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BODY IRON STORES AND RISK OF CANCER

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A high level of available tissue iron may increase the risk of cancer through its contribution to the production of free oxygen radicals. Serum iron, total iron-binding capacity (TIBC) and transferrin saturation levels were studied for their prediction of different cancers in a cohort of 41,276 men and women aged 20–74 years and initially free from cancer. During a mean follow-up of 14 years, 2,469 primary cancer cases were diagnosed. Excess risks of colorectal and lung cancers were found in subjects with transferrin saturation level exceeding 60%. The relative risks, adjusted for age, sex and smoking, were 3.04 for colorectal cancer and 1.51 for lung cancer, in comparison with subjects having lower levels. The risk of lung cancer was inversely related to serum TIBC, with a relative risk between the highest and lowest quartiles of 0.69 for men and 0.19 for women. For the risk of stomach cancer, we detected inverse relationships with serum iron and with transferrin saturation and a positive relationship with TIBC, but these associations weakened when the cancer cases occurring during the 5 first years of follow-up were excluded. High iron stores may increase the risk of colorectal cancer, whereas low iron stores may be an early sign of occult stomach cancer.

It has been suggested that a high level of available tissue iron increases the risk of cancer by increasing the production of DNA-damaging free oxygen radicals, and by enhancing the growth of cancer cells (Stevens and Kalkwarf, 1990). Cohort studies on overall cancer risk have mainly shown the association of an elevated risk with high iron stores (Stevens *et al.,* 1986, 1988) and of a decreased risk with low-level stores (Selby and Friedman, 1988). Of the few studies reporting site-specific results, one cohort study has shown a positive association between available iron stores and colon cancer risk (Stevens *et al.,* 1988), and one case-control study has revealed a similar association between dietary iron and rectal cancer (Freundenheim *et al.,* 1990). Corresponding associations have also been reported for lung cancer (Stevens *et al.,* 1988; Selby and Friedman, 1988) and for cancers of the esophagus and the bladder (Stevens *et al.,* 1988, 1993). In contrast, 3 cohort studies have suggested an inverse association between available iron stores and risk of stomach cancer (Stevens *et al.,* 1988; Akiba *et al.,* 1991; Nomura *et al.,* 1993).

In a preliminary study based on a Finnish population with a relatively low prevalence of hemochromatosis (Karlsson *et al.,* 1988), we found only a non-significant association between transferrin saturation and overall cancer mortality, suggesting that the possible associations may be site-specific (Takkunen *et al.,* 1989). In the present study, we investigate whether there is an elevated incidence of cancers of certain sites in persons with high available iron stores in this same cohort of Finnish men and women.

MATERIAL AND METHODS

During the period 1966–1972, the Mobile Health Clinic of the Social Insurance Institution carried out multiphase screening examinations in several regions of Finland (Knekt *et al.,* 1988). Altogether 62,440 men and women aged 15 years or older from rural, semi-urban and industrial communities throughout the country were invited to participate in the study. The participation rate was 82.5%.

All participants completed a pre-mailed questionnaire (checked at the baseline examination) with information about place of residence, occupation and smoking. For the purpose of analysis, occupations were divided into main classes according to the Nordic Standard Classification of Occupations, an adaptation of the ILO classification (Brockington, 1967). Subjects were classified according to smoking status as never-smokers, ex-smokers, smokers of cigars or pipe only, smokers of less than 15 cigarettes a day, and smokers of 15 cigarettes or more a day. The first 2 categories were also combined to create a class of non-smokers. Body height and weight were measured at the baseline examination, and the body mass index [weight(kg)/height^o(m^o)] was calculated.

Venous blood samples were taken after overnight fasting. Hemoglobin was determined in about 88% of the study population, whereas hematocrit (packed cell volume, PCV), serum iron and total iron binding capacity (TIBC) were determined in all the persons examined. Transferrin saturation was determined as the serum iron percentage of TIBC. Hemoglobin and PCV-values were determined from EDTA-blood samples; Hb by the cyanmethemoglobin method (van Kampen and Zijlstra, 1961) and the hematocrit value by the microhematocrit method. Serum samples were immediately frozen to −20°C and analyzed after 1–3 weeks of storage. Serum iron and TIBC were determined with a Technicon (Tarrytown, NY) AutoAnalyzer. The coefficients of variation calculated from repeated analyses of control series were 3.7% for serum iron and 3.4% for TIBC.

