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RESEARCH

Association between Heavy Metals and Trace Elements in Cancerous and Non-cancerous Tissues with the Risk of Colorectal Cancer Progression in Northwest China

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Abstract

Alterations in heavy metals and trace element levels may be associated with various cancers. However, the role of this interaction in colorectal cancer (CRC) progression is unclear. In recent years, Principal Component Analysis (PCA) and Bayesian Kernel Machine Regression (BKMR) models have provided new ideas for analyzing the effects of metal mixtures on CRC progression. Herein, we assessed the differences in the levels of arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), nickel (Ni), selenium (Se), and zinc (Zn) in tumors and adjacent healthy tissues, to investigate the relationship between heavy metals/trace elements and CRC progression. Surgical samples of CRC and noncancerous tissues were collected, and trace metal levels were analyzed using inductively coupled plasma mass spectrometry (ICP-MS). Logistic regression, PCA, and BKMR models were used to investigate the relationship between heavy metals and trace elements and the degree of tumor differentiation and lymph node metastasis in CRC. Cancer tissues showed lower As, Cd, Co, and Cr concentrations, and higher Se concentrations than healthy tissues ($P < 0.05$). In addition, CRC patients with poorly differentiated tumors and/or positive lymph node metastases had lower levels of Cd, Zn, Cu, and Se ($P < 0.05$). Logistic regression showed that single metal concentration was negatively correlated with CRC progression. PCA and BKMR models also showed that the metal mixture concentration was negatively correlated with CRC progression, with Cd contributing the most. Overall, changes in heavy metal and trace element levels may be related to the development of CRC; however, further mechanistic studies are required.

Keywords Colorectal cancer · Heavy metals · Trace elements · Cancer progression · Cadmium · Tissue

Introduction

With continuing economic development, changes in diet, and reduction in physical activity, the incidence of colorectal cancer (CRC) is continuing to rise [1]. Globally, CRC is the third most common malignancy and the second most common cause of death due to malignancy, and has become a serious public health problem threatening human health [2]. According to the National Cancer Statistics released by the National Cancer Center in 2022, CRC ranks second in incidence and fourth in death among all malignant tumors in China [3], and China has become one of the countries with the heaviest burden of CRC worldwide [4]. Therefore, early identification of risk factors for CRC is extremely important for its prevention and treatment.

Previous studies have suggested that environment and genetics are major factors contributing to the development of cancer [5], with environmental factors responsible for

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80% of cancer cases [6]. Recently, heavy metals have gained increasing interest as common pollutants in the environment as they can enter the human body through the digestive tract, respiratory tract, or skin, thereby increasing the risk of a variety of diseases, including cancer [7, 8]. There is a dynamic balance of trace metals in the human body, and any disorder of essential or toxic metals may be linked to cancer development [9]. Essential metals, including zinc (Zn), selenium (Se), chromium (Cr), and cobalt (Co), exert anticancer, antioxidant, and other biological functions thanks to their role in metalloenzymes [10], while toxic metals, including arsenic (As), cadmium (Cd), copper (Cu), and nickel (Ni), are designated as Class I carcinogens by the International Agency for Research on Cancer (IARC), and are often associated with an increased risk of many cancers [11]. Therefore, analysis of changes in trace metals in CRC tissues has attracted significant attention. In most prior studies, blood or urine samples were used to analyze the risk of trace metals in cancer; however, these measurement technique only represent recent exposure and excretion levels [12, 13], while more direct analysis of changes in trace metals in cancer and non-cancerous tissues is needed to fully investigate their potential value in CRC.

Metals play a dual role in the development of CRC. Several studies have shown that exposure to heavy metals, such as Cd, As, Cr, and Ni, can increase the risk of CRC in populations [14, 15]. Interestingly, these non-essential metals have also been shown to kill CRC cells in vitro, including the standard cell lines Caco-2, HCT 116, and SW 620 cell lines, and exert potential anticancer effects [16, 17]. In addition, essential metals, including Zn, Se, and Cu, play an important role in the fight against tumors, especially with the development of nanotechnology, where nanometal particles show fewer side effects and higher anticancer efficacy [18, 19]. However, previous studies have focused on in vitro levels and have not validated the anticancer effects of metals in tissue samples from patients with CRC [20, 21].

Based on the above considerations, this study collected samples of CRC tumors and adjacent healthy tissue from CRC patients admitted to the First Hospital of Lanzhou University (Lanzhou, China), and quantitatively analyzed the concentrations of eight trace metals, As, Cd, Co, Cr, Cu, Ni, Se, Zn in the tissues. The aim of this study was to investigate the difference in trace metal levels between cancerous and non-cancerous tissues, and to evaluate the association of heavy metals and trace elements, both individually and in a mixture, with poor differentiation and lymph node metastasis of CRC by various statistical methods. We further aimed to identify the single component that contributes the most, to provide a basis for clinical prevention and treatment of colorectal cancer.

Materials and Methods

Patients

A total of 25 patients diagnosed with CRC and admitted to the First Hospital of Lanzhou University (Lanzhou, China) from January 2022 to June 2023 and participated in this study. All patients who were enrolled after treatment and/or before medically treatment underwent surgery and histopathological examination to confirm the diagnosis of CRC. Clinical features, including demographic and pathological data, were obtained from the medical records. Patients histologically confirmed to have CRC were eligible for inclusion in this study, whereas patients who declined to participate or undergo vitamin and mineral supplementation, as well as those with history of occupational exposure and other types of malignancy were excluded. Relevant patient information is shown in Table 1.

Before the start of the study, the study protocol was explained to all participants, and informed consent was obtained. During surgery, tumors and adjacent healthy tissues were obtained from each patient, and healthy tissues were required to be more than 5 cm from the edge of the cancer, most distal from the edge of the cancer, or located at the surgical margin. Tissue samples were immediately frozen in liquid nitrogen, and transferred to a -80 °C refrigerator for storage until testing.

Table 1 Baseline characteristics of the study population

Variables	CRC patients ($n=25$)	
	n	%
Sex		
Male	15	60.0
Female	10	40.0
Age (mean ± SD)	57.76 ± 9.71	
< 60 years	14	56.0
> = 60 years	11	44.0
Height (cm, mean ± SD)	167.96 ± 8.03	
Weight (Kg, mean ± SD)	62.16 ± 12.57	
BMI (kg/m^2, mean ± SD)	21.93 ± 3.56	
< 24	19	76.0
> = 24	6	24.0
Degree of tumor differentiation		
Good	10	40.0
Poor	15	60.0
Lymph node metastasis		
Negative	16	64.0
Positive	9	36.0

CRC, Colorectal cancer; SD, standard deviation; BMI, body mass index

This study was conducted in accordance with the principles of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the First Hospital of Lanzhou University (Lanzhou, China) (LDYYLL2020-103).

