ELSEVIER

Serum Iron, Copper and Zinc Concentrations and Risk of Cancer Mortality in US Adults

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PURPOSE: To examine the prospective association of serum iron, copper, and zinc with cancer mortality.
METHODS: The study sample included 3000 men and 3244 women free from cancer at baseline who participated in the Second National Health and Nutrition Examination Survey. Vital status at follow-up was identified by the Social Security Administration's death file and the National Death Index. Iron, transferrin saturation (TS), copper, and zinc were categorized into 4 levels using the 10^{th}, 50^{th}, and 90^{th} percentiles for cutoffs. Relative risks (RRs) were derived from the proportional hazard models after adjustment for a number of potential confounders.
RESULTS: Three hundred seven cancer deaths (ICD-9 140–195, 199–208) were identified during 83,664.4 person-years of follow-up. Cancer mortality per 1000 person-years was 3.7 (4.7 for men and 2.8 for women). For men and women combined, the adjusted RRs (95% confidence intervals, CI) for the four levels were 0.96 (0.57–1.61), 1.00 (reference), 1.12 (0.80–1.58), 1.86 (1.07–3.22) for iron; 0.97 (0.56–1.70), 1.00 (reference), 1.36 (0.99–1.87), 1.82 (1.10–3.02) for TS; 0.76 (0.44–1.31), 1.00 (reference), 1.10 (0.77–1.58), 1.89 (1.07–3.32) for copper; and 0.75 (0.50–1.13), 1.00 (reference), 0.64 (0.47–0.88), 0.84 (0.53–1.33) for zinc. When the exposures were analyzed as continuous variables, the adjusted RRs (CI) were 1.66 (1.03–2.68) for 100 μg/dl iron increase, 1.17 (1.01–1.36) for 10% TS increase, 1.98 (1.12–3.50) for 100 μg/dl copper increase, and 0.57 (0.16–1.96) for 100 μg/dl zinc increase. Sex differences in the adjusted RRs for iron, TS, and copper were suggestive.
CONCLUSION: People with higher serum iron, TS, or copper concentrations had an increased risk of dying from cancer.
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KEY WORDS: Cancer Mortality, Copper, Iron, Nutrition Surveys, Zinc.

INTRODUCTION

The biochemistry of iron, copper, and zinc suggests that these metals may play an important role in carcinogenesis (1–12). A number of studies (13–31) examined the relation of these metals with cancer risk in humans and many found a significant relation. However, the evidence linking iron, copper, and zinc to cancer is far from conclusive. This study was thus conducted to investigate the prospective association between serum concentrations of these metals at baseline and cancer mortality in a national cohort of US adults.

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METHODS

Data and Study Sample

Data from the Second National Health and Nutrition Examination Survey (NHANES II) and its Mortality Study (NH2MS) were used for this study. NHANES II was conducted on a nationwide probability sample of approximately 28,000 persons 6 months through 74 years of age from the civilian, non-institutionalized population of the United States. Started in February 1976 and completed in February 1980, the survey had a complex sample design consisting of a multistage, stratified, probability-based cluster sample of households throughout the United States. Details of the study design and methods of NHANES II are reported elsewhere (32).

NH2MS, a prospective cohort study, passively followed a subset of participants in NHANES II to identify mortality and deaths from specific causes (33). NH2MS cohort is comprised of adults who were 30 to 75 years of age at their NHANES II examination (n = 9252). In the mortality survey, mortality status was ascertained for the years 1976 to 1992. Two participants were not followed because of

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Selected Abbreviations and Acronyms

NHANES II = Second National Health and Nutrition Examination Survey
NH2MS = NHANES II Mortality Follow-up Study
ICD-9 = International Classification of Diseases, Ninth Revision
TS = transferrin saturation

incomplete personal identifying data and were considered lost to follow-up. The 9250 cohort members were traced in the NH2MS by searching national databases containing mortality and cause of death information. The length of follow-up period ranged from 12 to 16 years. 2145 (23%) of the NH2MS cohort were identified to be dead as of December 31, 1992.

For the purpose of this study, members of the NH2MS cohort who reported having cancer at NHANES II were excluded. The study subjects were further restricted to participants who had measurements of serum iron, total iron binding capacity, serum copper, and zinc, and who had no missing information on the covariates of interests, leaving a study sample of 6244 persons (Table 1).

