SERUM FERRITIN LEVELS AND TRANSFERRIN SATURATION IN MEN WITH PROSTATE CANCER

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Elevated body iron stores (serum ferritin >300 µg/L, transferrin saturation TS >50%) are associated with increased risk of liver and lung cancers. To determine whether such association also exists for prostate cancer (PC), we measured serum ferritin, serum iron, total iron-binding capacity (TIBC), and TS in serum samples from 34 men with newly diagnosed, untreated PC and 84 healthy men, ranging in age from 49–78 years. In contrast with other malignancies, men with PC had significantly lower mean concentrations of serum ferritin (156 µg/L) and TS (24.35%) than those without PC (ferritin, 245 µg/L; TS, 31.98%) ($p<0.05$). The 95% confidence intervals for ferritin were 109–203 µg/L and 205–286 µg/L, and those for TS were 20.29–28.4% and 28.35–35.61% for men with and without PC, respectively. Significant differences were observed between both groups in the distribution of serum ferritin (<100, 101–300, >300 µg/L) and TS (<16, 16–50, >50%) ($p<0.05$). A lower percentage of cases than of controls had serum ferritin (17.6% versus 29.8%) and TS (5.9% versus 14.7%) above normal. These differences persisted when the analysis was limited to African-American men (31 cases and 52 controls). Data suggest that elevated body iron stores are less common in men with PC compared to those without PC. (*J Natl Med Assoc.* 2004;96:641–649.)

Key words: serum ferritin ◆ iron overload ◆ iron deficiency ◆ transferrin saturation ◆ prostate cancer

INTRODUCTION

Cancer of the prostate is the most common non-skin cancer in American men and the fourth most common cancer in men throughout the world.[1,2] In 2003, 220,900 new cases are expected to be diagnosed in the United States, and 28,900 deaths are anticipated.[3] In addition to a family history of prostate cancer (PC), race, age, and certain dietary factors have been reported to increase the risk for PC.[2-7] Increased consumption of foods high in animal fat and an increased proportion of calories from animal fat have also been associated with a high risk for PC in all races.[5] In contrast, certain antioxidants, such as selenium and zinc, have been suggested to play a protective role for PC.[8,9]

A number of clinical, epidemiological, and experimental studies suggest that elevated body iron stores increase the risk of cancer overall and, specifically, cancer of the liver, lung, colon–rectum, esophagus, gastrointestinal tract, and pancreas.[10-13] Data collected during the first National Health Assessment and Nutritional Examination Survey (NHANES I) conducted in the United States between 1971 and 1975 also suggested that moderate elevations of body iron stores assessed by transferrin saturation (TS) above 40%, were associated with increased risk and mortality from cancer.[14]

There are two possible mechanisms by which iron may increase the risk of cancer. The first is by increasing the production of free radicals thought to be carcinogenic and the second by regulating the activity of ribonucleotide reductase, the rate-limiting

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enzyme in the DNA synthesis pathway and, hence, cell proliferation.[15,16] Indeed, iron chelation by deferoxamine inhibits the proliferation of tumor cells and normal lymphocytes, and also induces apoptosis.[16-18]

There is a paucity of information on iron status and risk of PC. Therefore, the present study was designed to determine whether elevated body iron stores defined as serum ferritin >300 μg/L and/or TS>50% are associated with increased risk of PC. In the present study, we report for the first time that there is a negative correlation between body iron status and risk of PC.

PATIENTS AND METHODS

Patients

The study involved 118 men—34 with newly diagnosed and untreated PC and 84 without PC. Ninety-one percent of the men with PC (n=31) were African Americans, and 9% were caucasians. In the non-PC (control) group, 61.9% (n=52) were African Americans, 35.7% (n=30) were caucasians, and 2.38% (n=3) were other. The age ranges were 49–75 and 49–78 years for PC patients and controls, respectively. All men participated in an ongoing PC screening and early detection program at Louisiana State University Health Sciences Center in New Orleans. Recommendation for transrectal ultrasonography of the prostate was offered to those participants whose prostate-specific antigen (PSA) level was higher than 2.5 ng/mL for definitive histopathological diagnosis or had an abnormal digital rectal examination. All participants diagnosed with PC and included in the study were diagnosed and treated by the senior author (WR) between 1999 and 2001. PSA samples comprising the control group were chosen from a pool of approximately 6,000 participants based on the following criteria: a) PSA ≤2.5 ng/ml in whom the likelihood of having PC is very low (n=70); b) PSA level >2.5 ng/ml, with a negative biopsy for PC (n=10); c) men ages of 49–78 years, and d) no specific symptoms or complaints at the time of study entry. Since this was a retrospective study, no information had been collected on the dietary intake of iron or factors known to affect iron status, such as smoking, or recent blood loss or donation. The study and consent were approved by the Institutional Review Board of Louisiana State University Health Sciences Center, and informed consent was obtained from all participants prior to screening.