Heavy Metals and Trace Elements Analysis

For heaby metal and trace element analysis, 0.1 g of the dry tissue sample was accurately weighed, placed in 6 ml mixed acid (65% concentrated nitric acid: 50% hydrogen peroxide = 1:5), covered, and subjected to microwave digestion. The temperature settings used for the procedure are listed in Table S1. The digestion solution was placed on an electric heating plate to remove excess nitrogen oxides in the sample, and the treated sample was then transferred to ultra-pure water in a 10 ml volumetric bottle and set for determination after the solution was clarified [22].

Trace metal concentrations in colorectal tissues were quantified using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700x, Agilent Technologies, USA) at the Gansu Pharmaceutical Inspection Institute. The following eight metals were analyzed based on previously published data: As, Cd, Co, Cr, Cu, Ni, Se, and Zn. The parameter Settings of ICP-MS are shown in Table S2.

A mixed standard solution containing 8 metals with a concentration of 1000 μg/mL was purchased from the Chinese Academy of Metrology to prepare a six-point standard curve, including 0. The linear regression equation, correlation coefficient, linear range, limit of detection (LOD), and limit of quantification (LOQ) of each trace metal are presented in Table S3.

The determination of the selected metals followed strict quality control procedures. Multi-element internal standards (germanium [Ge], terbium [Tb], and indium [In]), purchased from the National Nonferrous Metals and Electronic Materials Analysis and Testing Center were analyzed to evaluate the recovery studies and accuracy of the measurements. Table S3 shows the recovery rates and relative standard deviations (RSD) for this study, indicating that the method had good accuracy and precision.

Statistical Analyses

SPSS software (version 22.0; IBM SPSS Statistics) and R Studio (version 4.1.0) were used for statistical analyses. Descriptive statistics (mean and standard deviation [SD] or frequency [percentage] and medians [interquartile ranges]) were applied to analyze the clinical characteristics of the subjects. Kolmogorov–Smirnov and Shapiro–Wilk tests were further used to determine the normality of the data distribution (Table S4). Spearman's Rank correlation was used to evaluate the correlations between trace metals in this study, and the paired samples Wilcoxon signed-rank test was used to compare differences in cancer and adjacent healthy tissues. Logistic regression models were constructed to assess the risk between trace metals for poor differentiation and lymph node metastasis of tumors, plot receiver operating characteristic (ROC) curves, and calculate the area under the curve (AUC) to assess the diagnostic performance of the trace metals.

Principal component analysis (PCA) can be used to analyze the interactions between multiple metals, which is carried out using a data matrix, where the original data points located in the original variable space are projected onto a subspace of lower dimensions, thus classifying the metal mixture as uncorrelated components based on its correlation. Factors with eigenvalues > 1 were considered PCA factors (PCFS). The principal component score was subsequently calculated to describe the relative position of a single metal on the principal component, and the eigenvector of the principal component was analyzed to determine its weight on the principal component. This method reduces the number of components while preserving information in the original variable [23]. Logistic regression models were then fitted between the principal component scores, binary tumor differentiation, and lymph node metastasis to estimate the risk of the different factor components.

Furthermore, the Bayesian Kernel Machine Regression (BKMR) model overcomes the shortcomings of traditional statistical methods, which may be limited by multicollinearity and model selection errors, to more reliably assess the combined effects of multiple trace metals on tumor differentiation and lymph node metastasis. The BKMR model can further evaluate the individual effects of multiple metals and the cumulative effects of the total mixture, assess the interaction between two metals, and estimate the posterior inclusion probability (PIP) to screen for key trace metals that affect the outcome of the event. The significance level was set at $P < 0.05$.

Results

Characteristics of the Study Subjects

The mean age of all patients was 57.76 years, including 15 males (60.0%) and 6 overweight patients (25.0%) (Table 1). Subjects were divided into two age groups: middle-aged (< 60 years) and elderly subjects (≥ 60 years). Patients were further divided into two categories based on body mass index (BMI): non-overweight patients (< 24 kg/m^2) and overweight patients (≥ 24 kg/m^2). According to the degree of tumor differentiation and lymph node metastasis, 40.0% of the CRC patients had good differentiation (highly differentiated), and 36.0% of the CRC patients were diagnosed with lymph node metastasis.

Elemental Analysis of Tumor and Adjacent Healthy Tissues

Table 2 shows the median interquartile range (IQR) for trace element levels in CRC and adjacent healthy tissues. Cd, Co, and Cr concentrations were significantly lower in cancer tissues than in adjacent healthy tissues, whereas Se concentrations were significantly higher in cancer tissues ($P < 0.05$ or 0.01). Although Ni and Zn concentrations in cancer tissues were lower than those in healthy tissues, the differences were not significant, and Cu concentrations showed no significant difference cancer and healthy tissues ($P > 0.05$).

The trace metal contents of cancer tissues stratified according to sex, age, BMI, degree of tumor differentiation, and tumor lymph node metastasis are shown in Table S5-S9. Metal concentrations in cancer tissues did not differ significantly according to sex, age, or BMI (Table S5-S7). However, the median concentrations of Cd, Cu, and Zn were significantly lower in patients with poorly differentiated CRC than in patients with highly differentiated CRC ($P < 0.05$ or 0.01) (Table S8). We further found that node-positive patients had lower levels of Cd, Se, and Zn than node-negative patients with CRC (Table S9), suggesting that these trace metals may play an important role in influencing tumor progression.

Single-element Models

Using multivariate logistic regression models, we estimated the association between trace metals and risk of poorly differentiated CRC and lymph node metastasis. Crude models showed that high Cu levels (OR: 0.703; 95%CI: 0.510–0.970) were negatively associated with poor CRC differentiation ($P < 0.05$); these associations showed borderline significance after adjusting for sex, age, and BMI ($P = 0.053$). We further observed an inverse association between metals, including Cd, Se, and Zn, and positive lymph node metastases in CRC (all $P < 0.05$), with ORs of 0.990 (95% CI: 0.982–0.998), 0.993 (95% CI: 0.987–0.999), and 0.923 (95% CI: 0.861–0.988), respectively, all of which were consistent even after adjusting for confounding factors (Table 3). These results indicate that elevated levels of these trace metals may help reduce the risk of poorly differentiated CRC and lymph node metastasis.

