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A prospective cohort examination of haematological parameters in relation to cancer death and incidence: the Busselton Health Study

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Abstract

Background: Cancer risk is associated with serum iron levels. The aim of this study was to evaluate whether haematological parameters reflect serum iron levels and may also be associated with cancer risk.

Methods: We studied 1564 men and 1769 women who were enrolled in the Busselton Health Study, Western Australia. Haematological parameters evaluated included haemoglobin (Hb), mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) and red cell distribution width (RCDW). Statistical analyses included t-tests for quantitative variables, chi-square tests for categorical variables and Cox proportional hazards regression modelling for cancer incidence and death.

Results: There was marginal evidence of an association between MCV (as a continuous variable) and non-skin cancer incidence in women (HR 1.15, 95% CI 1.013, 1.302; $p = 0.030$) but the hazard ratio was attenuated to non-significance after adjustment for serum ferritin (SF), iron and transferrin saturation (TS) (HR 1.11, 95% CI 0.972, 1.264; $p = 0.126$). There was strong evidence of an association between MCHC and prostate cancer incidence in men; the estimated hazard ratio for an increase of one SD (0.5) in MCHC was 1.27 (95% CI 1.064, 1.507; $p = 0.008$). These results remained significant after further adjustment for SF and iron; the estimated hazard ratio for an increase of one SD (0.5) in MCHC was 1.25 ($p = 0.014$, 95% CI 1.05 to 1.48).

Conclusions: The MCHC and MCV were associated with cancer incidence in a Western Australian population, although only MCHC remained associated with prostate cancer after adjusting with serum iron and TS (circulating iron) and SF (storage iron). Haematological parameters are thus of limited utility in population profiling for future cancer risk.

Keywords: Iron, Full blood count, Cancer

Background

Iron is an essential micronutrient for human health as it participates in a vast range of metabolic processes [1–4]. Deficiency or excess of iron have both been implicated as vital pathogenic processes of various chronic diseases. Iron deficiency is implicated in anaemia [5, 6], worsening symptoms of chronic heart failure [7, 8] and restless leg syndrome [9, 10]. On the other hand, iron excess as observed in hereditary haemochromatosis and haematological disorders such as thalassaemia major and sickle cell disease has been associated with liver cirrhosis, type two diabetes mellitus and cardiomyopathy [11–20].

Recent studies have implicated iron in the pathogenesis of cancer. In hereditary haemochromatosis an increased risk of cancer with iron overload has been demonstrated [21–24]. More recent population studies have shown even at high physiological levels of iron, there was increased risk of cancer [25–27]. On the contrary, depletion of iron has been proposed to have a protective role on cancer

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development [28–35]. In our previous study of the Busselton population, we found that higher concentrations of serum iron or TS were associated with an increased incidence of non-skin cancer in women, increased risks of breast cancer and of cancer death [25]. Thus iron status may be useful in stratifying risk for cancer.

Iron is essential for erythropoiesis [36], and low serum iron parameters may be reflected by changes in haematological parameters such as a reduction in mean haemoglobin (Hb), mean corpuscular volume (MCV), mean cell haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC) and an increase in red cell distribution width (RCDW) [37, 38]. Conversely, several studies of individuals with iron overload, such as in hereditary haemochromatosis, have shown that elevation in iron stores was associated with increased values of Hb, MCV, MCH, and MCHC [39–41].

The full blood count assay is a relatively cheap and easily measured laboratory investigation that is conducted worldwide. In Australia it is estimated that approximately 12 million full blood counts are ordered per year [42]. Whilst serum iron biochemistry is also commonly performed, the full blood count is performed more than twice as frequently as iron studies [42]. The cost of the full blood count is approximately half the cost of iron studies in Australia and elsewhere [43–45].

Given the positive association between iron levels and cancer incidence and death from our previous study [25], we aimed to assess the utility of haematological parameters such as the Hb, RCDW, MCV, MCH and MCHC as surrogate markers of iron bioavailability to determine the associations between these parameters and cancer death and incidence in the Busselton population.

Methods

Study population

Busselton is a city situated in the southwest of Western Australia and more than 90% of its residents consist of individuals with Anglo-Celtic ancestry. The residents of this coastal city have been regularly surveyed since the introduction of the Busselton Health Study in 1966. A follow-up health survey of survivors from surveys during 1966 to 1987 was performed in 1994 and 1995 [46, 47]. Inclusion criteria for this study were individuals who participated in the 1994/1995 survey aged 25–79 years and who had relevant data, no history of cancer at the time of survey, not taking haemopoietic agents and SF ≥20 μg/L. This study was approved by the Busselton Population Medical Research Institute and ethics approval was obtained from the Human Research Ethics Committee of the Health Department of Western Australia (Project number 2011/60).