Laboratory Tests

Various measurements were made on previously frozen (-80°C) serum samples. PSA levels were measured by the Bayer Immuno 1TM assay (Bayer Corporation, Tarrytown, NY). Serum ferritin levels were measured by enzyme immunoassay with commercial kits purchased from RAMCO (Houston, TX). Serum iron and TIBC were measured by colorimetry with kits purchased from Sigma (St. Louis, MO). Test samples, standards, and controls were assayed in duplicate according to manufacturer's recommendations. TS was calculated by dividing serum iron by TIBC. Elevated body iron stores were defined as serum ferritin above 300 μg/L and TS >50%.[12,19-20] Reduced body iron stores were defined as serum ferritin less than 12 μg/L and TS <16%.[21] In those men with inflammation (see below), the threshold for reduced body iron stores was defined as serum fer-

Table 1. Mean Age, PSA, and Blood Concentrations of Inflammatory Markers in Men with and without Prostate Cancer

	All Men with PC	All Men without PC	P Value	African Americans with PC	African Americans without PC	P Value
N	34	84		31	52	
Age, years	60.65 ± 1.27	59.05 ± 0.89	0.3188	60.94 ± 1.27	56.46 ± 0.96	0.006
PSA, ng/mL	10.34 ± 1.23	1.52 ± 0.19	0.0001	10.73 ± 1.94	1.52 ± 0.19	0.0001
AGP g/L	0.97 ± 0.05	0.855 ± 0.03	0.0325	0.975 ± 0.053	0.864 ± 0.03	0.0565
ACT, mg/L	356 ± 96	368 ± 8.52	0.482	361 ± 17.7	372 ± 11	0.586
CRP, mg/L	5.63 ± 1.02	3.79 ± 0.65[a]	0.132	5.98 ± 1.097	4.14 ± 0.98[b]	0.23
Cp, mg/L	425 ± 19	440 ± 16[c]	0.626	427 ± 17.2	466 ± 25[d]	0.304

Values are mean ± SEM. Abbreviations: ACT=antichymotrypsin, AGP=a1-acid glycoprotein, CRP=C-reactive protein, Cp=ceruloplasmin, PSA=prostate specific antigen. Samples sizes: a=83; b=51; c=71; d=41.

ritin <100 µg/L.[22] To rule out the presence of an inflammatory process—a factor known to increase serum ferritin and reduce serum iron (hence, TS), we measured serum levels of alpha1-acid glycoprotein (AGP), C-reactive protein (CRP), antichymotrypsin (ACT), and ceruloplasmin (Cp) by radial immunodiffusion.[20,23] Polyclonal antibodies against the various acute phase proteins produced in rabbits, and standard and control serum samples were purchased from Dako Corporation (Carpinteria, CA). Inflammation was recorded as being present when the concentration of at least two of the four acute phase proteins were above the cut-off points suggested by Dako Corporation or those reported in the literature:[24] AGP >1 g/L, CRP >10 mg/L, ACT >500 mg/L, and Cp >500 mg/L.

Statistical Analysis

Descriptive statistics, analysis of variance (ANOVA), and correlation coefficients were performed by a microstatistical program (Microsoft Inc., Indianapolis, IN) as described in the literature.[25] Since serum ferritin levels are skewed, they were logarithmically transformed before ANOVA was performed. Antilogarithm serum ferritin levels were recalculated to determine geometric means. Serum ferritin and TS were also compared by ANOVA as a function of PC status and age (years: <51, 51–55, 56–60, 61–70, and 71), and inflammation status as defined in the preceding paragraph. The 95% confidence intervals (CI) were calculated as follows: $\bar{x} \pm 1.96 \times SEM$, where $\bar{x}$ = the mean of the group, SEM = standard error of the mean, 1.96 a Z score that describes the location (standard deviation) of a particular value relative to the population mean. Details on the derivation and use of the formula are described in the literature.[25] The level of significance was set at $p<0.05$.

