenger molecule playing a pivotal role in the physiological and pathophysiological regulation of many genes in various organs. It was found that the higher the RCC tumor grade, the lower the nitric oxide synthase activity, suggesting that nitric oxide may also be involved in RCC development [24].

Using serum samples collected by the New York University Women's Health Study (NYUWHS), a prospective cohort study of hormonal and environmental factors and cancer in women [25,26], we have examined (1) the reliability of serum iron, ferritin, and nitrite measurements over a 2-year interval in 40 healthy women; (2) the association of serum levels of iron, ferritin, and nitrite with renal cancer risk in the 24 incident RCC cases diagnosed among all cohort participants after enrollment and 48 individually matched control subjects. Because the blood samples were drawn before clinical diagnosis of the RCC, the parameters that we measured were less likely to be influenced by the presence of the tumor.

2. Materials and methods

2.1. Subjects

The NYUWHS is a prospective study of 14,275 women 34–65 years of age who attended the Guttman Breast Diagnostic Institute, a breast cancer-screening center in New York City, between March 1985 and June 1991 [25–27]. Women were classified as post-menopausal at entry if they reported any one of the following: (1) no menstrual cycles during the 6 months preceding enrollment; (2) total bilateral oophorectomy; (3) age of 52 years or above and history of hysterectomy without total bilateral prior to natural menopause. Women who had taken hormonal medications in the 6 months preceding their visit were also not eligible. After written informed consent was obtained, demographic, medical, anthropometric, reproductive, and dietary data were collected using self-administered questionnaires. Thirty milliliters of non-fasting peripheral venous blood was drawn at enrollment and follow-up visits. After centrifugation, serum samples were divided into 1 ml aliquots and immediately stored at −80 °C for subsequent biochemical analyses. About 50% of the subjects have had at least one follow-up visit.

2.2. Reliability study

NYU Women's Health Study participants who had given blood on three or more occasions with a yield of 11 or more aliquots per visit, who had not been diagnosed with cancer or cardiovascular disease, and who had not been selected as a control in any case–control study nested within the cohort were eligible for the reliability study. One hundred and twenty serum samples collected at yearly intervals from 40 healthy women (20 pre-menopausal and 20 post-menopausal) were used for the reliability analysis. Levels of serum iron, ferritin, and nitrite (NO_2^-) were measured for the reliability coefficients (RCs) studies.

2.3. Nested case–control study

Cases of RCC were identified through the active follow-up of the cohort by questionnaires mailed approximately every 2 years and telephone interviews for non-respondents, as well as by record linkages with the state-wide cancer registries in New York, New Jersey, Connecticut, and Florida and with the US National Death Index. Medical and pathology reports were requested to confirm the diagnosis. For each case subject, two controls were selected at random from the risk set of women who were alive and free of cancer at the time of diagnosis of the case (index date), and who matched the case on menopausal status at the enrollment, date of birth (±6 months), and number (1, >1) of blood donations.

2.4. Laboratory analyses

Fat was separated from the sera by centrifugation at 12,000 rpm for 15 min (Marathon MicroA Centrifuge, Fisher Scientific, Pittsburgh, PA). The clear serum from the lower part of the tube was carefully transferred to an Eppendorf tube with a 1 ml tuberculin syringe (Beckton Dickinson and Company, Franklin Lakes, NJ) and stored frozen at −80 °C until analyses. The serum was thawed just before use by incubation on ice for 30 min and all assays were performed in 96-well microplates.

Serum iron was determined by Fe^{2+}-ferrozine complex formation using a diagnostic kit from Sigma. In brief, 30 μl serum samples were added in duplicates to wells containing 135 μl of serum iron buffer. After incubation at 37 °C for 10 min, the absorbance was determined at 560 nm using a UV-Vis microplate reader (SpectraMax Plus, Molecular Devices, Sunnyvale, CA). Five microliters of iron color reagent (ferrozine) were then added, the plate incubated (37 °C for 15 min), and absorbance measured at 560 nm. Iron concentration was determined from the iron standard curve constructed within the same microplate.

