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RESEARCH ARTICLE

Connecting gastrointestinal cancer risk to cadmium and lead exposure in the Chaoshan population of Southeast China

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Abstract

Cadmium (Cd) and lead (Pb) pose a serious threat to human health because of its carcinogenicity. China ranks first according to the Global Cancer Report for 2014 in newly diagnosed gastrointestinal cancers and cancer deaths. The aim of the present study was to evaluate the association of Cd and Pb burden with the risk of gastrointestinal cancers in a hospital-based case-control study from southern regions of China, Chaoshan area. A total of 279 hospitalized patients were recruited in this study, of which 167 were gastrointestinal cancer cases (70 esophageal cancer, 51 gastric cancer, and 46 colorectal cancer), and 112 controls were recruited from two hospitals in the Chaoshan area of southeast China. Basic clinical data and information on gender, age, and other demographic characteristics were collected from medical records. Blood Cd and Pb levels were detected by graphite furnace atomizer absorption spectrophotometry (GFAAS). Blood Cd/Pb levels and over-limit ratios between cases and controls were compared by Mann-Whitney *U* and Kruskal-Wallis *H* tests. We used logistic regression to estimate odds ratios (ORs) as measures of relative risk and explored the relationships between blood Cd/Pb levels and gastrointestinal cancer risk and clinicopathological characteristics. Median levels of blood Cd and Pb in cases (2.12 and 60.03 μg/L, respectively) were significantly higher than those of controls (1.47 and 53.84 μg/L, respectively). The over-limit ratios for Cd (≥ 5 μg/L) and Pb (≥ 100 μg/L) in the cases were both higher than that of controls. Blood Cd levels had a tendency to accumulate in the human body with gender, age, and tobacco smoking, while blood Pb levels only were associated with tobacco smoking. The logistic regression model illustrated that gastrointestinal cancers were significantly associated with blood Cd levels and blood Pb levels. The concentrations of Cd and Pb in patients with T3 + T4 stage were markedly higher than in patients with T1 + T2. On the other hand, blood Cd levels were dramatically increased in the distant –metastasis (M1). Blood Cd and Pb levels are significantly higher in gastrointestinal cancers compared to controls. Cd and Pb appear to be risk factors for gastrointestinal cancers in Chaoshan region, and higher levels of Cd and Pb may promote the occurrence and progression of gastrointestinal cancers.

Keywords Blood cadmium levels · Blood lead levels · Esophageal cancer · Gastric cancer · Colorectal cancer

Introduction

The gastrointestinal tract, including the esophagus, stomach, and intestine, is a unique organ system which has the highest cancer incidence and cancer-related mortality (Bishak et al. 2015). Gastrointestinal cancers are responsible for 20% of the new cancer cases and 15% of the cancer-related deaths worldwide (Herszényi & Tulassay 2010). Data from GLOBOCAN 2012

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have shown that colorectal cancer is the third most common cancer in men and the second in women worldwide, while gastric and esophageal cancer is the fifth and eighth most common malignancy in the world, respectively (Ferlay et al. 2015). China ranks first according to the Global Cancer Report for 2014 in newly diagnosed gastrointestinal cancers and cancer deaths with regard to esophageal cancer and gastric cancer (Organization 2014).

Numerous studies concluded that all cancer-causing factors originate from both the environment and genetics (Machalek et al. 2016; Takayama and Gelboin, 1980). However, the role of environmental factors might be more important than that of the genetics. It has been acknowledged that environmental factors are attributed to 80% of cancer cases (Parsa 2012). Recently, one potential environmental risk factor that has attracted considerable attention is the exposure to heavy metals. Epidemiological and experimental studies show an association between heavy metals exposure and cancer incidence in humans and animals (Joseph 2009; Sun et al. 2017).

