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Red cell indices as predictors of cancer risk: findings from a large prospective cohort study

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Abstract

Background Red blood cell disorders have been implicated in tumorigenesis. Nevertheless, the association between red cell indices (RCIs), which reflect the health status of red blood cells, and the risk of cancer has yet to be determined.

Methods This was a prospective cohort study involving 455,897 participants who were free of cancer at baseline and had measurements of RCIs, namely mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and hemoglobin (Hb). The associations of RCIs with overall and site-specific cancer risk were examined by using multivariate Cox proportional hazards regression models with RCIs mutually adjusted. The dose–response relationships were investigated via restricted cubic splines.

Results Over a median follow-up of 10.9 years, 47,177 participants were diagnosed with cancer. MCV (Q5 vs Q1: fully-adjusted HR = 0.83, 95% CI: 0.78–0.88) and MCH (HR = 0.83, 95% CI: 0.79–0.87) exhibited a non-linear and inverse association with the overall cancer risk (both *P* values for nonlinear < 0.001). Conversely, RDW showed a linear and positive association with the overall cancer risk (HR = 1.19, 95% CI: 1.15–1.23, *P* for linear < 0.001). For site-specific cancers, MCV and MCH exhibited inverse associations with the risks of lymphoma, leukemia, breast cancer, and kidney cancer, while RDW was positively associated with the risks of these malignancies.

Conclusions Our findings indicate that MCV, MCH, and RDW have clinical significance as potential biomarkers for predicting cancer risk. Further studies are needed to elucidate the underlying mechanisms driving these associations.

Keywords Red cell indices, Hemoglobin, Cancer incidence, Cohort study

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Background

Red blood cells indices (RCIs) are a set of calculated parameters that can characterize the size, volume and concentration of red blood cells (RBCs) [1]. Specific incidces include hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) [2]. Abnormal RCIs may reflect various health conditions, such as anemia, cardiovascular disease, inflammation, and nutritional deficiencies [3]. Specifically, red blood cell alterations may exacerbate inflammatory diseases by facilitating the release of pro-inflammatory cytokines and amplifying oxidative stress [4]. Moreover, dysfunction of red blood cells could result in hypoxia and immunosuppression, which may also influence the risk of carcinogenesis [5–7].

Although several cohort studies have investigated the association between certain RCIs and cancer risk [8–10], few have offered a comprehensive perspective on the association of RCIs with both overall and site-specific cancer risks. Based on UK primary care electronic patient records, a cohort study of 85,439 participants reported that MCV < 85 femtolitres was associated with an increased risk of cancer [9]. The study did not analyze the association between other RCIs and site-specific cancer risk. In addition, a prospective cohort study found a positive association between MCHC and prostate cancer risk [8], while another cohort study reported an inverse association [10]. Furthermore, few studies have investigated the dose–response relationship between RCIs and cancer risk. Therefore, a systematic assessment of the association between RCIs and cancer risk is needed, which could provide new insights into carcinogenesis and reveal new biomarkers for cancer risk prediction.

In the current study, we conducted a prospective analysis to examine the association of RCIs with overall and site-specific cancer risk, utilizing data from the UK Biobank, a large-scale cohort involving over 0.5 million participants.

Methods

Study participants

The UK Biobank is a prospective cohort comprising 502,463 middle aged and elderly participants who were recruited from 22 assessment centers across the United Kingdom during 2006 and 2010 [11]. At baseline, the participants completed a self-administered touchscreen questionnaire, providing details on sociodemographic information, lifestyle behaviors, and their disease history. They also underwent physical measurements of body weight and height, and provided blood samples at recruitment.

In this study, participants were excluded if they withdrew consent during the study period ($n = 58$), had a prior cancer diagnosis at recruitment ($n = 23,807$), or lacked data pertaining to RCIs ($n = 22,701$). Finally, 455,897 participants were included in the analyses (Additional file 1: Fig. S1).