Subsequently, we plotted the ROC curve for each trace metal (Fig. 1) and calculated the area under the curve (AUC) (Table S10), finding that Cd (AUC: 0.807, 95%CI: 0.625, 0.989), Cu(AUC: 0.867, 95%CI: 0.712, 1.000) and Zn (AUC: 0.820, 95%CI: 0.645, 0.995) showed a satisfactory diagnostic ability to predict poor differentiation of CRC, among which Cu had the highest diagnostic performance, with a sensitivity of 0.867 and a specificity of 0.800 for its optimal threshold. In addition, Cd, Se, and Zn showed good diagnostic performance in predicting lymph node metastasis in CRC, among which Cd showed the best predictive ability. ROC analysis further showed that the AUC value of Cd was 0.910, its sensitivity was 0.889, and its specificity was 0.875, which was consistent with the results of the logistic regression model described above.

Principal Component Analysis (PCA)

Spearman's correlation analysis was performed to investigate the correlation between the eight metals in cancer and adjacent healthy tissues (Fig. S1–S3). We found significantly strong positive correlations between As and Cr (r = 0.661), As-Ni (r = 0.646), Co-Cr (r = 0.859), Co–Ni (r = 0.803), and Cr-Ni (r = 0.950) in CRC tissues and moderate positive correlations between As and Co (r = 0.575), Cd-Zn (r = 0.482), and Se-Zn (r = 0.556). In the case of adjacent healthy tissues, significant strong positive correlations were found between As-Co (r = 0.750), As-Ni (r = 0.724), Co-Cr (r = 0.712), Co–Ni (r = 0.832), Cr-Ni (r = 0.791), and Cu–Zn (r = 0.613), while As-Cr (r = 0.589), and Cd-Cu (r = 0.502), Cd-Zn (r = 0.482), and Se-Zn (r = 0.438) showed moderate positive correlations. In addition, the correlation coefficients

Table 2 Differences in trace metals levels between CRC and adjacent healthy tissue samples

Element	Adjacent healthy tissues	Tumor tissues	*P* Value
As (ng/g)	30.83(18.97–86.44)	19.36(13.70–44.74)	0.003**
Cd (ng/g)	396.73(251.22–810.09)	344.43(133.64–502.49)	0.002**
Co (ng/g)	84.99(43.89–131.65)	46.34(31.05–80.30)	0.007**
Cr (μg/g)	5.63 (2.61–10.39)	2.71 (1.59–5.86)	0.012*
Cu (μg/g)	11.14 (9.15–14.93)	13.09 (9.89–16.15)	0.192
Ni (μg/g)	3.55 (2.02–6.35)	2.36 (1.29–4.93)	0.061
Se (μg/g)	0.51 (0.39–0.72)	0.67 (0.54–0.82)	0.016*
Zn (μg/g)	92.78 (78.59–114.66)	85.64 (69.374–96.99)	0.069

CRC, colorectal cancer; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc. All data are shown as median (IQR). * Indicates the statistically significant difference, * $P < 0.05$; ** $P < 0.01$

Table 3 Adjusted OR (95% CI) of poor differentiation and lymph node metastasis of CRC per 1-unit single trace metals

Variable	Element	Model 1		Model 2	
		OR (95% Cl)	*P* Value	OR (95% Cl)	*P* Value
Poor differentiation of CRC	As	1.002 (0.975, 1.030)	0.890	0.998 (0.962, 1.035)	0.898
	Cd	0.998 (0.996, 1.000)	0.127	0.998 (0.996, 1.001)	0.189
	Co	0.997 (0.973, 1.022)	0.822	0.996 (0.968, 1.024)	0.766
	Cr	1.008 (0.768, 1.323)	0.954	0.982 (0.716, 1.346)	0.909
	Cu	0.703 (0.510, 0.970)	0.032*	0.655 (0.427, 1.005)	0.053
	Ni	1.093 (0.712, 1.677)	0.686	1.134 (0.674, 1.909)	0.635
	Se	1.000 (0.997, 1.003)	0.826	1.001 (0.998, 1.004)	0.646
	Zn	0.965 (0.920, 1.013)	0.149	0.965 (0.918, 1.013)	0.150
Lymph node metastasis in CRC	As	1.000 (0.972, 1.028)	0.985	0.994 (0.962, 1.027)	0.701
	Cd	0.990 (0.982, 0.998)	0.016*	0.990 (0.981, 0.998)	0.020*
	Co	1.000 (0.975, 1.025)	0.973	0.997 (0.971, 1.024)	0.828
	Cr	0.870 (0.642, 1.181)	0.372	0.826 (0.588, 1.162)	0.272
	Cu	0.887 (0.731, 1.076)	0.225	0.865 (0.685, 1.0093)	0.224
	Ni	0.958 (0.620, 1.478)	0.845	0.909 (0.569, 1.452)	0.690
	Se	0.993 (0.987, 0.999)	0.039*	0.983 (0.969, 0.999)	0.032*
	Zn	0.923 (0.861, 0.988)	0.022*	0.855 (0.748, 0.976)	0.021*

CRC, colorectal cancer; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc; BMI, body mass index; OR: odds ratio; CI: confidence interval

Model 1 adjusted with nothing; Model 2 adjusted with age, gender, and BMI

All data are shown as OR (95%CI) and were analyzed using logistic regression analysis

* $P < 0.05$

between tumors and healthy tissues were mostly positive and low to moderate (less than 0.50), while the Zn content in healthy tissues was significantly negatively correlated with the As (r = 0.491), Co (r = 0.418), Cr (r = 0.474), and Ni (r = 0.407) content in cancer tissues.

PCA was performed to analyze the elements of cancer tissues of patients with CRC to achieve dimensionality reduction. As shown in Table S11, three principal component factors with eigenvalues greater than 1 were extracted, among which Factor 1 accounted for 48.52% of the total variance and exhibited high load scores for Cr, Ni, Co, As, and Zn. Factor 2 accounted for 19.25% of the total variance and had high load scores for Se and Cd. Factor 3 accounted for 13.49% of the total variance and exhibited a high loading score for Cu.

The logistic regression model showed that each 1-unit increase in the factor 3 score (OR: 0.237; 95%CI: 0.062, 0.904) was negatively associated with the risk of poor differentiation of CRC ($P < 0.05$). An inverse correlation between factor 2 and the risk of lymph node metastasis in CRC was also observed (Table 4). After adjusting for confounders, the negative association between factor 3 and poor CRC differentiation remained significant, which was consistent with the results of the single-element model.

The ROC curves of the three factors were plotted (Fig. 2), revealing that Factor 3 and Factor 2 had satisfactory diagnostic performance in predicting poor differentiation and lymph node metastasis of CRC, with AUC values of 0.880 (95% CI: 0.742, 1.000) and 0.958 (95% CI: 0.887, 1.000), respectively (Table S12).

Combined Effect of Metal Mixtures

We further included the abovementioned eight metals in the BKMR analysis to assess the combined effect of trace metal mixtures on poor differentiation and lymph node metastasis in CRC. First, we verified the importance of these eight metals for the risk of poor differentiation and lymph node metastasis in CRC. The PIPs results obtained in Fig. 3 show that Cd, Cu, Se, and Zn were highly important in CRC, especially Cd (PIP of 0.989 and 0.955, respectively) (Table S13).