RESULTS

Information on tumor stage was available in 85% (n=29) of PC patients. The tumor stage was T1 in 24 patients, T2 in four patients, and there was only one patient whose tumor stage was T3. Gleason's score varied from 3 to 10. In the overall study population, there was no significant difference in mean age between cases and controls. However, African Americans with PC were 4.48 years older than those without PC (Table 1, p=0.006). As expected, the mean concentrations of PSA were significantly higher in PC patients (including African Americans) than in controls (Table 1, p<0.0001). Men with PC had significantly higher mean AGP concentrations than those without PC (p=0.033). Both groups had nearly identical mean levels of ACT, Cp, and CRP. The differences in the concentrations of PSA and AGP were maintained when the analysis included only African-American men from both cohorts (p=0.0001 for PSA and p=0.0565 for AGP).

In contrast to what we expected, men with PC had significantly lower mean concentrations of serum ferritin and TS but higher TIBC than those without PC (Table 2, p≤0.04). Differences between both study groups persisted when the analysis

Table 2. Concentrations of Indicators of Iron Status in Men with and without Prostate Cancer

	All Men with PC	All Men without PC	P Value	African Americans with PC	African Americans without PC	P Value
N	34	84		31	52	
Serum ferritin, µg/L	156 ± 24	245 ± 21	0.043	157 ± 26	242 ± 25	0.0297
Log ferritin, µg/L	1.997 ± 0.082	2.2226 ± 0.048	0.035	1.9919 ± 0.087	2.214 ± 0.063	0.0391
Ferritin geometric mean, µg/L	99	167		98	164	
Ferritin 95% CI*	109 to 203	205 to 286		106 to 208	193 to 291	
Serum iron µmol/L	16.78 ± 1.58	18.497 ± 1.08	0.2778	16.97 ± 1.7	18.16 ± 1.02	0.528
TIBC, µmol/L	69.87 ± 2.67	60.43 ± 2.27[a]	0.0178	69.07 ± 2.78	59.52 ± 2.77[b]	0.025
TS, %	24.35 ± 2.07	31.98 ± 1.85[a]	0.0139	24.798 ± 2.24	32.12 ± 2.22[b]	0.0283
TS%, 95% CI*	20.29 to 28.41	28.35 to 35.61		20.41 to 29.19	28.49 to 36.47	

Values are mean ± SEM. *95% CI for age unadjusted data. 95% CI=mean ± 1.96 x SEM (see text and Ref 25 for details). Sample sizes: a=68, b=41. For serum iron the sample sizes were 70 and 42 for the overall study population and African-American men, respectively.

included only African-American men (Table 2, p≤0.04). For both serum ferritin and TS, there was very little overlap in the 95% CIs between the groups. In contrast to serum ferritin, TIBC, and TS, there were no significant differences in serum iron concentrations between cases and controls.

When the analysis was limited to men without inflammation (as defined in the methods), the differences between men with and without PC persisted for serum ferritin and TIBC (overall study population, p≤0.04; African-American men, p=0.055 for TIBC, and p=0.033 for log serum ferritin, Table 3). Although the same trend was observed for TS, the differences became nonsignificant. In the subgroup of men with inflammation present, the same trend was also observed, but the differences were not significant for serum ferritin and TIBC (data not shown). Interestingly, the 10 PC patients with inflammation (at least two acute phase proteins above normal) had significantly lower mean serum iron concentration (12.63 ± 1.88 μmol/L) and TS (18.84 ± 3.79%) than the six men with PC and also with inflammation (serum iron 22.08 ± 3.87 μmol/L and TS, 39.79 ± 9.36%) (p≤0.027).

When the results of serum ferritin and TS were further analyzed as a function of PC and age (inclusive of men with inflammation and both races), the same trend was observed as for the overall study population. In each age group (<51, 51–55, 56–60, 61–65, 66–70, >70 years), the mean concentrations of serum ferritin and TS of PC patients tended to be lower in men with than in those without PC. However, the differences between both groups were significant only for the age range 51–55 and >70 years (p<0.05, Figure 1). The lack of significant differences between both cohorts in men with different age categories was in part due to the small sample sizes.