RCI measurements

RCIs were measured within 24 h of blood collection using a Beckman Coulter LH750 Hematology Analyzer at the centralized processing laboratory of the UK Biocenter (Stockport, UK). Specifically, Hb concentration was extracted directly as instrument measurement by the photometric method, with an operating range of 0.0–99.9 g/dL. MCV and RDW were derived from the RBC histogram by the instrument, with operating ranges of 0.0–300.0 fL and 0.0–99.9%, respectively. MCH (determined as the mass of Hb in the average RBC) and MCHC (determined as the average mass of Hb per the relative volume of RBC) were extracted as calculated values by the instrument, with operating ranges of 0.0–99.9 pg and 0.0–99.9 g/dL, respectively. More detailed information regarding RCIs and quality control procedures can be viewed at https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=220.

Covariate assessment

Covariates were collected from the baseline questionnaire, including demographic characteristics (age, sex, race, college or university degree, and Townsend deprivation index), fasting status, lifestyle (smoking status, pack years of smoking, alcohol consumption, and physical activity intensity), body mass index (BMI), medical history (prevalent cardiovascular diseases (CVDs) and diabetes), family history of cancer, female-specific factors (menopause status and hormone replacement therapy (HRT)), neutrophil-to-lymphocyte ratio (NLR), and nonsteroidal anti-inflammatory drug (NSAID) use. The Townsend deprivation index was calculated based on residential data including unemployment, non-car ownership, non-home ownership, and household overcrowding [12]. Physical activity intensity was assessed using metabolic equivalent task (MET)-hours per week, covering walking, and moderate, and vigorous exercise. For covariates with missing data, the median imputation was applied for continuous variables and the missing indicators for categorical variables.

Ascertainment of outcomes

New cancer occurrences during follow-up were identified according to the International Classification of Diseases Version 10th codes (C00-C97) through linkage to the national cancer registry, with data sourced from National Health Service (NHS) Digital for England and

Wales and the NHS Central Register maintained by the National Records of Scotland. Overall cancers included all types of cancers except non-melanoma skin cancer (C44). Blood system cancers included lymphoma (C81-C88) and leukemia (C91-C95). Digestive system cancers encompassed esophageal cancer (C15), stomach cancer (C16), colorectal cancer (C18-C20), liver cancer (C22), and pancreatic cancer (C25). Reproductive system cancers comprised breast cancer (C50), uterine cancer (C54-C55), and prostate cancer (C61). Urinary system cancers included kidney cancer (C64-C65), and bladder cancer (C67). Respiratory system cancers consisted of laryngeal cancer (C32) and lung cancer (C33-C34). The analysis of individual cancer types was restricted to those with a minimum count of 150 cases (Additional file 1: Table S1).

Statistical analysis

The follow-up duration was calculated from the date of baseline assessment to the date of cancer diagnosis, death, loss to follow-up (absence of record linkage updates resulting from emigration from the UK or withdrawal of consent), or the follow-up deadline (29 February 2020, for England and Wales, and 31 January 2021, for Scotland), whichever occurred first. For evaluating the association between RCIs in quintiles and cancer risk, Cox proportional hazards regression models were employed to compute hazard ratios (HR) and 95% confidence intervals (CIs). The proportional hazard assumption was verified by Schoenfeld residuals. Model 1 was adjusted for age at assessment, sex (male, female), race (white, non-white), and fasting status (yes, no). Model 2 was additionally adjusted for potential confounders including college or university degree (yes, no), Townsend deprivation index, BMI, physical activity, smoking status (never, previous, current), pack-years of smoking, alcohol consumption (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily/almost daily), family history of cancer (yes, no), prevalent CVDs (yes, no), diabetes (yes, no), and for females, menopausal status (yes, no) and HRT (yes, no). The full model was further mutually adjusted for other four RCIs. Linear trend tests were performed by inputting the median value of each RCI category as a continuous variable into the models. Moreover, multivariate restricted cubic splines with 3 knots (located at the 10th, 50th, and 90th percentiles) were applied to to explore the dose–response relationship between RCIs and cancer risk. To detect potential nonlinearity, a likelihood ratio test was employed to contrast the model containing solely linear terms with the one incorporating both linear and cubic spline terms.

Stratified analyses were conducted according to age ($\leq 60, > 60$ years), sex (male, female), BMI ($< 30, \geq 30$ kg/m^2), current smoking status (yes, no), physical activity (below median, above median), colorectal cancer subsite (colon cancer, rectal cancer), and family history of cancer (yes, no). We calculated the *P* value for heterogeneity in the associations of RCIs and overall cancer risk using the contrast test method. Sensitivity analyses were performed as follows: (1) excluding 34,353 participants with baseline hematological diseases; (2) excluding 6,839 cancer cases diagnosed within the first two years of follow-up; (3) excluding outliers of five red cell indices; (4) further adjusting for other biochemical indicators, including serum glucose, triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, and C-reactive protein; and (5) further adjusting for NLR and NSAID use. Spearman correlation was performed to estimate the correlations between RCIs and NLR.