Cadmium (Cd) and lead (Pb) are rated as group I and IIB carcinogenic environmental contaminants respectively, by the International Agency for Research on Cancer (IARC). Cd is easily absorbed by crops and vegetables, such as rice, wheat, and potatoes and can reach high concentrations in shellfish and certain seeds. Therefore, relevant chronic exposure occurs mainly due to dietary intake with respect to the general population (Åkesson et al. 2014; Song et al. 2017). Exposure to Pb occurs mainly via inhalation of lead-contaminated dust particles or aerosols, and ingestion of lead-contaminated food, water, and paints (Toxfaqs 2003). The National Health and Nutrition Examination Survey (NHANES) has assessed the magnitude of Pb exposure by age, gender, and degree of urbanization (Pirkle et al. 1994). Cigarette smoking and alcohol consumption are also important sources of chronic exposure to Cd and Pb (Pirkle et al. 1994; Pizent et al. 2001).

Chaoshan is located in the east coast of Guangdong Province in China. This region is the origin of the Min Nan dialect Teochew. It is also a part of the Hercynian economic zone and the Silk Road on the sea. The pollution of trace metal elements in the harbor and coastal waters of the eastern Guangdong coastal area is serious, and Pb is the main pollution factor in the waters of the Shantou port and the waters around Nanaodao (Sun 2004). In addition, reports of heavy metal pollution in Nanao island, Chaoshan area, have been reported (Qiao et al. 2010; Yang-Guang et al. 2013). It is also reported that some rivers in Chaoshan area are seriously polluted by heavy metal, especially lead and cadmium pollution. Heavy metal contaminations such as Cd, Co, Cr, Cu, Ni, Pb, and Zn have been assessed from printed circuit board recycling, surface dust samples of recycling workshops, adjacent roads, a schoolyard, and an outdoor food market in Guiyu, China, a village intensely involved in e-waste processing. It has been reported that Pb has the potential to pose serious health risks to workers and local residents (Leung et al. 2008). Another study also showed that Pb and Cd levels in soil and road dust from the polluted area were significantly higher compared with the reference area (Yekeen et al. 2016). Increased evidence has established that a single Pb or Cd exposure can cause gastrointestinal cancers (Bishak et al. 2015; Martley et al. 2004; Mohajer et al. 2013; Rodríguez Martín et al. 2006). Thus, we conducted a hospital-based case-control study to compare blood Cd and Pb levels in gastrointestinal cancers patients and controls, and evaluate the interaction between the two metals and clinical characteristics.

Materials and methods

Subjects

In this case-control study, participants recruited were native inhabitants living in the Chaoshan area (including the cities of Shantou, Chaozhou, and Jieyang, and other neighboring areas). We gave detailed explanations of the study and potential consequences prior to enrollment when the patient was hospitalized or applied for physical examination between June and December in 2014 from Cancer Hospital of Shantou University Medical College and Shantou Central Hospital. We received the written informed consent from the participants, including 180 cancer cases and 120 healthy controls. The participation rate in the case and control group reached 92.7 and 93.3%, respectively. Excluding unqualified blood samples and 167 GI (gastrointestinal) cancer cases (70 esophageal cancer, 51 gastric cancer, and 46 colorectal cancer cases) with an average age of 59.07 years were consecutively recruited. All cases were newly diagnosed and previously untreated. Clinical characteristics, including basic medical data, were obtained from medical records. One hundred and twelve controls were recruited and found no disease in the subsequent B-ultrasound, imaging examination, and hematological examination. The controls had a relatively lower average age of 47.09 years old in this study. Cases and controls had no distinction between geographic or cultural groups since they were the native aborigines in Chaoshan, and most of them were farmers and workers. Both cases and controls had no family history of cancer or occupational exposure to Cd or Pb. Information of lifetime consumption of tobacco and alcohol drinking was also collected. All participants were given informed consent after receiving detailed explanations of the study and potential consequences prior to enrollment. This study was undertaken with the approval of the Human Ethical Committee of the Cancer Hospital of Shantou University Medical College.

Data collection

Clinical characteristics, including demographic information and basic medical data, were obtained from medical records. Information regarding socio-demographic characteristics, occupation history, tobacco and alcohol use, medical history, family history of cancer, clinical stages and tumor, node and metastasis (TNM) staging, and other clinical features, were collected.

Collection of blood samples

A total of 2-ml venous blood samples were collected by nurses and stored, in K-EDTA-containing metal-free vials, in a − 70 °C freezer until analysis. To avoid contamination, all plastic tubes and containers used for Cd and Pb determination were washed thoroughly, soaked with dilute nitric acid, rinsed with deionized water, and then dried before using.

