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IRON AND THE RISK OF CANCER

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Four epidemiological studies have been performed that are generally consistent with the hypothesis that increased available body iron stores increase the risk of cancer or of general mortality. In a study based on the First National Health and Nutrition Examination Survey in the United States (NHANES), 232 men who developed cancer over a ten year period had a mean transferrin saturation of 33.1% at least 4 years before diagnosis, whereas 3,113 men who did not develop cancer had a transferrin saturation of 30.7% ($p = 0.002$). The hypothesis is based on two possible biological mechanisms. First, iron can catalyse the production of oxygen radicals and these may be proximate carcinogens. Second, iron may be a limiting nutrient to the growth and replication of a cancer cell. There are at least five areas of potential research related to iron and cancer based on these biological mechanisms: (1) etiology of cancer, (2) etiology of radiation-induced cancer, (3) prognosis after cancer diagnosis, (4) cancer risk resulting from therapy, and (5) interactions with other biochemical factors. An unexpected finding of the human studies done to date has been a highly significant negative association of serum albumin and long term cancer risk. Serum albumin is lower in smokers and older people, however, the negative association persists after controlling for these factors.

Key words: **Cancer, Iron, Oxidative stress, Epidemiology.**

INTRODUCTION

Body iron status may play an important role in risk of infections and of cancer, both etiology and prognosis. Reviews of the biological mechanisms have covered the role of iron in infection and cancer,[1] the mechanisms by which cells acquire iron in microorganisms,[2] plants, and animals,[3] the role of iron in virulence of enteric pathogens,[4] and the possible role of iron in radiation-induced cancer.[5]

Studying the possible consequences of these hypothesized biological mechanisms in humans is difficult. No one facet of human biology can be studied independently of all the others. This is particularly difficult in long term studies of cancer. The first problem is definition of a measurable attribute that assesses iron status, and that yields a quantitative indication ranging from 'high' to 'low' corresponding either directly or inversely to 'high' and 'low' iron. Such a measure must be inexpensive in time and money, reproducible, and well tolerated by study subjects. The studies done to date have used serum measures such as ferritin, transferrin, transferrin saturation, and total iron binding capacity (TIBC) prior to diagnosis of cancer. To interpret the results, assumptions have been made that these measures are related to iron status and that some other underlying condition, such as inflammation, is not invalidating the results. In general, there is a direct correlation of serum ferritin and transferrin saturation with available body iron stores, and an *inverse* correlation of serum transferrin and TIBC with iron stores; that is, high iron stores results in high ferritin and transferrin saturation, and low serum transferrin and TIBC.

The results of four published studies will be compared in this paper, and results from a new study of stomach cancer in Japanese atomic bomb survivors will be summarized.

METHODS

The methods of the reported studies have been similar. Each has been based on a study population followed prospectively.

Stevens *et al.*[6] studied the relationship of serum ferritin and transferrin to subsequent risk of death over a ten year period in the Solomon Islands (referred to as *Solomons*). Outcome in this study was all-cause mortality which probably did not include a large proportion of cancer deaths. Six subpopulations of Solomon Islanders were first

examined during the period 1966–70 as part of the Harvard–Solomon Islands project.[7] The overall objective of the project was to define a longitudinal sample of the indigenous Solomon Islands population and to investigate the subsequent effects of Westernization. At the start of the study a blood sample was taken, demographic characteristics were recorded, a medical examination was performed, and anthropometric measurements were taken on each of approximately 2500 individuals. The alive-dead status of each of these people was determined as of 1978 by anthropologists in the Solomon Islands. The stored serum of each person who had died, and a selected age-sex matched control who had not died, were tested for ferritin and transferrin. There was no adjustment for smoking.

During the period 1975–78, 21,513 male Chinese government workers were enrolled in a study[8] of the effect of hepatitis B virus on risk of primary hepatocellular carcinoma (PHC). Stevens *et al.*[9] reported on a study of serum ferritin and transferrin level in serum stored since enrollment in 192 of these men who developed PHC, or died of any cancer, by 1983, and in 358 age matched control males who had not died or developed cancer (referred to as *Taiwan*). There was no adjustment for smoking.

Selby and Friedman[10] reported on over 175,000 members of a health plan in northern California followed from 1964 to 1973 (referred to as *Kaiser*). Each subject had a baseline medical examination during this period, and a measurement of TIBC. The population was followed through 1980, and incident cases of cancer recorded in the large database. TIBC was compared between cases and those who did not develop cancer over the study period. Cases occurring within 2 years of the blood tests were excluded from the analyses, and adjustment was made for age and smoking.