To account for multiple testing in our primary analysis concerning the association between the five RCIs and cancer risk, we applied the Bonferroni correction, setting $\alpha = 0.01$ (0.05 divided by 5) as the threshold for statistical significance. All of the above analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics

Over a median follow-up of 10.9 years (interquartile range: 10.1 to 11.6), 47,177 incident cancer cases were diagnosed. Baseline characteristics of the participants are shown in Table 1. Participants who developed cancer tended to be older, male, and current smokers. Additionally, they were more like to consume alcohol frequently, have a family history of cancer, as well as have prevalent CVDs and diabetes.

Association between RCIs and overall cancer risk

We found that MCV, MCH, and MCHC were inversely associated with overall cancer risk (Q5 vs. Q1, fully-adjusted HR = 0.83, 95% CI = 0.78 to 0.88; HR = 0.83, 95% CI = 0.79 to 0.87; and HR = 0.92, 95% CI = 0.89 to 0.96, respectively) (all *P* for trend < 0.001) (Table 2). In contrast, RDW was positively associated with overall cancer risk (HR = 1.19, 95% CI = 1.15 to 1.23) (*P* for trend < 0.001) (Table 2). Hb was not statistically associated with overall cancer risk.

In the dose–response relationship analysis (Fig. 1), non-linear inverse relationships were observed for MCV and MCH with overall cancer risk (*P* for nonlinear < 0.001), whereas a linear positive relationship was identified between RDW and overall cancer risk (*P* for nonlinear = 0.722 and *P* for linear < 0.001).

Association between RCIs and site-specific cancer risk

We further investigated the associations of MCV, MCH, and RDW with site-specific cancers, including those of blood, digestive, reproductive, urinary, and respiratory

Table 1 Baseline characteristics of UK Biobank participants included in this study[a]

Characteristic	Overall (*n* = 455,897)	No cancer (*n* = 408,720)	Cancer cases (*n* = 47,177)
Age at assessment, years	56.37 (8.10)	55.96 (8.12)	59.97 (6.94)
Male, %	46.21	45.41	53.13
White race, %	94.16	93.94	96.09
College or above, %	32.48	32.84	29.41
Townsend deprivation index	−1.31 (3.09)	−1.31 (3.08)	−1.30 (3.12)
BMI, kg/m^2	27.41 (4.77)	27.36 (4.76)	27.81 (4.79)
Physical activity, MET-hours/week	41.55 (41.22)	41.59 (41.22)	41.17 (41.16)
Smoking status, %[b]			
Never	54.61	55.51	46.86
Previous	34.31	33.71	39.57
Current	10.57	10.30	12.97
Pack years of smoking	9.92 (15.03)	9.49 (14.48)	13.63 (18.74)
Alcohol consumption, %[b]			
Never	7.96	7.98	7.79
Special occasions only	11.39	11.39	11.42
One to three times a month	11.10	11.22	10.12
Once or twice a week	25.79	25.94	24.47
Three or four times a week	23.19	23.24	22.72
Daily or almost daily	20.35	20.01	23.27
Postmenopause, %[c]	59.83	58.95	68.69
Ever HRT use, %[c]	37.74	37.06	44.53
Family history of cancer, %	34.70	34.15	39.49
Prevalent CVDs, %	5.73	5.44	8.29
Diabetes, %	5.17	4.98	6.87
Red cell indices			
Hemoglobin, g/dL	14.19 (1.24)	14.18 (1.24)	14.28 (1.25)
MCV, fL	91.10 (4.60)	91.06 (4.58)	91.42 (4.76)
MCH, pg	31.45 (1.92)	31.43 (1.89)	31.56 (2.14)
MCHC, g/dL	34.51 (1.07)	34.51 (1.05)	34.52 (1.28)
RDW, %	13.49 (0.98)	13.47 (0.97)	13.58 (1.02)