Within the PC population, there were no significant differences in mean serum ferritin between the 24 men with tumor stage T1 (149 μg/L, range 5.55 to 566 μg/L) and the five men with tumor stage T2 or T3 (199 μg/L, range 37.2–492 μg/L). We also found no significant differences in TS (mean, 24.3%, range 9.2–50.87%, versus mean 19.7%, range 7.43–27.2%) between both subgroups, respectively. There was no significant correlation with serum ferritin and Gleason's score (r=0.241). There were also no significant differences in mean serum ferritin concentrations and TS between PC patients with and without tissue inflammation (no data shown).

Serum ferritin levels ranged from 5.55–566 μg/L (median, 115 μg/L) in men with PC and 8– 843 mg/L (median 209 μg/L) in those without PC. In the subgroup of African-American men, the range and median were: 5.55–566 μg/L and 126 μg/L for cases and 8–752 μg/L and 223 μg/L for controls, respectively. The distribution (2.5th to 95th percentiles) of serum ferritin and TS is summarized in Figure 2, respectively. Between the 10th and the 95th percentiles, there was no overlap between men with and without PC in

Table 3. Concentrations of Indicators of Iron Status in Men with and without Prostate Cancer and Inflammation

	All Men with PC	All Men without PC	P Value	African Americans with PC	African Americans without PC	P Value
N	24	78		21	48	
Serum ferritin, μg/L	158 ± 28	250 ± 21	0.0308	157 ± 26	248 ± 27	0.0535
Log ferritin, μg/L	1.9952 ± 0.103	2.2491 ± 0.046	0.0135	1.987 ± 0.12	2.2457 ± 0.06	0.0325
Ferritin geometric mean, μg/L	99	177		97	176	
Ferritin 95% CI	103 to 213	209 to 291		106 to 208	195 to 301	
Serum iron μmol/L	18.51 ± 2	18.16 ± 1.12	0.873	19.04 ± 2.24	17.75 ± 1.05	0.5578
TIBC, μmol/L	70.14 ± 3.41	60.22 ± 2.42[a]	0.0348	68.92 ± 3.89	59.33 ± 2.95[b]	0.0548
TS, %	26.82 ± 2.558	31.23 ± 1.8[a]	0.189	27.84 ± 2.83	31.21 ± 2.19[b]	0.3532
TS%, 95% CI*	21.8 to 31.84	27.7 to 34.76		2.29 to 33.39	26.92 to 35.5	