Immediately afterward, we analyzed the dose responses of the included metals. As shown in Fig. 4, Cu and Cd were inversely correlated with the risk of poor differentiation of CRC, while Cd, Se, and Zn were negatively correlated with the risk of lymph node metastasis, whereas the exposure–response curves of other metals showed a flat trend, which failed to prove a difference.

The combined effect of mixed exposure to the eight metals (Fig. 5) showed that the risk of poor differentiation and lymph node metastasis of CRC can be significantly

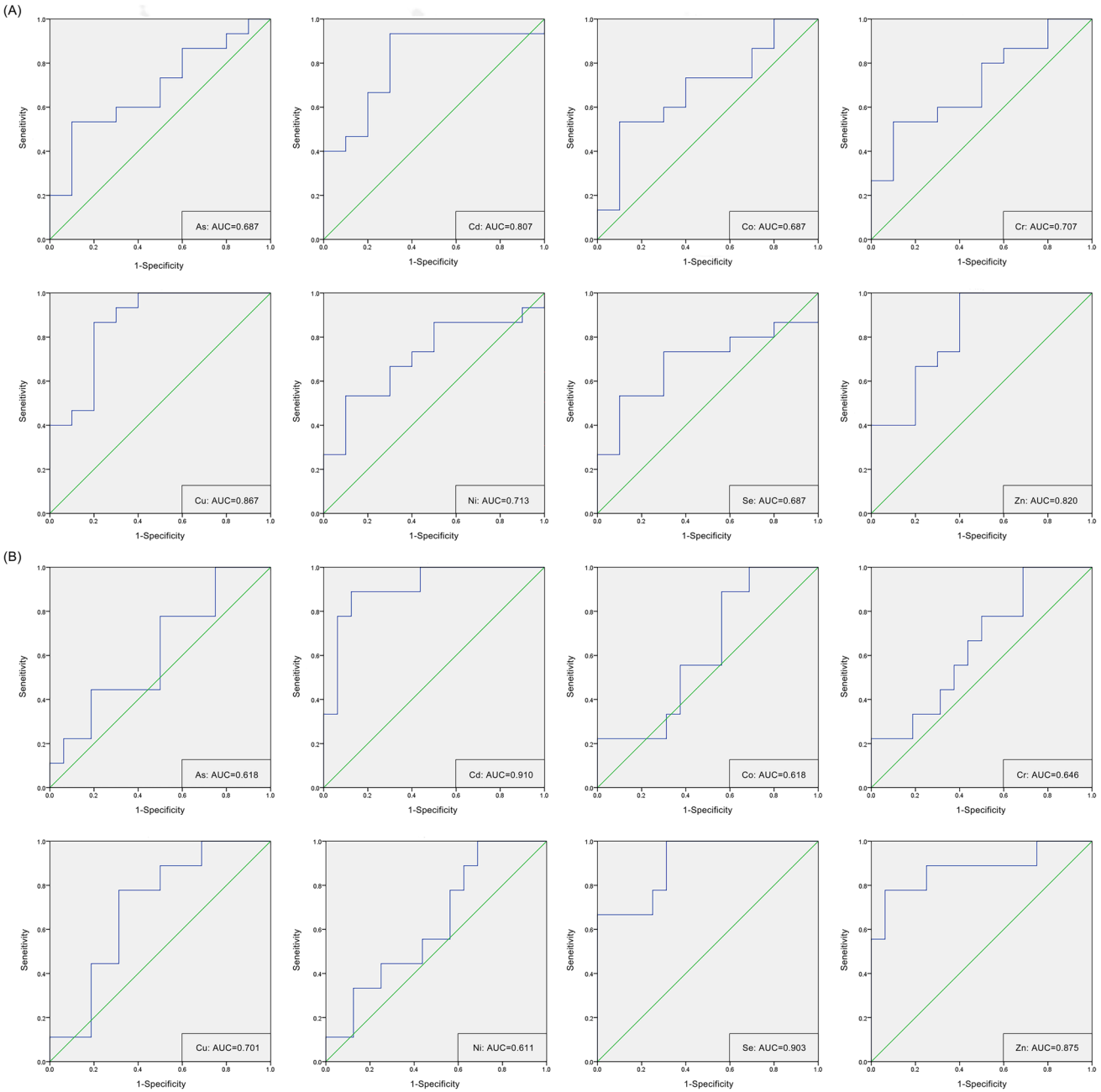

Fig. 1 The ROC curves for each trace metal. ROC curves for each trace metal were used to predict poor differentiation (**A**), and lymph node metastasis (**B**) of CRC. ROC, receiver operating characteristic; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

reduced when the concentration of all metals is higher than the median; this negative relationship becomes more pronounced as the concentration increases.

In addition, the contribution of single metals to poor differentiation and lymph node metastasis in CRC at different percentiles (25th, 50th, and 75th percentiles) was analyzed (Fig. 6). The results showed that poor differentiation of CRC was significantly negatively correlated with Cu and Cd, while lymph node metastasis of CRC was negatively correlated with Cd. No other heavy metals were associated with the malignant progression of CRC.

The interactions between these trace metals are the focus of this study. Through the pairwise interaction model of the elements, we found interactions between Cd and the other elements (Fig. 7). It can be seen that when Cd is fixed at P25, P50, and P75, the negative relationship between Cu and poor differentiation of CRC is weakened, as i the negative relationship between Se and Zn and lymph node metastasis

Table 4 Adjusted OR (95% CI) of poor differentiation and lymph node metastasis of tumors per 1-unit increase in PCA-derived factor score

Variable	PCA-derived factors	Model 1		Model 2	
		OR (95% Cl)	*P* Value	OR (95% Cl)	*P* Value
Poor differentiation	Factor 1	1.390 (0.590, 3.275)	0.452	1.413 (0.504, 3.965)	0.511
	Factor 2	0.622 (0.264, 1.468)	0.278	0.646 (0.255, 1.633)	0.356
	Factor 3	0.237 (0.062, 0.904)	0.035*	0.180 (0.039, 0.838)	0.029*
Lymph node metastasis	Factor 1	1.443 (0.621, 3.355)	0.394	1.388 (0.564, 3.413)	0.475
	Factor 2	0.043 (0.003, 0.617)	0.021*	0.001 (0.000, 7.676)	0.128
	Factor 3	0.620 (0.250, 1.538)	0.302	0.596 (0.219, 1.618)	0.310

CRC, colorectal cancer; PCA, Principal component analysis; OR, odds ratio; CI, confidence interval. Model 1 adjusted with nothing; Model 2 adjusted with age, gender, and BMI. All data are shown as OR (95%CI) and were analyzed using logistic regression analysis. * $P<0.05$