Abbreviations: *BMI* Body mass index, *CI* Confidence interval, *CVDs* Prevalent cardiovascular diseases, *Hb* hemoglobin, *HR* Hazard ratio, *HRT* Hormone replacement therapy, *MCH* Mean corpuscular hemoglobin, *MCHC* Mean corpuscular hemoglobin concentration, *MCV* Mean corpuscular volume, *MET* Metabolic equivalent of task, *RCI* Red cell indice, *RDW* Red cell distribution width

[a]Values are mean (standard deviation) for continuous variables and percentages for categorical variables

[b]The total did not sum to 100% because a small proportion of participants chose "prefer not to answer" or "do not know"

[c]Among females only

systems (Fig. 2). In the blood system, MCV and MCH demonstrated inverse associations with the risks of lymphoma (Q5 vs. Q1, fully-adjusted HR = 0.68, 95% CI = 0.55 to 0.86 and HR = 0.81, 95% CI = 0.66 to 0.98, respectively) (both *P* for trend < 0.01) and leukemia (HR = 0.50, 95% CI = 0.38 to 0.67 and HR = 0.64, 95% CI = 0.49 to 0.83, respectively) (both *P* for trend < 0.01). In contrast, RDW exhibited positive associations with the risks of both malignancies (lymphoma: HR = 1.37, 95% CI = 1.19 to 1.57 and leukemia: HR = 2.00, 95% CI = 1.66 to 2.42) (both *P* for trend < 0.001).

For digestive cancers, MCV exhibited an inverse association with esophageal cancer risk (HR = 0.64, 95% CI = 0.43 to 0.97) (*P* for trend < 0.05). In contrast, MCV and MCH exhibited positive associations with colorectal cancer risk (HR = 1.25, 95% CI = 1.04 to 1.51; HR = 1.26, 95% CI = 1.08 to 1.48, respectively) (both *P* for trend < 0.05). Additionally, RDW showed positive associations with the risks of esophageal, stomach, liver, and pancreatic cancers (HR = 1.53, 95% CI = 1.23 to 1.90; HR = 1.42, 95% CI = 1.09 to 1.85; HR = 1.48, 95% CI = 1.13 to 1.93; and HR = 1.27, 95% CI = 1.05 to 1.54, respectively) (all *P* for trend < 0.01).

For reproductive system cancers, MCV and MCH were inversely associated with breast cancer risk (HR = 0.84, 95% CI = 0.72 to 0.97 and HR = 0.80 95% CI = 0.72 to 0.90, respectively) (both *P* for trend < 0.05). MCH also exhibited an inverse association with prostate cancer risk (HR = 0.80, 95% CI = 0.71 to 0.90) (*P* for trend < 0.01). Conversely, RDW was positively associated with breast cancer risk (HR = 1.10, 95% CI = 1.03 to 1.18) (*P* for trend < 0.01).

In terms of urinary and respiratory system cancers, MCV and MCH were inversely associated with kidney cancer risk (HR = 0.71, 95% CI = 0.55 to 0.99 and HR = 0.64, 95% CI = 0.49 to 0.82, respectively) (both *P* for trend < 0.05). Conversely, RDW was positively associated with the risks of kidney cancer and lung cancer (HR = 1.28, 95% CI = 1.07 to 1.52 and HR = 1.45, 95% CI = 1.30 to 1.62) (both *P* for trend < 0.05).

Stratified analysis

In the stratified analyses by age, sex, BMI, current smoking status, and physical activity, colorectal cancer subsite, and family history of cancer, the associations of RCIs with overall cancer risk were generally similar across the subgroups despite several exceptions (Additional file 1: Fig. S2, Table S2 and S3). For example, the inverse association of MCV and MCH with overall cancer risk was more pronounced in males (both *P* heterogeneity < 0.05). The positive association for RDW with overall cancer risk were stronger among current smokers and participants without family history of cancer (both *P* heterogeneity < 0.05).