The present study covers 41,276 persons (18,813 men and 22,463 women) aged 20–74 years from whom serum iron and TIBC determinations were obtained and who had never had cancer. Information concerning subsequent cancer incidence, available through the nationwide Finnish Cancer Registry (Teppo *et al.,* 1980), was linked to the baseline data. During a mean follow-up of 14 years, to the end of 1984, 2,469 cancer cases were registered.

For descriptive purposes the age-adjusted mean levels of several descriptive and potential confounding factors among cancer cases and non-cases were estimated using the general linear model (Cohen and Cohen, 1975). Cox's proportional hazards model was used to estimate the association between iron, total iron-binding capacity, and transferrin saturation and the risk of cancer, adjusting for different confounding factors (Kalbfleisch and Prentice, 1980). Relative risks were computed for quartiles of these serological variables, using the lowest quartile as the referent category. Statistical significances were assessed using likelihood ratio tests based on the models.

RESULTS

The subjects who subsequently developed cancer were older and more often current smokers than the others (Table I). Male cancer cases had a lower body mass index and a lower level of hemoglobin than cancer-free subjects.

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TABLE I – AGE- AND SMOKING-ADJUSTED MEAN LEVEL OF DIFFERENT FACTORS AMONG CANCER CASES AND CANCER-FREE SUBJECTS

Factor	Men			Women		
	Cases (n = 1,370)	Cancer-free (n = 21,085)	*p* value	Cases (n = 1,099)	Cancer-free (n = 17,714)	*p* value
Age[1] (years)	54.9	39.5	<0.001	53.1	42.3	<0.001
Smoking[2] (%)	65.7	51.6	<0.001	18.6	16.7	0.10
Height (cm)	172.8	172.5	0.14	159.6	158.9	<0.001
Weight (kg)	73.2	74.7	<0.001	65.3	64.5	0.03
BMI (kg/m^2)	24.5	25.1	<0.001	25.7	25.6	0.62
Hb[3] (g/100 ml)	15.2	15.3	<0.001	13.6	13.6	0.34
Hematocrit (vol%)	46.0	46.1	0.18	41.9	42.0	0.51

[1]Adjusted for smoking.–[2]Adjusted for age.–[3]Numbers of cases and cancer-free subjects are 1,233 and 18,839, respectively, for males and 982 and 15,258, respectively, for females.

TABLE II – AGE- AND SMOKING-ADJUSTED MEAN LEVEL OF SERUM IRON, TIBC AND TRANSFERRIN SATURATION AMONG CANCER CASES AND CANCER-FREE SUBJECTS

Site of cancer	Men				Women			
	Number of individuals	Serum iron (μg/100 ml)	TIBC (μg/100 ml)	Transferrin saturation (%)	Number of individuals	Serum iron (μg/100 ml)	TIBC (μg/100 ml)	Transferrin saturation (%)
No cancer	21,085	115.7	340.3	34.5	17,714	99.9	353.9	28.9
Cancer, all sites	1,370	116.0	338.5	34.8	1,099	99.4	355.7	28.6
Lung	416	114.5	333.2**	34.8	24	109.0	337.6	32.6
Prostate	130	118.1	344.0	34.8	—	—	—	—
Stomach	120	107.0*	350.5*	30.8**	76	95.7	357.3	27.2
Colon	27	120.4	327.1	37.3	57	103.4	353.6	29.7
Rectum	49	118.1	338.6	35.4	40	108.9	372.2*	30.0
Pancreas	43	115.9	337.1	35.3	46	103.0	363.8	29.1
Urinary organs	82	115.6	341.2	34.4	36	100.1	352.1	28.7
Nervous system	42	122.1	348.5	35.3	29	110.8	356.7	31.1
Lymphomas/ leukemia	63	116.6	334.7	35.2	59	98.7	348.8	29.1
Skin: basal cell	155	116.6	337.4	35.3	152	100.0	355.5	29.1
Breast	—	—	—	—	192	100.2	353.9	29.0
Endometrium	—	—	—	—	57	96.4	363.7	27.4
Ovary	—	—	—	—	57	90.7	354.7	26.4
Cervix	—	—	—	—	60	92.6	355.3	27.1
Other sites	243	119.5	339.2	36.0	214	98.6	355.0	28.2
p value for heterogeneity		0.55	0.04	0.16		0.73	0.66	0.79

Test for difference from the mean of cancer-free subjects: $^{**}p < 0.01$, $^{*}p < 0.05$.