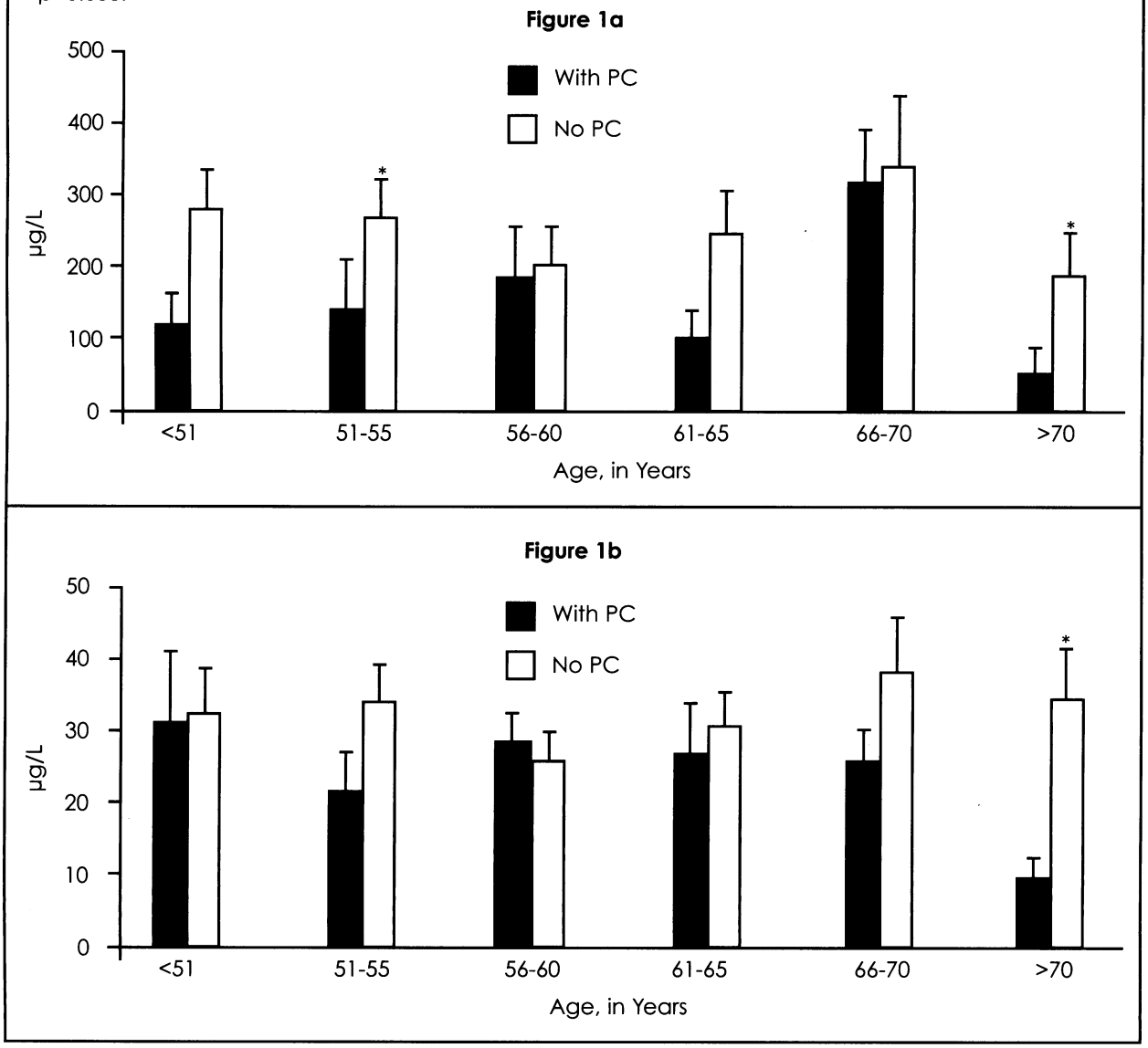
Values are mean ± SEM. Abbreviations: NS=not significant. *95% CI for age unadjusted data. Sample sizes: a=62; b=37. For serum iron, the sample sizes for serum iron iron were 64 for all controls and 38 for African-American men.

the distribution of both measurements.

In the overall study population (Figure 3a) and the subgroup of African-American men (Figure 3B), there were differences between cases and controls in the distribution of men with serum ferritin in three ranges: below normal (<12 or <100 μg/L in men with inflammation), normal (101–300 μg/L), and above normal (>300 μg/L) (χ^2=7.925, p=0.019, for overall; study population and χ^2=4.672; p=0.097, for African-American men). A lower percentage of men with PC than of those without PC had serum ferritin concentrations above 300 μg/L. When the threshold of serum ferritin was raised to 100 μg/L in men with inflammation, 35.3% of all men with PC (n=12) and 11.9% of those without PC (n=10) had reduced body iron stores (χ^2=7.797, p<0.01). Moreover, in the subgroup of African-American men, the same trend was observed (Figure 3a, χ^2=4.73, p<0.05).

As for serum ferritin, significant differences

Figure 1. Serum ferritin (A) and transferrin saturation (B) in men with and without PC and by age range. Sample sizes varied from 3 to 8 and 9 to 21 for serum ferritin in cases and controls, respectively; and 3 to 8, and 5 to 18, for transferrin saturation in cases and controls, respectively. *p<0.05, compared with cases and of the same age range. For serum ferritin, *p≤0.07; for transferrin saturation, *p=0.038.