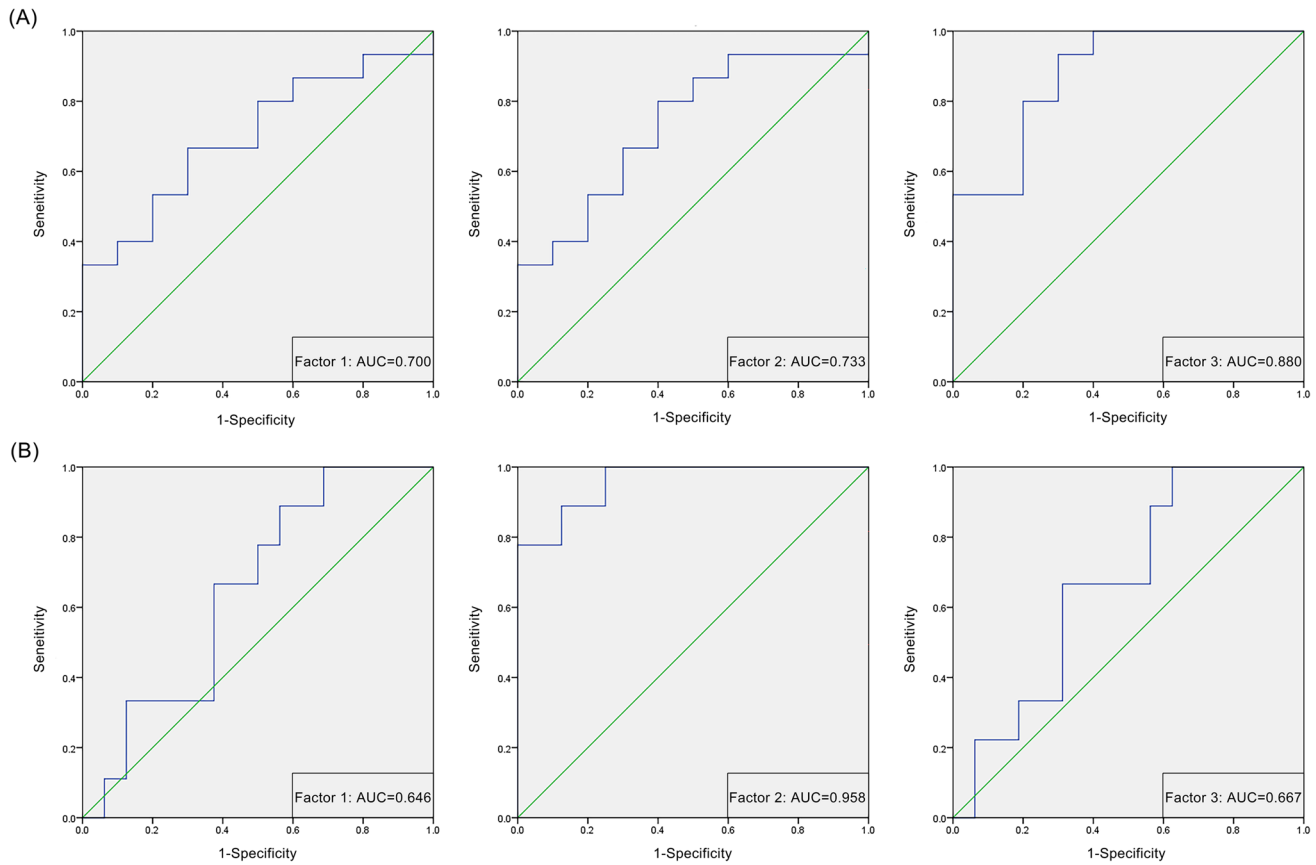

Fig. 2 ROC curves for each principal factor. The ROC curves for each principal factor were used to predict poor differentiation (**A**), and lymph node metastasis (**B**) of CRC. ROC, receiver operating characteristic; CRC, colorectal cancer

of CRC is also weakened, suggesting that Cd and Cu, Se, and Zn play an antagonistic role in CRC progression.

Discussion

Prior researchers have extensively search for the causes and treatments of cancer, and while several studies have assessed differences in trace metal levels in many cancers, including breast, kidney, and gallbladder cancers [24–26], their role in CRC remains elusive. In this study, we found that the concentrations of As, Cd, Co, and Cr in CRC tissues were generally lower than those in adjacent healthy tissues, whereas the opposite was true for Se. In addition, we used multiple statistical models to assess the effects of single and mixed trace metals on the poor differentiation and lymph node metastasis of CRC, showing that high concentrations of metals inhibit CRC invasion and metastasis, and determined

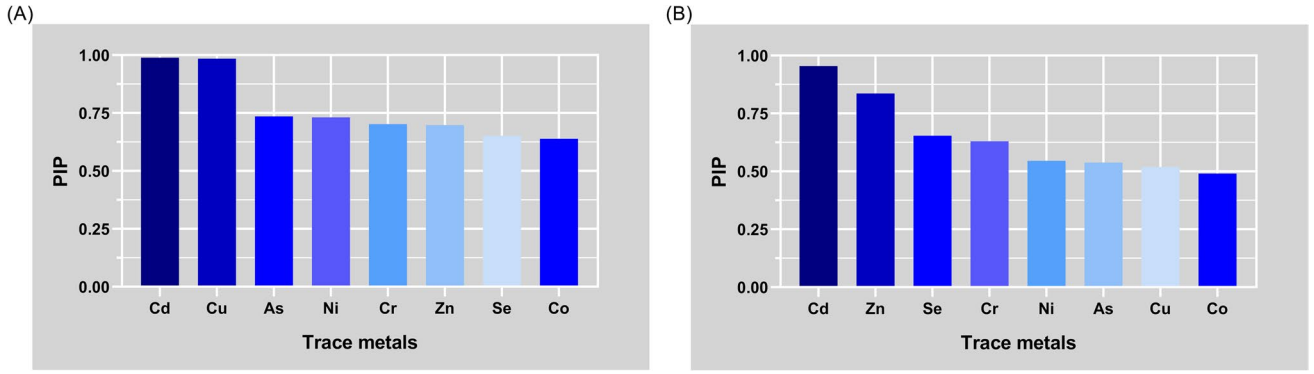

Fig. 3 Posterior inclusion probability values of each trace metal in the BKMR model. (**A**) trace metals mixtures and poor differentiation of CRC, and (**B**) trace metals mixtures and lymph node metastasis of CRC. Trace metals were logarithmically converted. The model was adjusted for age, sex, and BMI. CRC, colorectal cancer; BMI, body mass index; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