Clinical and biochemical measurements

Participants of this survey completed a comprehensive health and lifestyle questionnaire and were subject to various measurements and tests [46]. Data on smoking, alcohol intake, menopausal status, use of iron supplements, and history of blood donations was obtained from the questionnaire. Alcohol use was classified as light, moderate and heavy if intake was < 140 g/week, 140–420 g/week and > 420 g/week, respectively. Trained assessors obtained data on anthropometric measures such as waist circumference, weight and height, from which body mass index (BMI) was derived. Blood pressures were measured after five minutes of rest in a seated position.

After an overnight fast at time of the survey, blood samples were collected from the participants. Their serum was separated and stored at − 70 °C. Serum biochemical measurements of haematological indices (Hb, MCV, MCH, MCHC, RCDW), iron indices (iron, TS, SF), lipids (high density lipoprotein (HDL) cholesterol, triglyceride), glucose and insulin, liver function enzymes and proteins (alanine transaminase (ALT), gamma-glutamyl transferase (GGT), albumin, bilirubin) and a marker of inflammation (C-reactive protein; C-RP) were performed using standard protocols by PathWest Laboratories (Nedlands, Western Australia). Using the following equation: (fasting insulin (μIU/mL) x fasting glucose (mmol/L)) ÷ 22.5, the Homeostasis Model Assessment-estimated insulin resistance (HOMA-IR) score was calculated.

Cancer outcomes

By accessing the Death Register and Cancer Register from the Western Australian Department of Health within the time frame of January 1994 until June 2014, the incidence of cancer and death records were collected [48]. Cancer variables analysed included death from (non-skin) cancer (ICD10 C00-C42, C45-C97), incident non-skin cancer (ICD10 C00-C42, C45-C97), incident prostate cancer (men only, ICD10 C61), incident breast cancer (women only, ICD10 C50), and incident colorectal cancer (ICD10 C18-C21) where an incident case is a non-fatal or fatal case.

Statistical analyses

Statistical analyses were performed using SAS® 9.4. Log transformation of data was performed for variables that had positively skewed distributions (SF, iron and TS, triglycerides, glucose, HOMA-IR, ALT, GGT, C-RP). Differences in characteristics between men and women were examined using t-tests for quantitative variables and chi-square tests for categorical variables. The associations between haematological parameters (Hb, MCV, MCH, MCHC and RCDW) and cancer incidence and death were examined using Cox proportional hazards regression modeling. Haematological parameters were examined both as a continuous variable and in three gender-specific approximate tertile categories. The estimated hazard ratios with 95% confidence interval were reported for each of the haematological parameters in relation to cancer incidence and death

in men and women based on cancer and mortality follow-up to 30 June 2014. 95% confidence intervals for a hazard ratio that do not include the value 1 are significant at the 5% level (i.e. $p < 0.05$). All models were adjusted for age, smoking, alcohol consumption, BMI, and waist circumference. Modelling of breast cancer risk in women was also adjusted for menopausal status.

Results

A total of 1564 men and 1769 women met the study inclusion criteria. Baseline demographic, anthropometric and biochemical characteristics of the cohort, stratified according to gender, are presented in Table 1. The study cohort comprised of 47% men, with a mean age of 51 ± 14 years, and 53% of women with a mean age of 52 ± 15 years. Approximately 57% of women were post-menopausal and a third of these women used hormone replacement therapy. Oral contraceptives were used by 27% of pre-menopausal women. More men were current smokers or ex-smokers and also consumed more alcohol than women. A small proportion of the Busselton cohort was taking iron supplements to treat iron deficiency, 0.6% of men and 4.7% of women respectively, and about a third of men and women reported a history of blood donation. Hb and MCHC were significantly higher in men ($p < 0.001$) whereas MCV, MCH and RCDW were similar in men and women. SF, iron and TS levels were higher in men than in women ($p < 0.001$) and had positively skewed distributions. With the exception of HDL cholesterol and C-RP levels, all the other measured variables were also higher in men than in women ($p < 0.001$).

A total of 202 cohort participants died from cancer during the 20-year follow-up period and 191 were non-skin cancer deaths. A total of 588 participants had an incident non-skin cancer. A greater proportion of men developed non-skin cancer compared to women (19.4% in men versus 16.1% in women) whilst a similar proportion of non-skin cancer deaths and incident colorectal cancers were recorded for both men and women during the follow-up period. Of the sex-specific cancers, the proportion of men who were diagnosed with prostate cancer and women who were diagnosed with breast cancer was 8.2% and 5.2%, respectively.