Ferritin in sera was determined according to a previously published protocol [28]. In brief, an antibody to a mixture of human spleen and liver ferritin was used as the capture antibody to coat an ELISA plate. Human liver ferritin was used as the standard (Roche Molecular Bio-Chemicals (Indianapolis, IN). The conjugate of peroxidase and antibody to human spleen and liver ferritin was then added to serve as the detector to determine the amount of ferritin bound to the capture antibody. Tetramethylbenzidine (TMB) was then added as the peroxidase substrate, and the absorbance of the peroxidase-mediated TMB oxidation product was determined at 450 nm using the UV-Vis microplate reader.

Nitrite (NO_2^-) was measured using Griess reagents as previously described [29]. Sixty microliters of serum samples were used. After adding 50 μl 1% sulfanilamide (Griess reagent 1), followed by the addition of 50 μl 0.1% *N*-(1-napthyl)ethylenediamine (Griess reagent 2), the absorbance was determined at 540 nm after 10 min incubation.

As a quality control measure of the assays, quadruplicates of one laboratory control serum sample were tested within the same microplate. All inter- and intra-assay laboratory coefficient of variations (CVs) for serum iron, ferritin, and nitrite measurements were ≤12%.

2.5. Statistical methods

The reliability was estimated by the intraclass correlation coefficient. Variance components were obtained in an ANOVA analysis assuming a one-way random effects model. Reliability coefficients were computed using the log-transformed data. Exact 95% confidence intervals (CI) were calculated [30]. In the nested case–control study, the non-parametric Wilcoxon rank–sum test was used to test for differences in continuous variables between cases and controls. To compute odds ratios (OR), serum measurements were categorized into above or below median level using the distribution of the cases and controls combined on the log-transformed values. The data were analyzed using the conditional logistic regression model, which is appropriate for a matched case–control study design. The group with below median level was used as the reference group. Likelihood ratio tests were used to assess statistical significance. All *P*-values are two-sided and *P*-values <0.05 were considered statistically significant. Because of the known association between obesity and iron levels, we conducted analyses adjusting for body mass index reported at time of blood donation. The effect of other potential confounders was explored by addition of the potential confounders in the logistic regression models. Besides body mass index, the final adjusted models included smoking history.

3. Results

Pre-menopausal women had a mean age (±S.D.) at first blood donation of 45.6 (±4.4) years and a mean body mass index of 25.6 (±4.2) kg/m^2. For post-menopausal women, the mean age was 59.9 (±2.3) years and the means body mass index was 24.9 (±5.0) kg/m^2. Mean times in storage of the serum samples were 15.1 (±0.5), 14.1 (±0.5), and 13.1 (±0.6) years for visits 1, 2, and 3, respectively.

Table 1 shows that average levels at first visit of serum iron, ferritin, and nitrite were higher in post-menopausal women than in pre-menopausal women, and the difference was statistically significant for serum iron ($P < 0.05$) and approaching significance for ferritin ($P < 0.08$). At visits 2 and 3, the same trends were observed (data not shown). Table 2 shows the RCs for the three parameters measured in the sera of all 40 subjects. Ferritin has the highest RCs, followed by nitrite, with higher RCs in pre-menopausal than in post-menopausal women. In contrast, serum iron has a low RCs, particularly in pre-menopausal women. This may be due to the variation in blood loss by menstrual cycling in pre-menopausal women.