Study Variables

Cancer mortality during the follow-up. Cancer mortality during the follow-up is the dependent variable of interest. In NH2MS, causes of death were obtained for 2103 out of the 2145 participants identified as deceased. Deaths were identified by matching personal identifiers to the National Death Index (NDI) for the years 1979 to 1992. The NDI includes all deaths in the US from 1979 forward. Social Security numbers were not available for matching. For the years 1976 to 1978, mortality follow-up was conducted by matching personal identifiers to the Social Security Administration's Mortality Tapes Matching System (SSA). Underlying causes of death with ICD-9 codes 140–195 and 199–208 were used to define cancer mortality. Years of follow-up were calculated using the exam date of NHANES II and the date of last known alive or the date of death during the follow-up for those who were deceased.

TABLE 1. Determination of study sample from the Second National Health and Nutrition Examination Survey and its Mortality Follow-up Study (NH2MS)

	Sample Size	Total Deaths	Cancer Deaths
NH2MS cohort	9,252	2,145	527
↓			
Exclude lost to follow-up	9,250	2,145	527
↓			
Exclude baseline prevalent cancer cases	8,787	1,966	454
↓			
Exclude no iron, copper, or zinc measurement	6,768	1,471	333
↓			
Exclude missing data for covariates	6,244	1,361	307

Serum iron, transferrin saturation, serum copper and zinc. Serum iron, transferrin saturation (the ratio of serum iron to total iron-binding capacity), serum copper and zinc concentrations measured at NHANES II were the exposure variables of interest. Serum iron and total iron-binding capacity (TIBC) were measured by a modification of the automated Technico AAII-25 Method, which was based on the procedures of Giovanniello et al. (34) and Ramsey (35). Serum copper and zinc were measured by atomic absorption spectroscopy by using a method optimized by Centers for Disease Control on procedures from Instrumentation Laboratory, Inc. (36) and Perkin-Elmer Corp. (37). Quality control tests showed that coefficients of variation ranged from 1.42% to 2.08% for serum iron, 1.92% to 2.83% for TIBC, 2.57% to 3.30% for serum copper, and 3.53% to 5.21% for serum zinc. Detailed procedures of measurement have been reported elsewhere (38).

Covariates. Available baseline information served as covariates in this study to control for potential confounding. Those variables included sex, age at NHANES II exam, race (White, African American, other), years of education, diabetes status, poverty index ratio, smoking status (nonsmoker, past smoker, current smoker), vitamin/mineral supplement use (regular user, irregular user, and nonuser), body mass index, serum vitamin C concentration, serum total cholesterol concentration, white blood cell count, and exam session (morning, afternoon, evening). Definitions and/or measurements for the variables have been described elsewhere (32, 38).

Statistical Analysis

Descriptive statistics including means, standard deviations, and percentages were used to describe and compare the characteristics of the study sample and NH2MS cohort to evaluate the similarity between them. The person-year approach was used to examine the crude association between individual exposure and cancer mortality. Serum iron, TS, serum copper, and zinc were categorized into four levels using the 10^{th}, 50^{th}, and 90^{th} percentiles of the distributions for men and women combined as cutoff. The category with values $\geq$ the 10^{th} percentile and $<$ the 50^{th} percentile served as the referent group. The reason for choosing these cut-values rather than quartiles was to investigate the effects of more marginal values of an exposure. Person-years of follow-up and number of cancer mortality events were categorized according to the level of each exposure, and the mortality rates for the different levels of the exposure were calculated.

The proportional hazard model was used to examine the association between an individual exposure and cancer

mortality with adjustment for the covariates of interest. In the analysis, the occurrence of cancer death was defined as a failure, and participants with all other situations were considered to be censored. Iron (or TS), copper, and zinc were analyzed simultaneously by including them in the same model. The relative risk of cancer mortality was estimated by the hazard ratio derived from the model. Each exposure variable was analyzed as a continuous variable to test if there was a linear relationship (trend) with cancer mortality. It was also included in separate models as a categorical variable to show possible non-linear associations. In addition to the multivariate analyses for the whole sample, the proportional hazard model also was performed for the sample excluding those who died of cancer within the first 3 years of the follow-up.