Table 2 shows the correlations between haematological parameters and iron parameters. Hb was weakly correlated with MCV and moderately positively correlated with MCH and MCHC (0.04 to 0.14). MCV and MCH were very strongly positively correlated (0.93 in men and women), however MCV was not correlated with MCHC whereas MCH was positively correlated with MCHC (0.30 in men and 0.36 in women). RCDW was weakly to moderately negatively correlated with Hb, MCV, MCH, and MCHC.

Hb was positively correlated with SF, iron and TS in both men and women (0.09 to 0.16). MCV and MCH showed stronger correlations with iron and TS (0.20 to 0.31) than with SF (0.08 to 0.10) in men and women. MCHC showed weak correlations with SF, iron and TS (− 0.02 to 0.12) in men and women. RCDW showed negative correlations with SF, iron and TS (− 0.12 to − 0.14) in men and negative correlations with iron and TS (− 0.16 to − 0.17) but not with SF (0.03) in women.

Estimated hazard ratios for Hb, MCV, MCH, MCHC, and RCDW both as continuous variables and in approximate tertile groups, in relation to cancer incidence and death after adjustment for cancer risk were determined. There were only two instances of possible associations between a haematological parameter and cancer incidence in men or women. There was marginal evidence of an association between MCV (as a continuous variable) and non-skin cancer incidence in women (hazard ratio 1.15, 95% CI 1.013, 1.302; $p = 0.030$) but the hazard ratio was attenuated to non-significance after adjustment for SF, iron and TS (hazard ratio 1.11, 95% CI 0.972, 1.264; $p = 0.126$). There was strong evidence of an association between MCHC and prostate cancer incidence in men; the estimated hazard ratio for an increase of one SD (0.5) in MCHC was 1.27 (95% CI 1.064, 1.507; $p = 0.008$). Men with a MCHC ≤34.1 g/100 ml had a significantly lower risk of prostate cancer compared with men who had a MCHC above this value. Further, these associations remain after further adjustment for SF, iron and TS with the estimated hazard ratio for an increase of one SD (0.5) in MCHC being 1.25 ($p = 0.014$, 95% confidence interval 1.05 to 1.48).

Haematological parameters did not exhibit any association with incidence or death for breast cancer in women or colorectal cancer in women or men. Blood donation was not associated with cancer incidence and death.

Discussion

To the best of our knowledge, this is the first large-scale population study to investigate the prospective association between haematological parameters as surrogate markers of iron bioavailability, and cancer incidence and death.

In this prospective, observational cohort study, we observed a strong association between MCHC and prostate cancer incidence that remained significant following adjustments for iron markers. There was also a marginal association between MCV and non-skin cancer incidence in women which was attenuated to non-significance after adjustment for iron markers. Hb, MCH and RCDW did not generate any significant association with cancer incidence or death.

We postulate that the overall weak correlation between haematological parameters and serum iron markers in our study may be attributed to the fact that changes in iron levels are reflected to some degree through red blood cell morphology [36, 49, 50]. Factors that could confound the association include diurnal variation in serum iron levels [51–56] and unmeasured changes in iron and

Table 1 Characteristics of the study cohort and number of cancers and cancer deaths by gender. Table shows mean (SD), percent or number (percent) for cancer outcomes