Serum levels of iron, ferritin, and nitrite were then measured in 24 women who developed renal cell carcinoma after enrollment in the cohort and 48 controls matching the cases on the age, menopausal status, and time of blood donation. The mean age (±S.D.) of the study population at blood donation was 56.9 (±6.3) years. The ethnic distribution was as follows: 67% Caucasians, 8% African–Americans, and 25% others. The mean body mass index was 25.4 (±3.6) kg/m^2 for case participants and 25.2 (±4.0) kg/m^2 for control participants. Among the cases, the median lag time between blood donation and diagnosis of RCC was 6.6 years (range, 1.8–12.2 years). There was a higher proportion of ever smokers in cases (53%) than in controls (37%) with smoking status missing for five cases and seven controls. As shown in Table 3, levels of serum iron, ferritin, and nitrite were slightly lower in the case than in the control subjects, but the differences were not statistically significant. The differences in levels of ferritin were somewhat larger between cases and controls in the analyses restricted to Caucasian women [average levels of ferritin in cases: 5.0 ng/ml (range 0.1–21.9 ng/ml, $n = 20$) versus control: 6.0 ng/ml (range 0.5–27.1 ng/ml, $n = 28$), $P < 0.35$]. No differences in serum iron or nitrite were observed in analysis limited to Caucasian women. In conditional logistic regression analyses, higher levels of ferritin appeared to be associated with a decrease in risk (adjusted OR = 0.55 in the above median versus the below median) and nitrite (OR = 0.52 in the above median versus the below median) after adjustment for smoking and body mass index (Table 4). ORs in the above median versus below median seemed further decreased to 0.28 (95% CI:

0.05–1.45) and 0.34 (95% CI: 0.07–1.58) for serum ferritin and nitrite in Caucasian women after adjusting for smoking. A slight increase in risk appeared for serum iron (OR = 1.12 in the above median versus the below median).

4. Discussion

The data in the present study indicate that, for ferritin, a single measurement may be sufficient to estimate long-term average level in a woman for epidemiological studies. Results from our nested case–control study suggest that risk of RCC may be inversely associated with ferritin and nitric oxide production as measured by serum ferritin and nitrite concentrations, respectively.

To our knowledge this is the first study to investigate the relationships between pre-diagnostic serum levels of iron, ferritin, nitrite, and risk of RCC later in life. The advantage of the case–control study nested within a prospective cohort is that case and control subjects originate from the same, well-defined source population, thereby minimizing the risk of selection bias. Furthermore, prospective studies offer the advantage that serum samples are obtained before the clinical manifestation of disease, therefore the observed association are less likely to be due to the effect of disease. The limitations of our study included its small sample size, resulting in a limited statistical power of the study, as well as the fact that data were based on one measurement from a single serum sample per individual. Therefore, caution is required in the interpretation of the results.

Ferritin is an iron storage protein found in all living organisms including mammals, bacteria, and plants [31]. Its ability to sequester iron gives ferritin the dual functions of iron detoxification with antioxidant properties and iron reserve with pro-oxidant properties. The role of ferritin in cancer is not fully understood. It has been shown that an elevated stomach cancer risk is associated with low serum levels of ferritin, with more than a three-fold excess among those in the lowest compared with the highest quintile [32]. Our findings of a possible protective role of ferritin in RCC are in an agreement with this observation.

It is noteworthy that ferritin has been proposed as a clinical marker for staging and predicting survival of RCC, particularly in the case of recurrence after surgical therapy [33,34]. It was shown that the mean serum ferritin level from the renal vein correlated with tumor stage and was significantly higher than that from the peripheral vein [34]. The mean cytosolic ferritin level of cancer tissue was also much higher than that from normal parenchyma [35,36]. However, the actual reasons for the ferritin increases in the RCC tissue remain unclear [36]. In our study, blood samples were collected on average 6.6 years before clinical diagnosis of RCC, suggesting that low serum ferritin in the RCC cases may be due to the translocation of ferritin from the circulatory system (blood) to the pre-cancerous tissue (kidney). This hypothesis is plausible because kidney is one of main organs for iron metabolism. If this is the case, it indicates that the translocation of ferritin from the blood to the renal tissue may have happened years before clinical diagnosis of RCC.