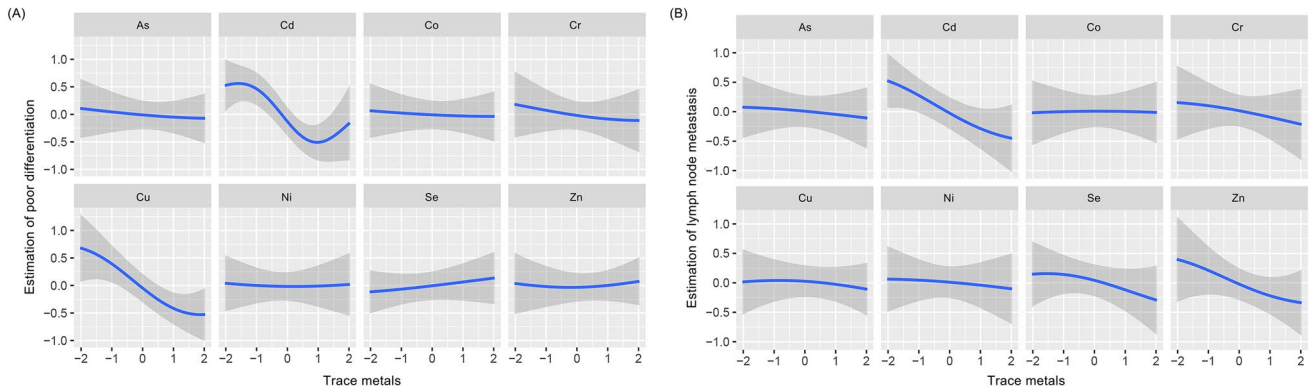

Fig. 4 Univariate dose–response (estimates and credible intervals) of each trace metal in the BKMR model. (**A**) trace metals mixtures and poor differentiation of CRC, and (**B**) trace metals mixtures and lymph node metastasis of CRC. Trace metals were logarithmically converted. The model was adjusted for age, sex, and BMI. CRC, colorectal cancer; BMI, body mass index; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

their diagnostic value in predicting tumor progression. This is the first report in Northwest China to assess metal concentrations in tissues from patients with CRC; as such, our results must be confirmed in a large sample population.

Multiple studies have reported significant changes in metal levels in patients with CRC. Juloski et al. found that the median concentrations of Cd, Cr, Co, Zn, and Hg in the cancer tissues of CRC patients were significantly lower than those in healthy tissues, whereas the median concentrations of Cu, Se, Ca, and Mg were significantly higher [27]. Furthermore, Türkdoğan et al. found that Cd, Co, Ni, Pb, Zn, Fe, and Mn in cancer tissues of CRC patients were very low compared to controls [6]. This is similar to our results, where we observed significantly lower levels of As, Cd, Co, and Cr in cancerous tissues, but significantly higher Se levels compared to the surrounding healthy tissues. However, previous studies have yielded inconsistent results. For example, Fatemeh et al. showed that patients with CRC had higher concentrations of Co, Cr, Ni, Pb, and Zn than a control group [15], while another study in the Chaoshan population of Southeast China indicated that a higher exposure to Cd and Pb may promote the occurrence and development of CRC [14]. These contradictory results may be related to differences in the included populations. The study population may be ordinary CRC patients who come from the upper gastrointestinal cancer epidemic area, or have a long history of exposure to metals [28]. The difference in element levels in the human body is closely related to environmental conditions. In addition, the samples analyzed in the different studies differed. Tissue, serum, whole blood, urine, and other samples are often used to analyze the differences in heavy metals and trace elements, and the metabolic process of elements in the body determines the concentration of changes in different specimens; this is also a possible reason to explain the inconsistent conclusions of different studies, and therefore needs to be further studied.

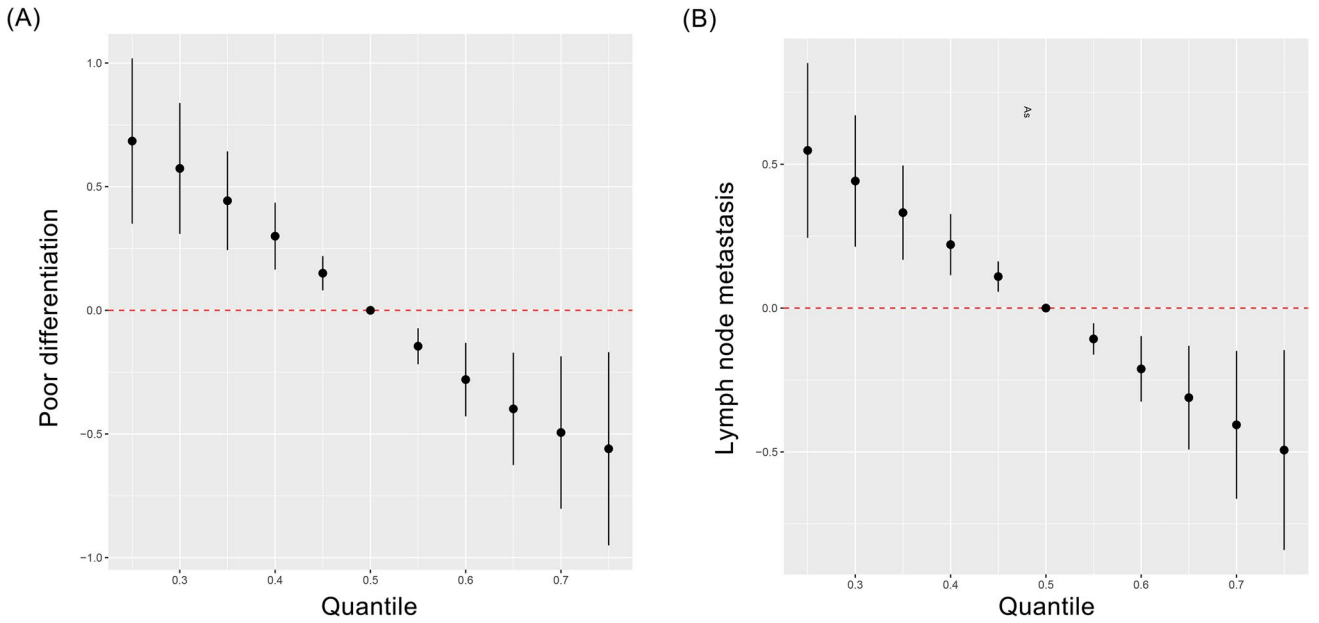

Fig. 5 Cumulative effect (estimates and credible intervals) across per 5th quantile above and below medians of total trace metals mixture in the BKMR model. (**A**) trace metals mixtures and poor differentiation of CRC, and (**B**) trace metals mixtures and lymph node metastasis of CRC. Trace metals were logarithmically converted. The model was adjusted for age, sex, and BMI. CRC, colorectal cancer; BMI, body mass index; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