Characteristic	Men ($n = 1564$)	Women ($n = 1769$)	p-value
Hb (g/dL)	151.4 (9.6)	135.5 (8.7)	< 0.001
MCV (fL)	89.0 (3.6)	89.1 (3.7)	0.225
MCH (pg/cell)	30.6 (1.3)	30.5 (1.4)	0.152
MCHC (g/dL)	34.4 (0.5)	34.3 (0.5)	< 0.001
RCDW	0.13 (0.01)	0.13 (0.01)	0.014
SF (μg/L)	228 (211)	101 (105)	
Log SF	5.17 (0.73)	4.33 (0.73)	< 0.001
Serum iron (μmol/L)	19.0 (5.6)	17.9 (5.7)	
Log serum iron	2.90 (0.30)	2.83 (0.33)	< 0.001
TS (%)	30.2 (10.5)	27.0 (13.9)	
Log TS	3.35 (0.34)	3.23 (0.36)	< 0.001
Age (years)	50.7 (14.4)	51.9 (15.1)	0.022
Smoking status			
Never	41.6	58.5	< 0.001
Ex	41.8	30.0	
Current	16.6	11.6	
Alcohol consumption Never	3.3	8.2	< 0.001
Ex	6.4	11.6	
Light	48.5	67.2	
Moderate/Heavy	39.1	8.6	
Unknown	2.7	4.4	
Menopausal status Pre/OC No	–	31.4	–
Pre/OC Yes	–	11.6	
Post/HRT No	–	38.4	
Post/HRT Yes	–	18.5	
Use of iron supplement	0.6	4.7	< 0.001
History of blood donation	34.6	28.9	< 0.001
Body mass index (kg/m^2)	26.7 (3.3)	25.9 (4.7)	< 0.001
Waist circumference (cm)	93.6 (9.9)	81.2 (11.8)	< 0.001
Systolic blood pressure (mm Hg)	127 (15)	122 (18)	< 0.001
Diastolic blood pressure (mm Hg)	78 (10)	73 (10)	< 0.001
High density lipoprotein chol (mmol/L)	1.21 (0.30)	1.54 (0.39)	< 0.001
Triglycerides (mmol/L)	1.47 (1.06)	1.21 (0.75)	
Log Triglycerides	0.21 (0.56)	0.05 (0.52)	< 0.001
Glucose, mmol/L	5.13 (1.43)	4.90 (1.22)	
Log Glucose	1.61 (0.18)	1.57 (0.17)	< 0.001
HOMA-IR	1.90 (5.11)	1.67 (2.13)	
log HOMA-IR	0.33 (0.68)	0.24 (0.65)	< 0.001
ALT (IU/L)	28.2 (16.3)	19.3 (10.6)	
Log ALT	3.23 (0.45)	2.86 (0.41)	< 0.001
GGT (IU/L)	31.0 (23.8)	21.8 (17.2)	
Log GGT	3.27 (0.53)	2.93 (0.50)	< 0.001
Bilirubin (μmol/L)	11.2 (5.3)	9.0 (3.8)	< 0.001

Table 1 Characteristics of the study cohort and number of cancers and cancer deaths by gender. Table shows mean (SD), percent or number (percent) for cancer outcomes *(Continued)*

Characteristic	Men ($n = 1564$)	Women ($n = 1769$)	*p*-value
Albumin (g/L)	45.9 (2.7)	44.7 (2.6)	< 0.001
C-RP (mg/L)	2.69 (7.30)	3.62 (10.08)	
log C-RP	0.26 (1.18)	0.54 (1.22)	< 0.001
Cancer outcomes			
Non-skin cancer death	94 (6.0)	97 (5.5)	0.514
Non-skin cancer	304 (19.4)	284 (16.1)	0.011
Prostate cancer	129 (8.2)	–	–
Breast cancer	–	92 (5.2)	–
Colorectal cancer	42 (2.7)	46 (2.6)	0.878

OC (oral contraceptives), *HRT* (hormone replacement therapy), *HOMA-IR* (Homeostasis Model Assessment – estimated insulin resistance), *ALT* (alanine transaminase), *GGT* (gamma-glutamyltransferase), *C-RP* (C-reactive protein)

haematological parameters in the timeframe between entry into the study and endpoint determination. Several studies have reported positive correlations between serum iron or SF levels with TS, MCV and MCH [57, 58], whilst others have shown no significant correlation between MCV with TS and SF [59, 60].

This study demonstrates consistent trends in associations between increasing iron or haematological parameters and incidence for some cancers. Interestingly, the association between MCHC and prostate cancer was independent of adjustment for iron parameters whilst that of MCV and non-skin cancer in women was dependent on iron. We hypothesise that the variation in our findings can be attributed to the fact that even though iron may contribute to cancer via induction of oxidative stress, changes in the red blood cell parameters may also reflect changes to the body as a result of long term oxidative stress that parallels the drive for carcinogenesis [61–71]. The association between MCHC and prostate cancer which remained significant after iron studies adjustments leads us to speculate that prostate carcinogenesis may be driven by alternative oxidative stress mediators possibly independent of iron. Although many studies have reported an association between oxidative stress and prostate cancer development, inconsistent reports have emerged on the association between iron and prostate carcinogenesis [72–79].

Whilst several studies have reported positive associations between MCHC and oral squamous cell carcinoma [80] or head and neck cancers [81], others found no statistically significant associations [82, 83].