As described earlier, NHANES II used a complex sampling design including stratification and cluster sampling. Sampling weights were assigned to the NH2MS data sets. Taking the design features into consideration, SUDAAN statistical software (39) was used and weighting was applied in the multivariate analyses.

RESULTS

Descriptive statistics (weighted percentages and means) for selected characteristics of the study sample and the NH2MS cohort were comparable (Table 2).

Total person-years of follow-up were 83,664.4 for the study cohort and 307 cancer deaths were identified during the follow-up. Cancer mortality (per 1,000 person-years) was 3.7 for the cohort as a whole, 4.7 for men and 2.8 for women. Cancer mortality (per 1,000 person-years) for the 4 levels were 3.9, 3.4, 3.5, and 5.2 for iron, 3.6, 3.2, 3.9, and 4.5 for TS, 2.8, 3.2, 4.2, and 4.4 for copper, and 4.5, 4.0, 3.1, and 3.6 for zinc. Sex specific mortality rates by levels of serum iron, TS, copper, and zinc are shown in Table 3.

TABLE 2. Comparison of the characteristics (percentages and means[¶]) of the study sample with Participants of the Second National Health and Nutrition Examination Survey and Its Mortality Follow-up Study (NH2MS)

	Study sample (n = 6,244)	NH2MS cohort (n = 8,987)*
Female (%)	51.9	52.0
White (%)	89.6	87.6
African American (%)	7.9	9.9
Past smoker (%)	26.1	25.5
Current smoker (%)	36.1	35.9
Diabetes (%)	4.2	4.2
Regular vitamin user (%)	26.3	25.7
Irregular vitamin user (%)	11.1	11.6
Examined at morning (%)	60.9	59.6
Examined at afternoon (%)	24.7	25.4
Mean age at exam (years)	48.7	49.0
Mean years of education	11.7	11.6
Mean body mass index	25.9	25.9
Mean serum cholesterol (mg/dl)	223.6	222.8

[¶]Weighted, calculated with weights provided in the data set for the mortality follow-up.
*Excluded participants who had cancer at NHANES II.

Results of the multivariate analyses for men and women combined are presented in Table 4. After adjustment for sex, age, race, education, poverty index ratio, smoking status, body mass index, diabetes status, regular vitamin use, exam session, serum cholesterol, serum vitamin C, and white cell count, a significantly increased risk of cancer mortality was observed in the groups who had the highest level of iron, TS, or copper. For example, the RR (CI) of cancer mortality for participants who had serum iron higher than 141 μg/dl was 1.86 (1.07–3.22) in comparison to those who had serum iron concentrations between 61 to 94 μg/dl. The relation between serum zinc and cancer mortality appeared to be nonlinear with a significantly reduced risk for people with serum zinc between 86 to 103 μg/dl compared with those with serum zinc between 70 to 85 μg/dl. There were 188 death events including 33 cancer deaths that occurred within the first 3 years of the follow-up. Similar findings were observed after exclusion of these early deaths (Table 4).

Multivariate analyses separately for men and women are shown in Table 5. For women, being in the highest level of iron or TS at baseline was associated with an increased risk of cancer mortality. For men, the association was much weaker if any. Both men and women tended to have higher cancer mortality if they had serum copper concentrations at the highest category, while the significant trend of association was observed only in men. Although there appeared to be sex differences in the associations, significance test of the interaction terms with sex in the proportional hazard models for men and women combined did not reach significance (result not shown). The relation between serum zinc and cancer mortality appeared similar for men and women (Table 5).

DISCUSSION

This study of a national cohort of United States adults suggests an increased risk of dying from cancer with higher levels of serum iron, TS, and serum copper at baseline in males and females. The association of cancer with serum iron and TS tended to be stronger among women, whereas the association with serum copper tended to be stronger among men. Although the study suggests a modification effect by gender, the result cannot be deemed conclusive due to insufficient power of analysis and should be viewed

TABLE 3. Cancer death events and mortality during follow-up among participants with different levels of serum iron, transferrin saturation (TS), serum copper, or serum zinc: The Second National Health and Nutrition Examination Survey and its mortality Follow-up Study