According to the GLOBOCAN database, the distribution of CRC shows significant age and sex differences [2]. The incidence of CRC increases with age, and men have a higher incidence than women [29, 30]. Several prior studies have also revealed that obesity increases the risk of CRC [31, 32]. Therefore, in our study, we conducted a stratified analysis based on patient age, sex, and BMI, and found that the vast majority of metals showed no differences in terms of

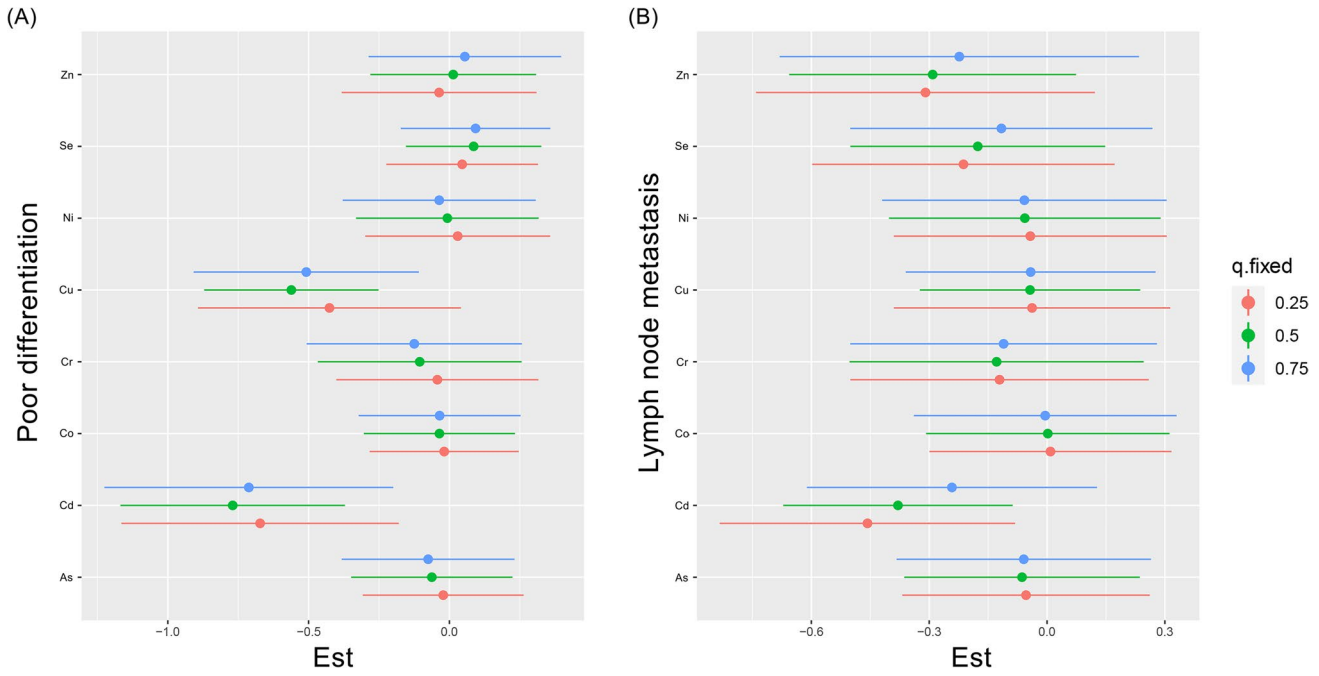

Fig. 6 Single-exposure risks (estimates and credible intervals) of each trace metal in the BKMR model. (**A**) trace metals mixtures and poor differentiation of CRC, and (**B**) trace metals mixtures and lymph node metastasis of CRC. Trace metals were logarithmically converted. The model was adjusted for age, sex, and BMI. CRC, colorectal cancer; BMI, body mass index; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

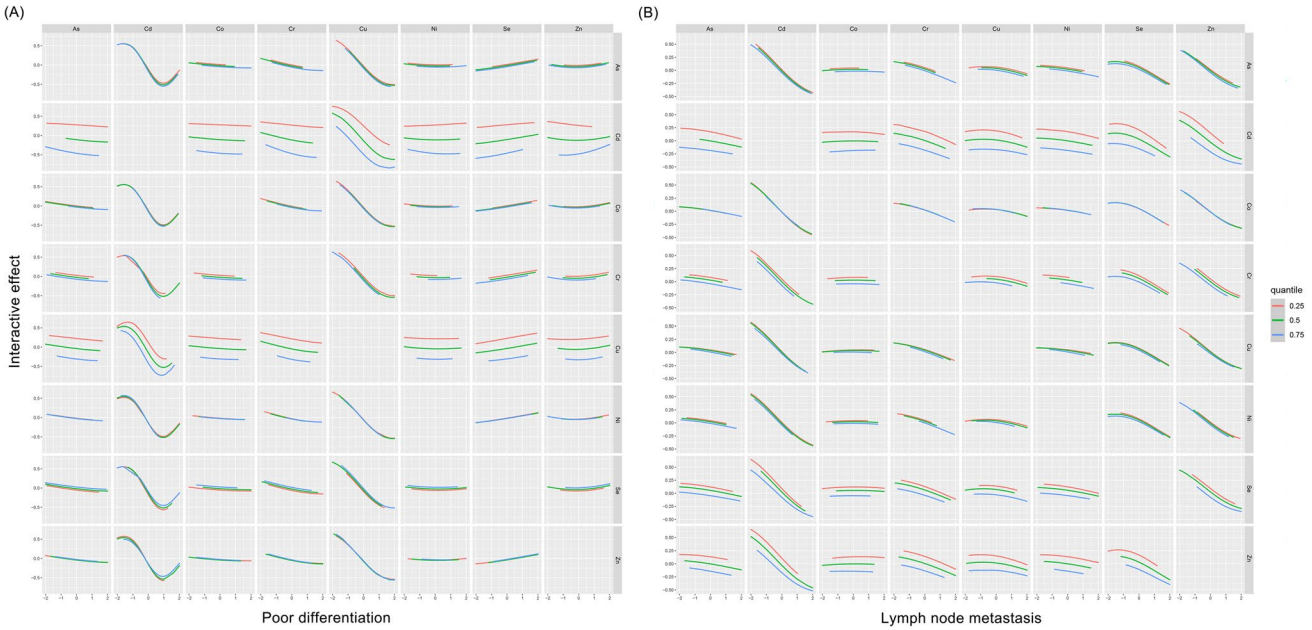

Fig. 7 Bivariate expose-response function of trace metals mixture in the BKMR model. (**A**) trace metals mixtures and poor differentiation of CRC, and (**B**) trace metals mixtures and lymph node metastasis of CRC. Trace metals were logarithmically converted. The model was adjusted for age, sex, and BMI. CRC, colorectal cancer; BMI, body mass index; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Ni, nickel; Se, selenium; Zn, zinc

age, sex, and BMI. However, previous studies have reported associations between Ni and other cancers; for example, one study found high concentrations of Ni in both blood and scalp hair samples in male patients with thyroid cancer [33, 34], higher mean Cu concentrations in endometrial cancer patients with higher BMIs [35], and altered levels of trace metals between ages in patients with esophageal and stomach cancer [36]. This study was unable to draw more associations between sex, age, BMI, and metal concentrations, but this may be related to the small sample size of the subjects, exposure to certain types of pollution, or assessment techniques. In future studies, we aim to recruit more patients with CRC from multiple hospitals and update our metal detection technology to explore the effects of sex, age, and BMI on trace element levels in patients with CRC.