No significant differences in mean levels of serum iron, total iron-binding capacity (TIBC) or transferrin saturation were observed between all the cancer cases combined and the cancer-free subjects (Table II). There was, however, considerable variation in the mean levels of single sites of cancer, with significant differences for TIBC ($p = 0.04$) and suggestive differences for transferrin saturation ($p = 0.16$) among men.

The age- and smoking-adjusted relative risk of all cancers combined did not vary significantly between quartiles of serum iron (Table III). There was, however, a significant inverse gradient between serum iron level and risk of stomach cancer among men ($p < 0.01$) and a suggestive similar association among women ($p = 0.17$), the relative risks (RR) between the highest and lowest quartiles being 0.60 [95% confidence interval, (CI) = 0.36–1.00] and 0.59 (CI = 0.30–1.15), respectively. Further adjustment for geographic area, occupation, hematocrit and body mass index did not notably alter the results (data not shown).

The age- and smoking-adjusted relative risk of cancer (all sites) between the highest and lowest quartiles of TIBC among men was 0.88 (CI = 0.76–1.02), and there was a significant inverse gradient ($p = 0.04$) (Table III). This association was mainly due to lung cancer, which was significantly inversely associated with TIBC ($p < 0.001$), with a relative risk of 0.69 (CI = 0.52–0.91). A suggestive inverse association ($p = 0.10$) was also observed among women with a relative risk of 0.19 (CI = 0.02–1.51). The associations persisted after adjustment for geographic area, occupation, hematocrit and body mass index, the relative risks being 0.70 ($p < 0.01$) and 0.16 ($p = 0.06$), respectively. They also persisted after exclusion of lung cancer cases occurring during the first 5 years of follow-up. On the other hand, there was a significantly positive gradient between TIBC and the occurrence of stomach cancer among men ($p < 0.05$), with a relative risk of 1.29 in the highest quartile. This gradient disappeared, however, after exclusion of the stomach cancer cases occurring during the first 5 years of follow-up (RR = 0.90, $p = 0.45$).

The relative risk of all cancers combined did not vary significantly between quartiles of transferrin saturation (Table III). There was, however, a significant inverse gradient ($p < 0.001$) for stomach cancer among men, with a relative risk of 0.55 (CI = 0.33–0.90) between the highest and the lowest quartiles, and a suggestive inverse gradient ($p = 0.10$) among women (RR = 0.60, CI = 0.31–1.13). The associations were somewhat altered by exclusion of the first 5 years of follow-up, the relative risks being 0.82 (CI = 0.45–1.48) for men and 0.74 (CI = 0.36–1.53) for women. There were no marked changes in the relative risks of cancer of all sites combined by transferrin saturation after excluding the stomach cancer cases from the analyses (data not shown).

Three percent of the total population had transferrin saturation levels of over 60%. A study of the risk of cancer of all sites combined, and of those sites with the highest incidence among subjects with transferrin saturation above 60% gave significantly elevated risks of cancer of all sites and of colorectal cancer (Table IV). As adjusted for age and smoking, the

TABLE III – RELATIVE RISK[1] (RR) OF CANCER, BY SITE, BETWEEN THE HIGHEST AND LOWEST QUARTILES[2] OF SERUM IRON, TIBC AND TRANSFERRIN SATURATION