Sensitivity analysis

The sensitivity analysis showed that the aforementioned associations remained robust after excluding participants with baseline hematological diseases (Additional file 1:

Table 2 Associations between red cell indices and overall cancer risk

Risk model	Quintile of Hb (g/dL), HR (95% CI)					*P* for trend
	Q1 (0.09–13.15)	Q2 (13.16–13.84)	Q3 (13.85–14.49)	Q4 (14.50–15.26)	Q5 (15.27–22.27)	
Cases, No	8,324	8,819	9,260	10,284	10,490	
Model 1[a]	ref	0.95 (0.92, 0.98)	0.95 (0.92, 0.98)	0.93 (0.90, 0.96)	0.95 (0.92, 0.98)	0.004
Model 2[b]	ref	0.96 (0.94, 0.99)	0.96 (0.93, 0.99)	0.93 (0.90, 0.97)	0.94 (0.91, 0.97)	< 0.001
Full model[c]	ref	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)	0.98 (0.95, 1.01)	0.99 (0.95, 1.02)	0.383
Risk model	Quintile of MCV (fL), HR (95% CI)					*P* for trend
	Q1 (52.10–87.81)	Q2 (87.82–90.20)	Q3 (90.21–92.20)	Q4 (92.21–94.54)	Q5 (94.55–160.30)	
Cases, No	8,871	9,240	9,164	9,314	10,588	
Model 1[a]	ref	0.96 (0.94, 0.99)	0.92 (0.89, 0.94)	0.93 (0.90, 0.96)	1.02 (0.99, 1.05)	0.448
Model 2[b]	ref	0.97 (0.95, 1.00)	0.92 (0.90, 0.95)	0.92 (0.89, 0.95)	0.98 (0.95, 1.01)	0.010
Full model[c]	ref	0.95 (0.91, 0.98)	0.87 (0.84, 0.91)	0.84 (0.80, 0.88)	0.83 (0.78, 0.88)	< 0.001
Risk model	Quintile of MCH (pg), HR (95% CI)					*P* for trend
	Q1 (14.20–30.20)	Q2 (30.21–31.10)	Q3 (31.11–31.88)	Q4 (31.89–32.77)	Q5 (32.78–95.67)	
Cases, No	9,094	9,081	9,189	9,514	10,299	
Model 1[a]	ref	0.92 (0.89, 0.95)	0.91 (0.89, 0.94)	0.91 (0.89, 0.94)	0.96 (0.94, 0.99)	0.024
Model 2[b]	ref	0.94 (0.91, 0.96)	0.92 (0.89, 0.95)	0.91 (0.89, 0.94)	0.93 (0.90, 0.95)	< 0.001
Full model[c]	ref	0.92 (0.89, 0.95)	0.89 (0.86, 0.93)	0.86 (0.83, 0.90)	0.83 (0.79, 0.87)	< 0.001
Risk model	Quintile of MCHC (g/dL), HR (95% CI)					*P* for trend
	Q1 (16.10–33.73)	Q2 (33.74–34.22)	Q3 (34.23–34.69)	Q4 (34.70–35.28)	Q5 (35.29–95.37)	
Cases, No	9,760	9,383	8,921	9,645	9,468	
Model 1[a]	ref	0.94 (0.91, 0.97)	0.92 (0.89, 0.95)	0.92 (0.90, 0.95)	0.91 (0.89, 0.94)	< 0.001
Model 2[b]	ref	0.95 (0.92, 0.97)	0.93 (0.90, 0.96)	0.93 (0.90, 0.96)	0.92 (0.90, 0.95)	< 0.001
Full model[c]	ref	0.96 (0.93, 0.99)	0.94 (0.91, 0.97)	0.94 (0.91, 0.97)	0.92 (0.89, 0.96)	< 0.001
Risk model	Quintile of RDW (%), HR (95% CI)					*P* for trend
	Q1 (10.78–12.80)	Q2 (12.81–13.17)	Q3 (13.18–13.50)	Q4 (13.51–14.00)	Q5 (14.01–38.96)	
Cases, No	8,324	8,545	9,436	10,214	10,658	
Model [a]	ref	1.04 (1.01, 1.07)	1.06 (1.03, 1.09)	1.11 (1.08, 1.14)	1.27 (1.24, 1.31)	< 0.001
Model 2[b]	ref	1.03 (1.00, 1.07)	1.05 (1.02, 1.08)	1.08 (1.05, 1.11)	1.20 (1.16, 1.23)	< 0.001
Full model[c]	ref	1.03 (1.00, 1.07)	1.05 (1.02, 1.08)	1.08 (1.05, 1.11)	1.19 (1.15, 1.23)	< 0.001