Utilizing the existing database on the *National Health and Nutrition Examination Survey I* in the United States, Stevens *et al.*[11] compared transferrin saturation and TIBC in those of the 14,707 subjects who developed cancer as of 1984 and those who did not (referred to as *NHANES*). The cohort was identified during the period 1971–75 as a probability sample of the United States adult population. An extensive dietary questionnaire was administered, a medical examination performed, anthropometric measurements made, and blood taken and analysed for a large number of constituents. Cases occurring within 4 years of the time the blood was taken were not included in the analysis, and adjustment was made for age and smoking. The blood was not saved.

A very recent study[12] has been completed of serum ferritin and transferrin and risk of stomach cancer in Japanese bomb survivors (referred to as *Japan*). From 1970 to 1972, blood was taken from members of the Adult Health Study of atomic bomb survivors at their biennial clinical examination at the Radiation Effects Research Foundation in Hiroshima and Nagasaki. There were 233 cases of stomach cancer diagnosed in this group over the years 1973 to 1983. Serum ferritin and transferrin level in the stored serum from 1970–72 for the cases was compared to the levels in a group of age, sex, city, and radiation matched controls. Adjustment was made for smoking.

RESULTS

The populations used for each of these studies were different, the metrics for assessment of iron status differed somewhat, and the outcomes were different. However, comparison of results may provide further insight into the possible effect of iron status on cancer risk. Serum ferritin and serum transferrin were used in the *Solomons* study of general mortality, *Taiwan* study of incidence of PHC and cancer death excluding PHC, and *Japan* study of stomach cancer incidence. The *NHANES* study used transferrin saturation and TIBC, whereas the *Kaiser* study used only TIBC.

Table 1 shows a comparison of the studies that used ferritin or transferrin saturation. Serum ferritin was significantly higher in males in the *Solomons* study who died than in those who did not die over a ten year period; the difference in females was not significant. In *Taiwan*, men who died of cancer had higher ferritin although not significantly so. Men who died of, or developed PHC had significantly higher ferritin than their controls. In the *NHANES* study, men who developed cancer (all types combined) had significantly higher transferrin saturation than controls, whereas female cases did not. The stomach cancer cases in the *Japan* study had significantly *lower* ferritin than controls.

Table 2 shows results for serum transferrin and TIBC. Transferrin was significantly lower in those who died than in those who did not in the *Solomons*. Men who died of cancer had significantly lower transferrin than those who did not in *Taiwan*. Female cancer cases in the *Kaiser* study, and males in the *NHANES* study had lower TIBC than controls. In the *Japan* study, stomach cancer cases had significantly *higher* transferrin than controls.

The *Solomons*, *Taiwan*, and *NHANES* studies gave results consistent with the hypothesis that *higher* iron stores increase risk of death or of cancer

Table 1. Mean serum level of ferritin (ng/ml) or transferrin saturation (%) in cases followed by that in controls. A higher level in cases is consistent with the hypothesis that cases had higher iron stores than controls prior to death or diagnosis

	Ferritin		Transferrin saturation	
	Cases	Controls	Cases	Controls
Solomons				
Males, death	71*	51.8		
Females, death	52	51		
Taiwan				
Males cancer death†	149.1	142.7		
Males PHC	121.4*	99.9		
NHANES				
Males, cancer incidence			33.1*	30.7
Males, stomach cancer			26.4	30.7
Females, cancer incidence			28.2	27.4
Japan				
Stomach cancer	49*	69.2		

*Significantly different from control.
†Excluding PHC, primary hepatocellular carcinoma.

Table 2. Serum levels of transferrin (mg/dl) or total iron binding capacity (TIBC, μmol/l) in cases followed by that in controls. A lower level in cases is consistent with the hypothesis that cases had higher iron stores than controls prior to death or diagnosis

	Transferrin		TIBC	
	Cases	Controls	Cases	Controls
Solomons				
Males, death	242*	269.7		
Females, death	244*	270.2		
Taiwan				
Males cancer death†	283.9*	307.7		
Males PHC	286.2	267.8		
Kaiser				
Males, cancer incidence			50.09	49.51
Females, cancer incidence			47.69*	48.37
Males, lung cancer			48.89	49.58
Females, lung cancer			45.34*	48.37
NHANES				
Males, cancer incidence			61.4*	62.9
Males, stomach cancer			67.0	62.9
Females, cancer incidence			66.4	66.5
Japan				
Stomach cancer	278*	269		

*Significantly different from control.
†Excluding PHC, primary hepatocellular carcinoma.

in men. The *Kaiser* study gave evidence for an association in women but not in men. There was a suggestion that, perhaps, women with very high transferrin saturation might also be at moderately elevated risk of cancer in the *NHANES* study.