Site of cancer	Men							Women						
	Number of cases	Iron		TIBC		Transferrin saturation		Number of cases	Iron		TIBC		Transferrin saturation	
		RR	p value[3]	RR	p value[3]	RR	p value[3]		RR	p value[3]	RR	p value[3]	RR	p value[3]
All sites	1,370	0.94	0.68	0.88	0.04	1.00	0.62	1,099	0.95	0.24	1.05	0.21	0.85	0.17
Lung	416	0.91	0.61	0.69	<0.001	1.15	0.51	24	1.66	0.38	0.19	0.10	2.06	0.20
Prostate	130	0.84	0.97	1.13	0.73	0.96	0.85	—	—	—	—	—	—	—
Stomach	120	0.60	<0.01	1.29	<0.05	0.55	<0.001	76	0.59	0.17	1.08	0.55	0.60	0.10
Colon	27	1.64	0.63	0.69	0.13	1.73	0.35	57	0.94	0.75	1.18	0.72	0.97	0.82
Rectum	49	1.29	0.82	0.62	0.68	1.04	0.71	40	0.99	0.22	2.47	0.02	0.94	0.66
Pancreas	43	1.13	0.94	0.75	0.57	1.24	0.74	46	0.99	0.80	1.80	0.19	0.69	0.91
Urinary organs	82	0.79	0.80	1.01	0.99	0.85	0.84	36	1.14	0.86	0.68	0.85	1.39	0.81
Nervous system	42	1.61	0.36	2.26	0.29	1.12	0.77	29	1.96	0.20	1.68	0.78	1.30	0.37
Lymphomas/leukemia	63	0.76	0.99	0.59	0.31	0.83	0.79	59	0.93	0.62	0.79	0.47	0.68	0.97
Skin: basal cell	155	0.81	0.90	0.71	0.33	0.92	0.66	152	0.94	0.73	0.94	0.68	1.11	0.90
Breast	—	—	—	—	—	—	—	192	0.85	0.95	1.00	0.95	0.78	0.98
Endometrium	—	—	—	—	—	—	—	57	1.07	0.44	1.33	0.17	0.83	0.32
Ovary	—	—	—	—	—	—	—	57	0.59	0.06	1.24	0.88	0.46	0.09
Cervix	—	—	—	—	—	—	—	60	0.82	0.19	0.83	0.82	0.67	0.28
Other sites	243	1.23	0.23	1.07	0.58	1.15	0.11	214	1.15	0.35	1.01	0.71	0.90	0.23

[1]Adjusted for age and smoking.–[2]The quartiles are based on the distribution of the total study population. Quartile divisions are: iron (μg/100 ml) ≤88, 89–111, 112–138, >138 in men and ≤69, 70–96, 97–125, >125 in women; TIBC (μg/100 ml) ≤308, 309–336, 337–369, >369 in men and ≤313, 314–348, 349–388, >388 in women; transferrin saturation (%) <26.0, 26.0–32.9, 33.0–41.3, >41.3 in men and <20.0, 20.0–27.8, 27.9–36.3, >36.3 in women.–[3]Test for trend.

TABLE IV – RELATIVE RISK[1] OF CANCER BETWEEN TRANSFERRIN SATURATION LEVELS OVER AND UNDER 60%, MEN AND WOMEN COMBINED

Site of cancer	Total population				First 5 years of follow-up excluded			
	Number of cases		Relative risk	95% confidence interval	Number of cases		Relative risk	95% confidence interval
	≤60	>60			≤60	>60		
All	2,380	89	1.43	1.16–1.77	1,754	66	1.44	1.13–1.84
Lung	418	22	1.51	0.98–2.32	305	14	1.33	0.78–2.28
Colorectum	162	11	3.04	1.64–5.62	124	11	3.98	2.13–7.41

[1]Adjusted for sex, age and smoking.

relative risk of cancer of all sites was 1.39 (CI = 1.08–1.79) among men and 1.48 (CI = 0.99–2.20) among women with transferrin saturation above 60% in comparison with subjects with lower saturation levels. The strongest association was observed for colorectal cancer, with a relative risk of 3.04 (CI = 1.64–5.62) for men and women combined. The association was present in both sexes and for colon as well as for rectal cancer and it persisted after further adjustment for geographic area, occupation, hematocrit and body mass index (data not shown), and after exclusion of the cancer cases occurring during the first 5 years of follow-up (Table IV).

DISCUSSION

In accordance with our preliminary study (Takkunen *et al.*, 1989), we found no linear gradient between indicators of body iron stores and the incidence of cancer of all sites combined in the present study. A recent study reported a trend for transferrin saturation which was mainly due to an elevated risk in the highest quartile (Stevens *et al.*, 1993). Although we could not find a significantly increased risk of cancer in the highest quartile of the transferrin saturation distribution, we, like Stevens *et al.* (1993), did find an elevated risk at levels exceeding the 60% transferrin saturation point. This threshold is regarded as a reasonably good screening limit for hemochromatosis, particularly in men (Edwards *et al.*, 1988), and thus values exceeding this level indicate, in many cases, increased iron stores of clinical importance. The lack of association at lower levels in the present study may partly be explained by the relatively low prevalence of hemochromatosis in the Finnish population (Karlsson *et al.*, 1988).