	Men and women				Men				Women			
	Sample size	Person-years	Events	Mortality	Sample size	Person-years	Events	Mortality	Sample size	Person-years	Events	Mortality
Total	6244	83664.4	307	3.7	3000	38793.5	181	4.7	3244	44870.9	126	2.8
Iron (μg/dl)*												
16–60	643	8352.8	33	3.9	247	2937.0	19	6.5	396	5415.9	14	2.6
61–94	2493	33234.9	113	3.4	1109	14238.6	62	4.4	1384	18996.3	51	2.7
95–140	2493	33818.4	118	3.5	1283	16884.4	73	4.3	1210	16934.1	45	2.7
141–321	615	8258.2	43	5.2	361	4733.5	27	5.7	254	3524.7	16	4.5
TS (%)*												
3.1–16.1	616	8112.7	29	3.6	210	2545.3	14	5.5	406	5567.4	15	2.7
16.2–26.1	2507	33671.9	108	3.2	1105	14304.3	59	4.1	1402	19367.6	49	2.5
26.2–39.6	2490	33496.6	132	3.9	1304	17037.5	82	4.8	1186	16459.1	50	3.0
39.7–94.3	631	8383.2	38	4.5	381	4906.3	26	5.3	250	3476.8	12	3.5
Copper (μg/dl)*												
49–95	609	8289.8	23	2.8	453	6118.3	19	3.1	156	2171.6	4	1.9
96–121	2505	34113.1	109	3.2	1507	20146.6	81	4.0	998	13966.5	28	2.0
122–157	2509	33127.4	139	4.2	947	11592.6	68	5.9	1562	21534.8	71	3.3
158–343	621	8134.1	36	4.4	93	936.1	13	13.9	528	7198.1	23	3.2
Zinc (μg/dl)*												
44–69	637	8083.8	36	4.5	261	3043.0	23	7.6	363	5040.9	13	2.6
70–85	2486	32926.3	133	4.0	1048	13201.3	73	5.5	1378	19725.0	60	3.0
86–103	2504	34051.4	107	3.1	1269	16732.2	60	3.4	1188	17319.2	47	2.7
104–225	617	8602.9	31	3.6	522	5817.0	25	4.3	189	2785.9	6	2.2

*These four groups were categorized using the 10^{th}, 50^{th}, and 90^{th} percentiles of the distributions of the whole sample as the cut-values. Mortality is per 1,000 person-years of follow-up.

with caution. The relation between serum zinc and cancer mortality was nonlinear and less conclusive.

The potential role of iron, copper, and zinc in cancer etiology is supported by several plausible mechanisms. As transition metals, iron and copper can generate the reactive oxygen species including hydroxyl radicals (1–4). These reactive oxygen species can attack DNA and cause DNA mutation, thus contributing to the pathological process of cancer. In addition to its role in the generation of oxygen species, iron may be a limiting nutrient to the growth and replication of cancer cells in the human body (5). Copper has been implicated in the activation of several organic peroxides and making them more carcinogenic (6, 7). In contrast, zinc may play an anti-carcinogenic role by stabilizing the structure of DNA, RNA, and ribosome (8). Zinc is also essential to the functions of several transcription factors, proteins that recognize certain DNA sequences and regulate gene transcription (9). Zinc protects against free radical injury (10) and may affect immune response (11, 12).

The relation between iron and cancer risk observed in this study is consistent with the finding from many human studies that higher circulating iron levels are associated with an increased risk of cancer (13–20). Stevens et al. (13, 14) reported the cancer incidence in the First National Health and Nutrition Examination Survey and its follow-up study. They found a positive association of cancer risk with serum iron and transferrin saturation, and an inverse association with TIBC. In a large prospective study of 41,276 men and women aged 20 to 74 years who initially were free of cancer (15), higher risk for colorectal and lung cancers was found in participants with transferrin saturation exceeding 60% in comparison to their counterparts. Merk et al. (16) found significantly reduced risk of cancer in blood donors in Sweden. Although there might be a "healthy donor" effect, their results are consistent with a protective effect of blood donation by virtue of lowering body iron level. While several other studies (17–20) reported results consistent with the hypothesis that high body iron stores increase the risk of cancer, there are a few studies (21, 22) that reported findings inconsistent with the hypothesis. For example, in a prospective study of 38,538 people who were followed for an average of 17.7 years, no significant association of transferrin saturation with epithelial, lung, or stomach cancer was observed in men or women (21).