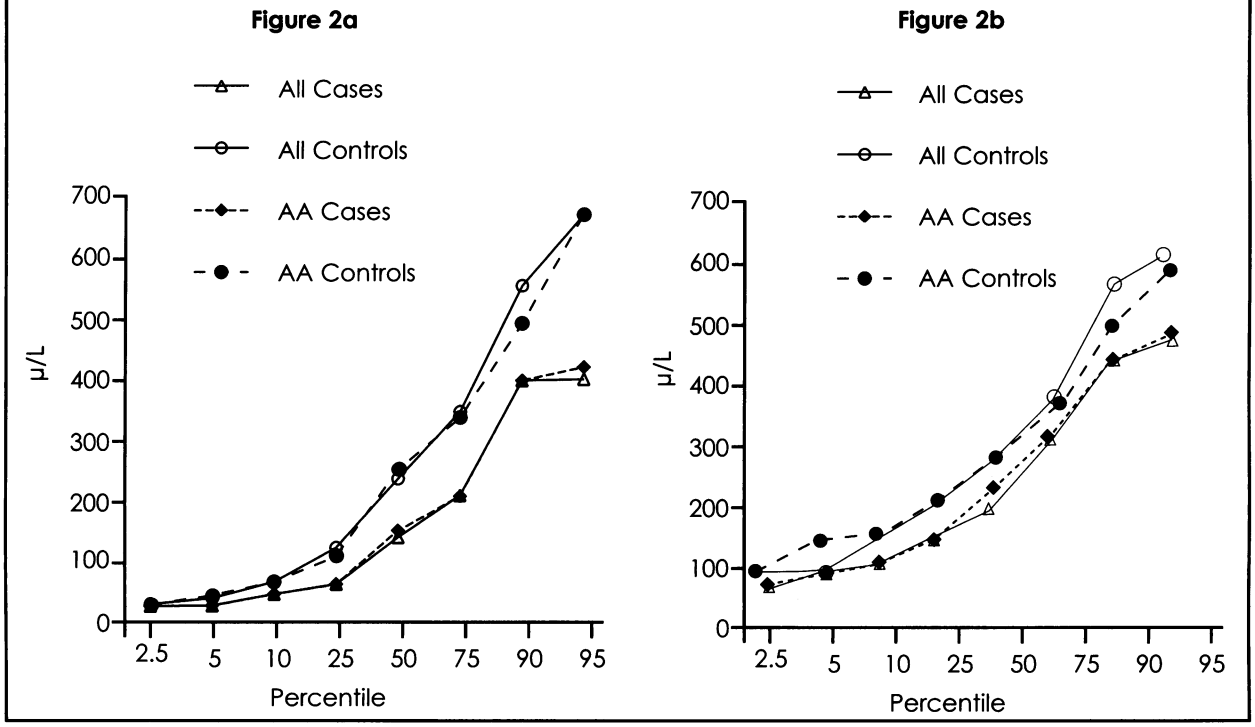
were also observed between men with and those without PC in the disitribution of TS in three ranges: below normal (<16%), normal (16–50%), and above normal (>50%) (Figure 3B; overall χ^2=10.15, df=2, p=0.0063; African-American men χ^2=7.35, p= 0.0254). A lower percentage of men with PC than of those without PC had TS >50% (Figure 3B). In contrast, in the overall study population (inclusive of men with inflammation), a higher percentage of men with PC than of those without PC had TS <16%, suggestive of reduced body iron stores (χ^2=8.085, p<0.05). When the analysis was limited to African-American men, the same trend was observed (Figure 3B, χ^2=4.976, p<0.05). When the analysis was limited to men without inflammation, we also observed a slightly higher percentage of African-American men with (28.57%) than of those without (8.1%) PC who had TS below normal (χ^2=3.44, p>0.05).

DISCUSSION

Ferritin is the main intracellular protein involved in iron storage, and its synthesis is regulated by body iron stores. Although the liver, spleen, and bone marrow contain the highest concentrations of stored iron, variable amounts are present in many other organs, including serum.[21] It is now generally accepted that serum ferritin concentrations reflect the amount of body iron stores since concentrations below 12 μg/L are always associated with depletion of body iron stores, whereas those above 300 μg/L are seen in persons with iron overload.[11,19-21] Each microgram of serum ferritin represents approximately 8 mg of stored iron.[26] Serum ferritin is mainly secreted by reticuloendothelial cells and contains very little iron. When body iron stores are depleted, the resulting low serum ferritin concentration is usually associated with an increase in TIBC.