Inconsistent results have been reported regarding the association between MCV and cancer. A retrospective Japanese study found that elevated MCV was associated with the presence of lymphoid and solid organ cancers [84]. In contrast, a study of 253 patients with involuntary weight loss who were investigated for cancer found that MCV was not associated with cancer [85]. We observed an association between MCV, as a continuous variable, and non-skin cancer incidence. A retrospective much larger Korean cohort study of 36,260 cancer-free, non-anaemic men and women found that elevated MCV by quartiles was related to higher all-cause mortality and liver cancer mortality. There was a

Table 2 Correlations between haematological parameters and iron parameters in men and women

	Hb	MCV	MCH	MCHC	RCDW	Log SF	Log iron	Log TS
Men								
Hb	1.000	−0.009	0.044	0.140	−0.111	0.127	0.156	0.088
MCV		1.000	0.930	−0.074	− 0.001	0.081	0.196	0.210
MCH			1.000	0.297	−0.110	0.118	0.216	0.223
MCHC				1.000	−0.298	0.112	0.077	0.061
RCDW					1.000	−0.123	−0.117	−0.135
Women								
Hb	1.000	0.065	0.101	0.117	−0.072	0.134	0.152	0.110
MCV		1.000	0.934	0.007	−0.143	0.101	0.272	0.291
MCH			1.000	0.360	−0.249	0.088	0.291	0.314
MCHC				1.000	−0.332	−0.020	0.107	0.121
RCDW					1.000	0.028	−0.178	−0.164

difference between genders with the highest quartile of MCV (≥95.8 fL) showing higher cancer mortality in men but not in women [86]. A retrospective study by Qu et al. observed that a high MCHC and MCV level was an independent prognostic factor for overall survival in non-small cell lung cancer [87]. We speculate the association between elevation of MCV and cancer in our study may be a consequence of long-term effects of iron-dependent oxidative stress on the red blood cell structure and cancer pathogenesis [86, 88]. This mechanism still remains ambiguous and further research is needed to elucidate this hypothesis.

Substantial variability of findings has been observed in studies that investigated the association between RCDW and various cancers. A positive association have been reported in colon cancer [61, 89] endometrial cancer [90] oesophageal cancer [91–94] renal cell carcinoma [95] or breast cancer [96–98], whilst other studies found no statistically significant associations [85, 99].

There are strengths and limitations of our study. Strengths of our study include a well-defined, community-based cohort with a long follow-up period and adjustment of associations for a wide range of potential confounders. We excluded patients who were using erythropoeisis-stimulating agents that can affect these hematological parameters. Weaknesses include the relatively limited cohort size, which may have limited power, and the limited number of time-points during the course of the follow-up. Furthermore, we tested five haematological parameters for five cancers in men and women raising the possibility of false positive findings. Hence, the significance of the discovered possible associations between MCV and non-skin cancer incidence in women ($p = 0.030$) and MCHC and prostate cancer incidence in men ($p = 0.008$) should be regarded with care. In the current study, data on potential confounders for specific cancer risk factors, such as intake of red meat, fish, fibre, saturated fat and vitamin and mineral levels were unavailable and thus may also contribute to the inconsistent finding with those of previously published studies. As study subjects self-reported their histories of smoking and alcohol use during their participation in the survey, this may also limit accuracy of data. The nature of any pathophysiological process effecting haematological parameters decades before the occurrence of cancer and which contributes to cancer development remains unclear.

Conclusions

In conclusion, both MCHC and MCV were associated with cancer incidence in a Western Australian population, although only MCHC remained associated with prostate cancer incidence after adjusting with serum iron and TS (circulating iron) and SF (storage iron). Haematological parameters are thus of limited utility in population profiling for future cancer risk.

Abbreviations

ALT: Alanine transaminase; BMI: Body mass index; C-RP: C-reactive protein; GGT: Gamma-glutamyl transferase; Hb: Haemoglobin; HDL: High density lipoprotein; MCH : Mean cell haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; RCDW: Red cell distribution width; SF: Serum ferritin; TS: Transferrin saturation

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Availability of data and materials

Access to the data from the 1994/95 Busselton survey is via application to the Busselton Population Medical Research Institute and access to linked data on cancer outcomes and deaths is via application to the Western Australian Department of Health Data Linkage Unit.

Authors' contributions

NA: contributed to interpretation of the results, responsible for writing the manuscript and final content of the manuscript. ACGC: contributed to the study design, interpretation of the results, writing of the manuscript and critical revision of manuscript. MWK: responsible for the statistical data analysis and interpretation of the results, participated in the writing of the manuscript and critically revised the manuscript. MLD: responsible for the statistical data analysis and interpretation of the results and participated in the writing of the manuscript. DT: participated in the interpretation of the results and critically revised the manuscript. JKO: was responsible for the conception and design of the study, interpretation of the results, and critical revision of manuscript. All authors: read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Busselton Population Medical Research Institute and ethics approval was obtained from the Human Research Ethics Committee of the Health Department of Western Australia (Project number 2011/60). Consent to participate in this study has been obtained by the Busselton Population Medical Research Institute.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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