The roles of copper and zinc in human cancer etiology are much less studied. Cross-sectional and case-control data (23–29) have shown higher serum copper and/or lower serum zinc levels in cancer patients. These data are difficult to interpret, however, because the temporal sequence of causation could not be determined. Only a few studies investigating the relation between serum copper (and/or zinc) and cancer risk used prospective designs. For example, in a

TABLE 4. Relative risks (RR)† and 95% confidence interval (95% CI) of total cancer mortality for different levels of serum iron, transferrin saturation (TS), serum copper, or serum zinc: The Second National Health and Nutrition Examination Survey and its Mortality Follow-up Study

	Men and women (n = 6,244)		Exclude deaths occurred within 1st 3-year follow-up (n = 6,056)	
	RR	95% CI	RR	95% CI
Iron (μg/dl)*				
16–60	0.96	0.57, 1.61	0.91	0.53, 1.55
61–94	1.00	Referent	1.00	Referent
95–140	1.12	0.80, 1.58	1.16	0.80, 1.68
141–321	1.86	1.07, 3.22	2.03	1.15, 3.56
Trend (per 100 μg/dl change)	1.66	1.03, 2.68	1.80	1.07, 3.03
TS (%)**				
3.1–16.1	0.97	0.56, 1.70	0.99	0.56, 1.76
16.2–26.1	1.00	Referent	1.00	Referent
26.2–39.6	1.36	0.99, 1.87	1.43	0.98, 2.08
39.7–94.3	1.82	1.10, 3.02	1.96	1.14, 3.36
Trend (per 10% change)	1.17	1.01, 1.36	1.20	1.02, 1.41
Copper (μg/dl)**				
49–95	0.76	0.44, 1.31	0.76	0.42, 1.39
96–121	1.00	Referent	1.00	Referent
122–157	1.10	0.77, 1.58	1.13	0.77, 1.65
158–343	1.89	1.07, 3.32	2.10	1.12, 3.95
Trend (per 100 μg/dl change)	1.98	1.12, 3.50	2.07	1.13, 3.79
Zinc (μg/dl)**				
44–69	0.75	0.50, 1.13	0.71	0.45, 1.10
70–85	1.00	Referent	1.00	Referent
86–103	0.64	0.47, 0.88	0.66	0.47, 0.93
104–225	0.84	0.53, 1.33	0.83	0.16, 2.29
Trend (per 100 μg/dl change)	0.57	0.16, 1.96	0.61	0.16, 2.29

RR, estimated using the hazard ratio derived from the proportional hazard model.
†Adjusted for sex, age, race, education, poverty index, smoking status, body mass index, diabetes status, vitamin/mineral use, exam session, serum cholesterol, serum vitamin c, and white cell count at baseline.
*Serum iron, copper, and zinc were included in the same model.
**TS, serum copper and zinc were included in the same model.

small study (30), 26 cancer cases were compared with matched controls. Mean baseline serum copper levels were found to be higher in cancer cases than in controls, although not significantly, while no differences were observed for serum zinc. In a nested case-control analysis of data obtained in a Dutch prospective follow-up study (31), cancer death (n = 64) and cardiovascular disease death (n = 62) cases and their matched controls were taken from a cohort of 10,532 persons examined between 1975 and 1978. Trace elements were measured in baseline serum samples. The adjusted risk of death from cancer and cardiovascular disease was about four times higher for subjects in the highest serum copper quintiles compared with those with normal levels. They also found an excess mortality in subjects with low copper status, suggesting a U-shaped relation. No significant change in the risk of death from cancer was found for subjects with low or high baseline levels of serum zinc, although a non-significant inverse relation of high serum zinc and reduced risk was observed.

Our study has a number of strengths. First, it has good external validity as the study is based on data from a nationally representative sample. Although some NH2MS participants were eliminated from the study due to lack of information on the variables of interest, the comparison of the study sample with the NH2MS cohort shows a similarity in a number of characteristics, indicating that bias from the selection of the study sample is unlikely. Second, the prospective nature of those data helps in determining a temporal sequence in the association. In addition, serum iron (or TS), copper, and zinc were included in analysis simultaneously, and this simultaneous adjustment may help

TABLE 5. Relative risks (RR)† and 95% confidence interval (95% CI) of total cancer mortality for different levels of serum iron, transferrin saturation (TS), serum copper, or serum zinc by sex: The Second National Health and Nutrition Examination Survey and its Mortality Follow-up Study