In a cohort study, Knekt et al. compared serum iron concentrations, TIBC capacity, and TS in 130 Finnish men who developed PC during a 14-year follow-up period with those of 21,085 men who did not.[27] They observed no significant differences between both groups. Stevens et al. also did not observe significant differences in mean serum iron,

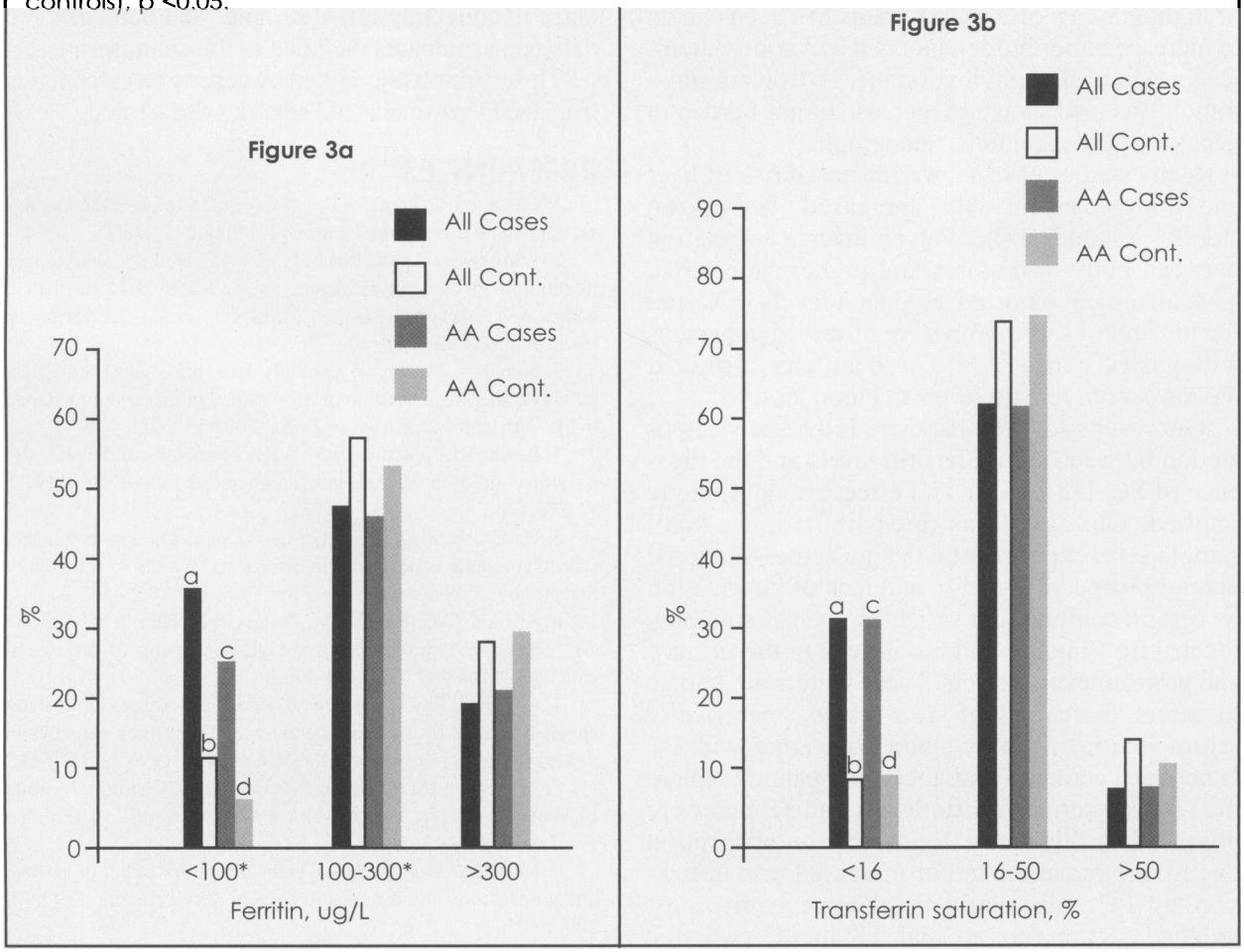
Figure 2. Percentiles of serum ferritin (A) and transferrin saturation (B) in men with and without PC. Abbreviations and sample sizes are: for serum ferritin, all cases=34 men with PC; all controls=84 men without PC; AA=31 African-American men with PC, and 52 African-American without PC. For transferrin saturation, sample sizes are: 34, 31, 68, 41, all men, and AA with PC, and all controls and AA without PC, respectively.



TIBC, and TS between men with and those without PC who were included in the NHANES I survey.[14] However, serum iron (hence, TS) is subject to wide daily and diurnal variations, and it is a poorer indicator of iron status than serum ferritin. In both cohort studies, data on serum ferritin were not reported.