Abbreviations: *BMI* Body mass index, *CI* Confidence interval, *CVDs* Prevalent cardiovascular diseases, *Hb* Hemoglobin, *HR* Hazard ratio, *MCH* Mean corpuscular hemoglobin, *MCHC* Mean corpuscular hemoglobin concentration, *MCV* Mean corpuscular volume, *MET* Metabolic equivalent of task, *RDW* Red cell distribution width

[a]Model 1: Adjusted for age at assessment, sex (female, male), race (white, non-white), and fasting status (yes, no)

[b]Model 2: Additionally adjusted for college or university degree (yes, no), Townsend deprivation index (continuous), body mass index (kg/m^2), physical activity (MET-hours/week), smoking status (never, previous, current), pack-years of smoking (continuous), alcohol consumption (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily/almost daily), family history of cancer (yes, no), prevalent CVDs (yes, no), diabetes (yes, no), and for women, menopausal status (yes, no) and hormone replacement therapy (yes, no)

[c]Full model: Additionally adjusted for other four red cell indices

Table S4), excluding cancer patients diagnosed within the initial two years of follow-up (Additional file 1: Table S5), excluding the participants with outliers of RCIs (Additional file 1: Table S6), further adjusting for the other hematologic parameters (Additional file 1: Table S7), and further adjusting for NLR and NSAID use (Additional file 1: Table S8 and S9).

Discussion

In this large-scale prospective cohort study, we systematically evaluated the association of RCIs with overall and site-specific cancers. We mainly found that MCV and MCH were inversely, while RDW was positively, associated with the risks of overall, lymphoma, leukemia, breast cancer, and kidney cancer. These results offer novel insight into the influence of hematologic parameters on cancer risk.

Only few prospective studies have assessed the association between RCIs and cancer risk. Consistent with our observations, a prospective cohort study of 25,383 participants with a follow-up of 15.7 years showed a positive association between RDW and cancer risk in men and post-menopausal women [13]. Additionally, a retrospective study based the health care system in Canada reported that increased RDW was associated with a higher risk of cancer [14]. Another case–control study involving 16,375 cancer cases and 161,995 controls found an inverse association between MCH and cancer risk [15]. However, the association between the other RCIs and cancer risk remains largely unknown. In this study, we observed a linear and positive association between