	Men		Women	
	RR	95% CI	RR	95% CI
Iron (μg/dl)*				
16–60	0.91	0.47, 1.76	1.05	0.45, 2.46
61–94	1.00	Referent	1.00	Referent
95–140	1.13	0.69, 1.85	1.04	0.67, 1.63
141–321	1.45	0.69, 3.04	2.55	1.30, 5.00
Trend (per 100 μg/dl change)	1.31	0.69, 2.51	2.25	1.20, 4.24
TS (%)**				
3.1–16.1	0.98	0.44, 2.21	1.02	0.47, 2.22
16.2–26.1	1.00	Referent	1.00	Referent
26.2–39.5	1.36	0.85, 2.17	1.30	0.85, 1.98
39.7–94.3	1.51	0.84, 2.72	2.45	1.12, 5.33
Trend (per 10% change)	1.09	0.91, 1.30	1.27	1.03, 1.56
Copper (μg/dl)**				
49–95	0.63	0.36, 1.12	1.28	0.39, 4.21
96–121	1.00	Referent	1.00	Referent
122–157	0.91	0.62, 1.33	1.31	0.80, 2.16
158–343	1.95	0.94, 4.04	1.82	0.93, 3.56
Trend (per 100 μg/dl change)	2.50	1.11, 5.64	1.51	0.75, 3.04
Zinc (μg/dl)**				
44–69	0.68	0.37, 1.26	0.75	0.34, 1.65
70–85	1.00	Referent	1.00	Referent
86–103	0.56	0.35, 0.89	0.79	0.46, 1.38
104–225	0.89	0.51, 1.55	0.71	0.30, 1.68
Trend (per 100 μg/dl change)	0.50	0.11, 2.27	1.12	0.17, 7.32

RR, estimated using the hazard ratio derived from the proportional hazard model.
†Adjusted for age, race, education, poverty index, smoking status, body mass index, diabetes status, vitamin/mineral use, exam session, serum cholesterol, serum vitamin c, and white cell count at baseline.
*Serum iron, copper, and zinc were included in the same model.
**TS, serum copper and zinc were included in the same model.

better estimate their independent effects. Finally, the exclusion of cancer deaths identified during earlier follow-up helped to eliminate undiagnosed prevalent cancer cases at baseline, and results from analyses with this exclusion, while being consistent with results from analyses without the exclusion, could better confirm the temporal sequence in the associations studied.

The validity and reliability of the exposure measurements (for example, compared with serum ferritin, serum iron, and TS are poorer measurements to reflect body iron store) and the over-time variability in the exposures have been argued in previous studies (40, 41). Other possible weaknesses of this study need also to be pointed out. First, cancer incidence is more favorable than cancer mortality as an outcome measure in a study of cancer etiology, since cancer mortality is influenced by both etiologic and prognostic factors. As cancer incidence data are not available in this study, we cannot exclude the possibility that iron, copper, and zinc play roles as prognostic factors rather than as etiologic factors in their relationships with cancer mortality.

Passive follow-up was used and misclassification of mortality status might exist. Previous studies have shown that 90% or more of all deaths can be identified from the NDI when social security numbers are not used as part of the matching criteria (42–44). For the years 1976 to 1978, mortality follow-up was conducted by matching personal identifiers to the SSA. No data exist on the effectiveness of matching to the SSA without social security numbers. Based on US mortality rates for 1976, 142 deaths were expected during the years 1976 to 1978; whereas 84 deaths were identified. Cause of death is missing for some decedents either because there was no matching record on the NCHS Multiple Cause of Death file or the death certificate was not found through the State Vital Statistics Office. Even if causes of death could be obtained by matching with the source files, their accuracy could not be confirmed in this study. The misclassifications of survival status and cause of death, however, were likely to be non-differential (not related to the exposures) since the exposures were measured before the occurrence of the outcome studied. Non-differential misclassification is likely to bias the association toward null (45).

In summary, the analysis of a national cohort of United States adults indicates inverse associations of cancer mortality with serum iron, TS, and serum copper. Notably, people with the highest level (top 10th percentile) of serum iron, TS, or serum copper at baseline had a high risk of dying from cancer. Modification effects by sex were suggestive and warrant further study. The relation of cancer risk with serum zinc appeared nonlinear and less conclusive. The findings suggest that serum iron, copper, and zinc may play an important role in cancer etiology.

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