Many previous epidemiological studies have investigated the relationship between trace metals and tumor progression. A study on Korean women with thyroid cancer showed that the tissue levels of Cd, Se, and Zn, especially Cd, were significantly higher in patients with advanced cancer [37]. In another study on metals and breast cancer progression, Cd content was found to be significantly associated with breast cancer type, stage, grade, lymph node status, and progesterone status [24]. Overall, our findings show that CRC patients with poorly differentiated tumors and lymph node metastases have lower levels of metals, including Cd, Cu, Se, and Zn, which is consistent with the results of previous studies. Mahmood et al. reported that serum levels of As and Cr were the highest in patients with stage IV CRC [38]. In addition, patients with stage III and IV CRC had significantly higher Cu/Zn ratios than those with lower stages [27].

We used a variety of statistical methods to assess the effects of metals on the risk of CRC progression. We found that both single and mixed metals were inversely associated with the risk of poor tumor differentiation and lymph node metastasis in patients with CRC. Metal exposure is thought to increase the occurrence of a variety of cancers. For example, prior studies have shown a significant association between elevated blood and urinary Cd concentrations and gastrointestinal cancer risk [4, 39], while one case–control study in Nigeria suggested that long-term Cd exposure may be associated with an increased risk of prostate cancer, particularly in patients with zinc deficiency [41]. However, these results are not contradictory, as previous studies used healthy people as controls, whereas this study used healthy tissue adjacent to the tumor as a control, which could avoid the external interference caused by different lifestyle and environmental factors (such as smoking, exercise status, diet, and housing environment). In the present study, we found that single and mixed trace elements were negatively associated with colorectal cancer. Our previous animal experiments demonstrated that Cd exposure inhibited the progression of DEN-induced early liver cancer [42]. Consistent with our results, Wang et al. revealed that common exposure to multiple metal mixtures may have a positive effect on

gastric precancerous lesions [43], and metals, such as Se and Cu, in tumors were found to have great potential in the treatment of CRC [44, 45].

In this study, Cd was found to be the metal with the highest contribution. Cd is classified as a Class I carcinogen by the IARC [46], and can contribute to cancer development by inducing oxidative stress and epigenetic regulation [47]. Similarly, As can induce excessive ROS production, damage the structure and function of specific proteins, and destroy the structure of macromolecules, such as lipids, carbohydrates, and DNA [48]. However, we also found that heavy metals, including Cd and As, may inhibit CRC progression. This paradoxical phenomenon may be related to the fact that Cd and As both delay tumor development by preventing angiogenesis [49, 50]. In addition, metallothionein (MTs) has been widely studied because of its detoxification effect on heavy metals [51], and it has been reported to be expressed at low levels in CRC, liver cancer, and other cancers [52, 53], resulting in CRC cells being more sensitive than normal cells when subjected to metal toxicity. This provides ideas for targeted clinical treatment of CRC and needs further research.

Essential metals, including Zn, Se, and Cu, are an important part of a variety of enzymes in the human body, and play an important role in inhibiting the production of free radicals, immune function, and cell growth to maintain normal physiological activities [54, 55]. In particular, Se and/or Se-linked proteins play an anti-tumor role through the activation of the apoptosis pathway, antioxidant activity, anti-angiogenesis, and cell cycle regulation, and are widely used in clinical studies in combination with proteins and polysaccharides, or as nanoparticles [56]. In addition, they can enhance immunity and DNA damage repair, and play a role in cancer suppression, contributing to cancer treatment and prevention [57, 58]. This situation is consistent with our study, which found that the above metals are significantly negatively correlated with poor tumor differentiation and lymph node metastasis, and have good diagnostic value. However, an excess of essential metals may also contribute to cancer by inducing peroxidation stress and cell death and proliferation [59, 60]. Current studies on the carcinogenic and cancer-inhibiting functions of these metals are mixed, and we are unable to provide an accurate and comprehensive interpretation of the existing results; therefore, further studies are needed.

The strength of this study is that it assessed differences in the distribution of eight common trace metals in tumors and adjacent healthy tissues in patients with CRC. Second, we used multiple statistical models to explore the association between single and mixed trace metals, poor tumor differentiation, and lymph node metastasis, which may contribute to the clinical treatment of CRC. This study had some limitations. Owing to the small sample size, more samples from multiple centers are needed to confirm our findings. In addition, the effects of confounding factors such as smoking status, eating habits, living environment, and occupational activities were not assessed. Finally, further in vivo and in vitro studies are required to elucidate the mechanisms underlying this cross-sectional study.

Conclusion

CRC remains a significant medical concern due to its extremely high morbidity and mortality rates. In this study, the distribution of eight types of heavy metals and trace elements in CRC and adjacent healthy tissues was evaluated. Cancerous tissues showed lower levels of As, Cd, Co, and Cr, as well as higher Se concentrations than healthy tissues, and CRC patients with poorly differentiated tumors and/or positive lymph node metastasis had lower levels of heavy metals and trace elements. In addition, multiple models have shown that tissue levels of heavy metals and trace elements, both individually and in combination, were negatively correlated with CRC progression, with Cd contributing the most. The results of this study provide clues for further exploration of trace metals in targeted therapy of CRC; however, further research is required to elucidate the mechanisms underlying the associations observed in this study.

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Author Contributions Honglong Zhang: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Visualization, Writing - original draft, Writing - review & editing. Jun Yan: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - review & editing. Guole Nie: Software, Investigation, Writing - review & editing. Xun Li: Resources, Conceptualization, Project administration, Supervision, Methodology, Writing-Reviewing and Editing, Funding acquisition.

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Data Availability The datasets are available from the corresponding author on reasonable request.

Declarations

Ethics Approval This study was conducted in accordance with the principles of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the First Hospital of Lanzhou University (LDYYLL2020-103).

Consent to Participate Written informed consent was obtained from all participants.

Consent to Publish All the participants gave their explicit consent for publication.

Competing of Interest The authors declare no competing interests.

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