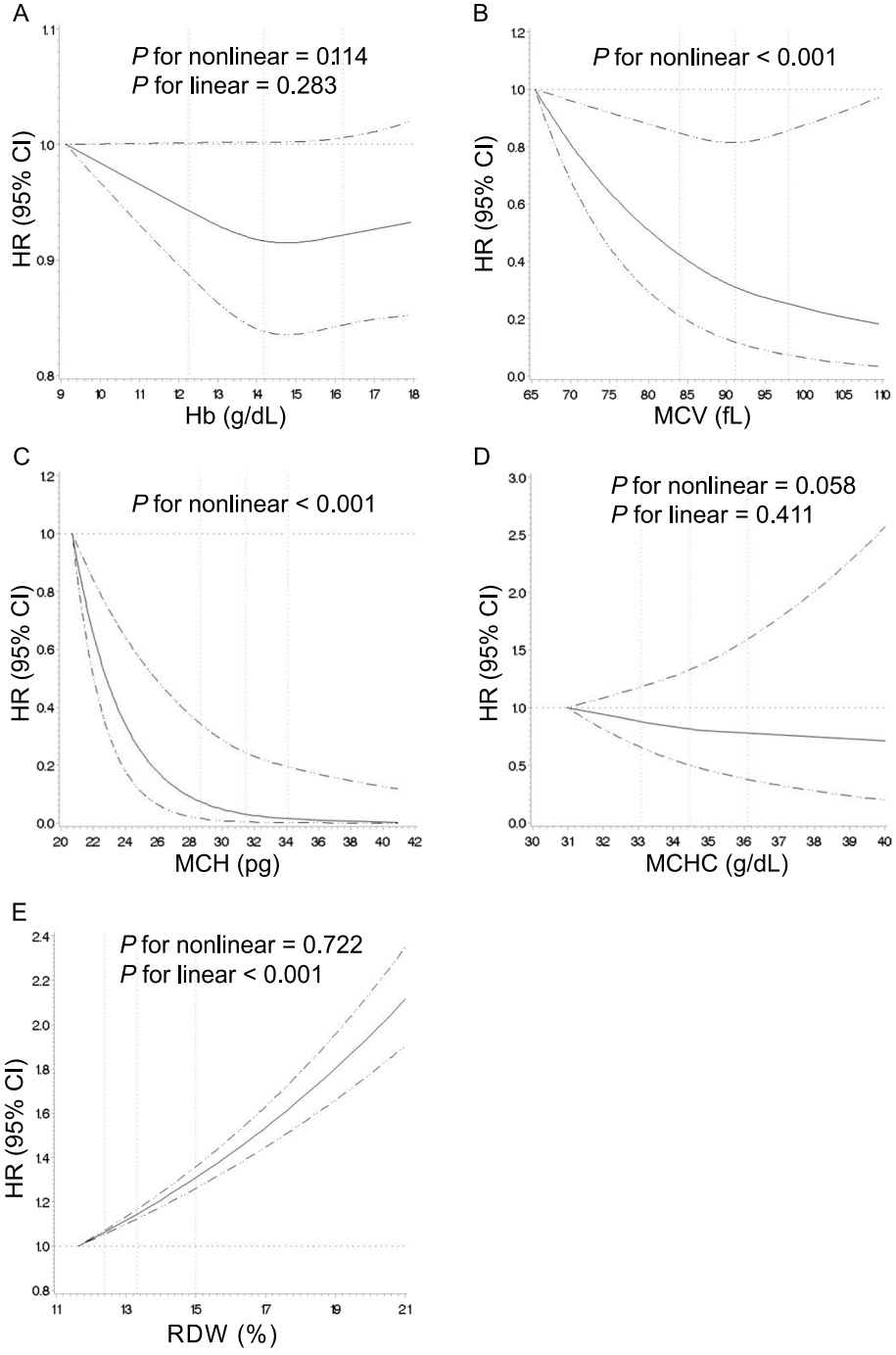

Fig. 1 Dose–response associations of Hb (**A**), MCV (**B**), MCH (**C**), MCHC (**D**), and RDW (**E**) with overall cancer risk in the full model. Solid lines represent estimates of HRs and dashed lines represent 95% CI. Abbreviations: CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width

RDW and cancer risk. Moreover, we found that MCV and MCH exhibited a non-linear and inverse association with cancer risk, as MCV and MCH increased, cancer risk initially dropped sharply and then stabilized.

The current study expanded the investigation into the associations between RCIs and site-specific cancers. In support of our findings, previous prospective cohort studies reported that lower MCV and higher RDW levels were associated with a higher risk of kidney cancer [16], and lower MCH level was associated with a higher risk of prostate cancer [17]. In addition, several retrospective studies conducted in cancer patients showed positive associations of RDW with the risks of leukemia [18], lung cancer [19], and esophageal cancer [20]. Other