Nitric oxide synthase catalyzes the oxidative conversion of L-arginine to NO and L-citrulline through a NADPH-dependent reaction. In experimental studies, NO formation is estimated by determining the amount of its end-products nitrate (NO_3^-) and NO_2^-, because NO is short-lived (half life, 10–60 s). The lower levels of nitrite in sera of RCC cases than those of controls are consistent with the previous observation that NOS activity was lower in RCC tissue than in non-malignant kidney tissue, and the higher the tumor grade, the lower the NOS activity [24]. Several studies suggest that NO may play a protective role in RCC, possibly contributing to interleukin-2-induced antitumor activity, an immunotherapeutic agent for RCC treatment [24,37,38].

Our studies indicate that serum iron has a low reliability coefficient. With greater variability of serum iron, a single measurement would include a large degree of measurement error and, as a consequence, observed association such as relative risk would be increasingly attenuated. Therefore, the low reliability coefficient of serum iron, as shown here, may contribute to the apparent discrepancies of the results observed in previous studies [15–18,20,21].

In conclusion, we found that high serum levels of ferritin and nitrite may be associated with a decreased risk of RCC. Further investigation in larger epidemiological studies appears warranted.

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Abbreviations

NYUWHS	New York university women's health study
RCC	renal cell carcinoma
RCs	reliability coefficients

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Table 1

Average levels of serum iron, ferritin, and nitrite from 20 pre-menopausal and 20 post-menopausal women at first visit

	Pre-menopausal (*n* = 20)		Post-menopausal (*n* = 20)		*P*-value
	Mean	S.D.	Mean	S.D.	
Serum iron (μM)	12.36	4.48	14.93	3.57	0.05
Ferritin (ng/ml)	8.55	7.72	13.37	9.34	0.08
Nitrite (μM)	8.36	5.30	8.48	8.78	0.96

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Table 2

Reliability coefficients (RCs) and 95% CI for each serum based on three yearly blood samples from 20 pre-menopausal and 20 post-menopausal women

	Pre-menopausal (*n* = 20)		Post-menopausal (*n* = 20)	
	RCs	**95% CI**	**RCs**	**95% CI**
Serum iron (μM)	0.03	0–0.33	0.26	0–0.56
Ferritin (ng/ml)	0.90	0.79–0.95	0.77	0.59–0.89
Nitrite (μM)	0.72	0.50–0.86	0.55	0.30–0.77

Table 3

Serum characteristics of RCC cases and controls, NYU Women's Health Study, 1985–2000

	Cases (n = 24)		Controls (n = 48)		P-value[a]
	Median	**Range**	**Median**	**Range**	
Serum iron (μM)	12.0	5.5–24.9	12.6	3.3–25.3	NS[b]
Ferritin (ng/ml)	5.3	0.1–22.7	5.8	0–31.0	NS[b]
Nitrite (μM)	40.4	9.2–93.2	42.1	4.3–112.7	NS[b]

[a] Wilcoxon rank–sum test.

[b] Not significant ($P > 0.05$).

Table 4

OR and 95% CI for the association of above the median compared to below median levels of serum iron, ferritin and nitrite with risk of RCC, NYU Women's Health Study, 1985–2000

	Cases, *N*	Controls, *N*	Unadjusted[a]		Adjusted[b]	
			OR	95% CI	OR	95% CI
Serum iron (μM)						
Below median (12.6 μM)	15	25	1.00		1.00	
Above median	9	23	0.59	0.17–1.79	1.12	0.24–5.17
Ferritin (ng/ml)						
Below median (5.8 ng/ml)	14	25	1.00		1.00	
Above median	10	23	0.78	0.29–2.08	0.55	0.15–2.01
Nitrite (μM)						
Below median (42.1 μM)	13	24	1.00		1.00	
Above median	11	24	0.87	0.35–2.15	0.52	0.17–1.60

[a] Except for matching factors (age, menopausal status, and date of blood donation).

[b] Adjusted for smoking (never, ever) and body mass index (continuous variable).