Serum ferritin is the best available indicator of iron stores which is suitable for population studies (Cook *et al.*, 1974; Lipschitz *et al.*, 1974), although transferrin saturation has also been considered to reflect tissue-iron stores reasonably well (Lipschitz *et al.*, 1974). TIBC varies inversely with iron stores but the association may be less reliable in persons with iron excess than in persons with normal or depleted iron stores (Weinfeld, 1964; Takkunen, 1976). Serum ferritin has been used in certain studies focusing on the association between tissue iron stores and cancer incidence (Stevens *et al.*, 1986; Akiba *et al.*, 1991; Nomura *et al.*, 1993), whereas transferrin saturation and TIBC have been used as indicators for body iron stores in the present and other studies (Stevens *et al.*, 1988, 1993; Selby and Friedman, 1988). It is possible that high transferrin saturation is not always primarily related to iron excess, but rather may also be secondarily due to other disorders. Chronic inflammations, which often precede some cancers, leading to decreased liver synthesis of transferrin and inefficient tissue iron utilization, may result in lower TIBC values and thus, at normal serum iron levels, to elevated transferrin saturation (Morgan, 1974). To what extent these conditions have caused high transferrin saturation and low TIBC levels in the present study population is unknown. The finding by us and others (Selby and Friedman, 1988) of an elevated risk of lung cancer associated with lower levels of TIBC may be explained by these events. In a normal population, this occurrence is of importance and accordingly high transferrin saturation remains a reasonably good indicator of high iron stores, regardless of the cause of the iron accumulation and utilizability of the iron in heme synthesis.

We found an elevated risk of colorectal cancer among men and women with a very high transferrin saturation level. This finding is supported by the results of a cohort study among men (Stevens *et al.,* 1988). It is also in agreement with the hypothesis that an excess of unabsorbed iron may elevate the risk of colon cancer (Graf and Easton, 1985; Nelson, 1992). Because of tight metabolic control of iron homeostasis, high tissue-iron stores lead to lower absorption of dietary iron (Finch and Huebers, 1982), and thus probably to a higher concentration of iron in the contents of the colon. This excess dietary iron may lead to synthesis of cancer-promoting free oxygen radicals (Nelson, 1992). The hypothesis is also supported by the finding of a stronger effect of dietary iron on rectal cancer risk in males with low intakes of antioxidant beta-carotene (Freundenheim *et al.,* 1990). According to some animal experiments, parenteral iron administration and thus high tissue-iron storage enhances colorectal carcinogenesis (Nelson, 1992). However, in spite of the suggestive results obtained in the present study and a theoretical background, our finding is based on relatively few cancer cases and thus no firm conclusions can be drawn.

Lower serum iron and transferrin saturation and higher TIBC were observed among stomach cancer cases than among cancer-free subjects in the present study, especially in men. This finding of an elevated risk of stomach cancer among subjects with lower iron stores is similar to that reported in 3 previous studies (Akiba *et al.,* 1991; Stevens *et al.,* 1993; Nomura *et al.,* 1993). It has been suggested that the association may be at least primarily due to occult cancer, involving a depression of iron levels through occult bleeding or poor iron absorption at early stages of the disease (Akiba *et al.,* 1991). Exclusion of the stomach cancer cases which occurred during the first 5 years of follow-up weakened the associations in the present study, in agreement with that suggestion. This observation has also been confirmed in a study suggesting a decrease in hemoglobin at early stages of stomach cancer (Nakamura *et al.,* 1982). The weaker associations among women may be due to greater variations in serum iron levels, related to menstrual cycles. They may also be due to the smaller numbers of cancer cases.

In general, the results of the present study are in line with the hypothesis that there is a causal connection between high body iron stores and an elevated incidence of cancer. Although theoretical explanations might be suggested (Weinberg, 1984; Halliwell and Gutteridge, 1989), the factual situation is much more complicated. First of all, there is hardly a clear continuous trend between body iron stores and cancer occurrence, the elevated risk being accentuated only in the group with extremely high iron stores. Furthermore, the cause-and-effect relationships may differ at the upper and lower ends of the iron store distribution. There may also be other important, but still largely unknown, site-related pathogenetic mechanisms, which further explain the role of excess iron as a possible promoter of carcinogenesis.

In conclusion, we found that persons with very high available body iron stores had an elevated risk of cancer of all sites combined and of colorectal cancer, in accordance with the hypothesis that excess iron acts as a cancer-promoting factor. On the other hand, we found an inverse association between iron stores and stomach cancer, which, however, may be due to occult cancer. Further studies are needed to confirm the findings of the present study, and as yet it is premature to assess impacts of body iron stores on the incidence of cancer or on public health.

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