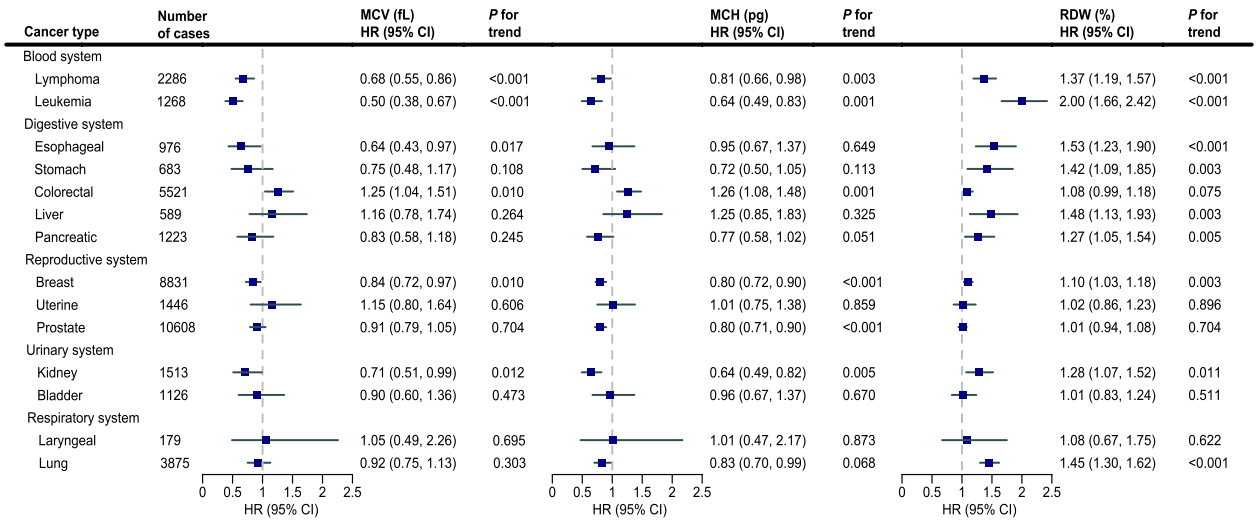

Fig. 2 Associations between RCIs (Q5 vs Q1) and site-specific cancer risk in the full model. Abbreviations: CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width

case–control studies found that compared with healthy controls, decreased MCV and MCH levels, and elevated RDW level, were detected in patients diagnosed with lymphoma [21], stomach [22], liver [22], pancreatic cancers [23], and breast cancer [22, 24]. Animal studies indicate that decreased levels of MCV and MCH are related to the overactivation of the inflammatory cytokine IL-6 signaling pathway [25], leading to impaired iron utilization and suppression of macrophage iron release, thereby promoting tumor progression [26, 27]. Elevated RDW level has been linked to increased levels of tumor necrosis factor-alpha, which can promote tumor cell proliferation [28].

We also observed positive associations of MCV and MCH with colorectal cancer risk. A retrospective study involving 1,878 colorectal cancer patients reported that MCV and MCH were positively associated with colorectal cancer risk [29], in line with our results. Elevated MCV and MCH may be implicated in macrocytic anemia caused by folate or vitamin B12 deficiency, leading to impaired DNA synthesis and thereby promoting carcinogenesis [30]. It is biologically plausible that MCV and MCH play differential roles in different cancers, and the underlying mechanisms related to colorectal cancer need further investigation.

Some studies reported that the association of MCV, MCH with overall cancer risk were stronger in men than women [31, 32], consistent with our findings. The difference may be attributed to the influence of hormonal factors, which needs further investigation. In addition, several studies hinted at a more pronounced association of RDW with overall cancer risk in smokers than nonsmokers [33, 34]. The current study confirmed the findings. Smoking may induce systemic inflammation and oxidative stress, thereby influencing RDW and modifying its effect on cancer risk [35, 36].

The current study has several strengths, including a large number of participants from a prospective cohort with a long follow-up period, a comprehensive pan-cancer analysis, and adjustment of a wide range of potential confounders. However, some limitations should be acknowledged. First, the absence of baseline treatment data in this study precludes the evaluation of the sustained status of abnormal RCIs. Second, the observational design limits causal inference and prevents complete elimination of residual confounding or unmeasured variables. Third, the ethnic homogeneity of the UK Biobank cohort constrains the extrapolation of these findings to diverse populations.

In conclusion, our findings provide valuable insights into the associations of MCV, MCH, and RDW with various cancer risk in the general population. Future studies are warranted to clarify the underlying mechanisms of these hematologic parameters in carcinogenesis.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Prevalent cardiovascular disease
Hb	Hemoglobin
HR	Hazard ratios
HRT	Hormone replacement therapy
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MET	Metabolic equivalent task
NSAID	Non-steroidal anti-inflammatory drug
NHS	National health service
NLR	Neutrophil-to-lymphocyte ratio
RBC	Red blood cell
RCI	Red cell indice
RDW	Red cell distribution width

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
CF: contributed to the analyses and interpretation of data; XC, YS, and JH: contributed to the drafting of the manuscript; XL, XC, WC, LH, and YM: contributed to the critical revision of the manuscript for important intellectual content; WZ and YD: contributed to the study design; DH: contributed to the study supervision and funding acquisition. All authors have read and approved the final manuscript.

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Data availability
The data generated during and/or analysed during the current study are available from the UK Biobank. http://www.ukbiobank.ac.uk/register-apply.

Declarations

Ethics approval and consent to participate
The UK Biobank was approved by the North West Multi-center Research Ethics Committee (REC reference: 11/NW/03820), and all participants provided informed consent.

Consent for publication
All authors approved the final manuscript and the submission to this journal.

Competing interests
The authors declare no competing interests.

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