Stomach cancer

In the *Japan* study, the association of serum ferritin and transferrin is in the *opposite* direction: lower iron is associated with increased stomach cancer incidence. There were only 8 cases of stomach cancer in the *NHANES* study and 24 in the *Taiwan* study. However, the male cases in *NHANES*, had a transferrin saturation of 26.4, lower than control, and TIBC of 67.0, higher than control. In the *Taiwan* study, stomach cancer cases also had lower ferritin than controls. Thus, the results of these 3 studies are consistent with each other.

Liver cancer

In the *Taiwan* study, liver cancer cases had greatly elevated ferritin prior to diagnosis. The highest ferritin values were found in those diagnosed less than 1 year after blood was drawn suggesting that elevated ferritin may be a marker of early PHC.

Albumin

Table 3 shows mean levels of serum albumin prior to diagnosis of disease in cases and controls. A consistent, and highly statistically significant, negative association of serum albumin level in men and risk of death and/or cancer is seen in these studies. Albumin is lower in smokers than non-smokers,[13] and decreases with age. However, the negative association persists after controlling for these factors.

Table 3. Serum albumin in cases and controls in three epidemiological studies

	Serum albumin (g/l) Cases	Controls
Solomons		
Males, death	39.1	41.5*
Females, death	40.1	40.6
Taiwan		
Males, cancer death†	42.0	44.0*
NHANES		
Males, cancer incidence	43.7	44.3*
Females, cancer incidence	43.3	43.4

*Statistically significant difference.
†Excluding PHC, primary hepatocellular carcinoma.

DISCUSSION

The role of iron status in risk of cancer, and in prognosis after diagnosis, deserves attention based on the suggestive evidence from the few published reports summarized here. Two additional studies have been reported in brief detail. Takkunen *et al.*[14] did not find a relationship of transferrin saturation and cancer risk in a cohort study in Finland. DeSousa *et al.*[15] examined prognosis in children with acute lymphocytic leukemia and found significantly fewer deaths in those with transferrin saturation of less than 36% at the start of the study than in those with a value 36% or higher.

Two possible mechanisms for a role for iron in cancer risk are, (1) iron can catalyse the production of oxygen radicals,[16] and (2) iron may be a limiting nutrient to existing cancer cells.[1] The studies done to date cannot distinguish between these two. However, they have different implications. If iron nutriture affects the growth and survival of a cancer cell, then high iron status may adversely affect prognosis after cancer diagnosis. If iron level plays an important role in oxidative stress, then high iron status may increase the dangers of exposure to ionizing radiation.[5]

Stomach cancer risk appears to be associated with *lower* iron stores. A mechanism whereby precursors of stomach cancer lead to lower iron stores[17] is a possible explanation discussed in the paper about the *Japan* study.[12]

Blumberg *et al.*[18] stated the hypothesis that the risk of PHC in chronic carriers of hepatitis B virus (HBV) is increased in those with high liver iron stores. Lustbader *et al.*[19] studied hemodialysis patients challenged with HBV, and found that those patients who became chronic carriers had higher serum ferritin prior to challenge than those who developed antibody. The evidence from the *Taiwan* study further implicates iron level in the etiology of HBV-induced PHC.

The negative association of serum albumin level and subsequent cancer risk in men seen in these epidemiological studies is an intriguing finding. It may result simply from confounding effects of age and cigarette smoking, although adjustment was made for these factors in the analyses. Albumin level is used clinically to assess protein-calorie status,[20] and low albumin suggests low protein intake. Pro-

tein intake, however, has been found to *increase* cancer risk in experimental animals;[21] low albumin in cancer victims appears inconsistent with the results from animal studies. Albumin is the most abundant serum protein and is important in the maintenance of osmotic pressure of blood, and in the transport of many substances. In particular, albumin may bind iron to inhibit the growth of bacteria,[22] and, by extension, of cancer cells.

There are many potential applications of the iron-cancer hypotheses. Weinberg and Weinberg[23] have suggested that blood donors might be at reduced risk of cancer by virtue of their chronically lowered iron level. Although asbestos is believed to be carcinogenic in humans, particularly in conjuction with cigarette smoking, Weinberg[24] has hypothesized that the difference in the carcinogenicity between amphibole asbestos (high cancer risk and high iron content) and serpentine asbestos (low cancer risk and low iron content) can be explained by the iron content of these respective silicates. Iron may influence cancer at some sites and not others. The data presented from the studies reviewed here shows evidence of increased overall cancer risk in those with high iron stores, although of *lower* stomach cancer risk. Graf and Eaton[25] argued that iron binding by phytate may account for a reduced colon cancer risk for those consuming a high fiber diet.

Due to the prominent place of iron in human physiology, and the high iron content of the western diet, it is important to pursue further research on the possible role of iron in risk of cancer.

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