In the present study, we observed lower concentrations of serum ferritin and TS but higher TIBC in men with PC than in those without PC. This is in contrast to what has been reported for cancer of the liver and lung.[10,14] The small differences persisted even after subjects were matched to controls by race and inflammatory status. TS and/or serum ferritin concentrations indicative of low body iron stores were observed more often in men with PC than those without PC. Conversely, TS and serum ferritin concentrations suggestive of elevated body iron stores were less often in men with PC than in those without PC. The median serum ferritin concentrations of African-American men without PC (223 µg/L) that we observed are very close to the value (approximately 200 µg/L) reported by Zacharski et al. for healthy African-American men (40–59 years of age) included in the NHANES III[28] (see Figure 2 of the citation). The median of our overall study population (209 µg/L) is also similar to the values of the

Figure 3. Percentage of men with and without PC with serum ferritin (A) and transferrin saturation (B) suggestive of reduced, normal, and elevated body iron stores. Abbreviations are: AA=African-American men; cases=men with PC; cont.=controls=men without PC.* For Figure 3 A, reduced body iron stores were defined as either serum ferritin <12 µg/L or <100 µg/L for men with inflammation. Normal body iron stores were defined as either serum ferritin 12–300 µg/L or 100–300 µg/L for men with inflammation. With each measurement (serum ferritin or transferrin saturation), bars followed by different letters are significantly different: a>b (all cases versus all controls); c>d (AA cases versus AA controls), p <0.05.



75th percentiles (182–209 μg/L) of American men (inclusive of different races) 48–76 years of age.[29] However, the median serum ferritin values of men with PC (115 μg/L overall and 126 μg/L for the African-American men) resemble those of the 50th percentile (111–128 μg/L) for men of the same age range.[29] Since we observed the expected inverse relationship between the concentrations of serum ferritin and TIBC in PC patients, our data suggest suboptimal body iron stores in men with PC.

Most studies on iron status and risk for cancer have focused on iron overload for two reasons. First, iron is a powerful catalyst of free-radical generation, and second, it is an essential growth nutrient. Although iron is not carcinogenic, it is known to induce hydroxyl radicals from the less reactive superoxide anion and hydroxyl peroxide via the Fenton reaction.[30] The highly reactive free radicals are thought to induce DNA mutations, and therefore, to be the mechanisms by which iron may increase the risk of cancer. Indeed, administration of high amounts of iron to rodents has been shown to increase tumor burden induced by various chemicals, such as dimethylhydrazine.[31,32] Iron administration was also shown to increase tumor burden in hepatocellular carcinoma xenographs.[33]

Many studies have shown increased risk of liver and lung cancer with increased body iron stores.[10,11,14] Studies showing an inverse correlation between body iron stores and higher cancer risk have also been reported. Reduced levels of serum ferritin and/or serum iron were observed in persons with gastric cancer.[24,34-36] These authors attributed the low serum ferritin levels to blood loss.

Our results suggest that there is a negative association between serum ferritin levels and the presence of PC, but a cause and effect are not directly implied. Our study has three limitations: small sample size, experimental design (cross-sectional but not prospective study), and lack of information on certain confounding variables, such as smoking, dietary iron intake, and blood loss in the urinary and gastrointestinal tracts. These factors are known to affect indicators of iron status, specifically serum ferritin.[36] Urinary blood loss in men with PC is not very common and, therefore, cannot explain the reduced serum ferritin levels and TS that were observed in this study. Reduced iron absorption due to inflammation and/or increased iron utilization by PC cells could be the mechanisms of reduced serum ferritin and TS in PC patients. Indeed, inflammation was more common in men with than in those without PC. While 25 of the 34 cases (73.5%) had some degree of inflammation (at least one acute phase protein above normal), only 26 of the 84 controls (30.95%) did. In PC patients, 29.4% (10/34) compared with only 7.14% (6/84) had at least two acute-phase proteins above normal.

In summary, our results suggest that elevated body iron stores are less common in men with PC than in those without PC. In fact, they suggest that reduced body iron stores are more common in PC patients than in non-PC men. This is the first study correlating body iron stores with PC. A prospective study is required to determine whether reduced body iron stores are a consequence or cause of PC related to a third factor which is directly influencing both the iron status and carcinogenesis domains.

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