Measurement of blood Cd and Pb levels

Levels of Cd and Pb in the blood were measured to assess internal exposure. The analytical method of blood Cd was described elsewhere (Organization 2014). Cd and Pb in whole blood were determined in the Laboratory of Environmental Medicine and Developmental Toxicology of Shantou University Medical College by graphite furnace atomic absorption spectrometry (GFAAS). GFAAS consisted of a Shimadzu AA-660 AAS and a GFA-4B graphite furnace atomizer and an ASC-60G auto sampler (Shimadzu Corporation, Kyoto, Japan) with an injection volume set at 20 ml. The main parameters used for Pb determination were a wavelength of 283.3 nm, a lamp current of 8 mA, a slit width of 1.00 nm, drying at 150 °C, ashing at 325 °C, and atomizing at 1400 °C. The accuracy of the method was controlled by recoveries between 95 and 107%, as determined from spiked blood samples. The parameters for Cd analysis were a wavelength of 228. 8 nm, a current of 8 mA, a slit width of 1.00 nm, drying at 150 °C, ashing at 350 °C, and atomizing at 1500 °C. The recoveries of this method were 100–102% as also determined from spiked blood samples.

Statistical analysis

We performed statistical analyses using SPSS statistical software version 19.0 (IBM SPSS Inc., Chicago, IL, USA). All statistical analyses were two-tailed and a $p < 0.05$ was considered statistically significant. Data analysis processed by using descriptive statistical methods that have mean and standard deviation (SD), and skewed data of variables are given in the median of inter-quartile range (IQR, P_{25}–P_{75}). Independent sample *t* tests were used to identify the age difference between the case and control groups. Since Cd and Pb concentrations in blood were not distributed normally, Mann-Whitney *U* and Kruskal-Wallis *H* tests were used only for data with a skewed distribution. *P* values were calculated using a chi-square test for categorical data. In addition, blood metal concentrations with inter-quartile range (P_{25}, P_{50}, and P_{75}) were utilized to calculate the adjusted odds ratio (OR) for cases. Data for the blood Cd or Pb concentrations were divided into two groups: a high-level group and a low-level group, taking 3.80 μg/L (P_{75}) as the threshold value for blood Cd level, and 90.86 μg/L (P_{75}) for the blood Pb level. Bivariate logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (95% CI) for clinical characteristics.

Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Results

General characteristics of the participants

Data from 167 cancer cases (70 esophageal cancer, 51 gastric cancer, and 46 colorectal cancer) and 112 controls were included in the present study. Table 1 presents the general characteristics of the cases in terms of gender, age, smoking history, alcohol consumption, TNM classification, clinical stages, and anemia. There were only age, gender, residence, smoking history, and alcohol consumption information for the control group. The mean age of the case group was older than that of the control group (59.065 ± 10.43 vs. 47.09 ± 19.81 years, $p < 0.001$). Male patients accounted for 74.25% of all the recruited case subjects. The prevalence rate was about threefold higher in males than in females, which is in agreement with other studies suggesting that gastrointestinal cancers occur two- to fourfold more frequent in men than in women (Stathopoulos & Tsiaras 2003). There were also more current smokers (27.54%) in cases than the controls (13.39%) ($p < 0.01$). Insufficient controls (2.68%) in this study were alcohol drinkers compared to 11.98% being alcohol drinkers in the cases ($p < 0.01$). Therefore, in the regression analysis, all the models were adjusted with the gender, age, tobacco smoking, and alcohol drinking variable. In addition, Table 1 displayed the distribution of cancer types for the cases, which were 41.92, 30.54, and 27.54% for esophageal cancer, gastric cancer, and colorectal cancer, respectively.

Blood Cd levels and blood Pb levels in cases and controls

The Cd values of three samples and Pb values of five samples were excluded due to insufficient quantity lack of blood.

Table 1 General characteristics of the participants

Characteristics	Cases ($n = 167$)	Controls ($n = 112$)	p
Age (yr), mean ± SD	59.065 ± 10.43	47.09 ± 19.81	*< 0.001*
Gender, *n* (%)			
Female	43 (25.75)	57 (50.89)	*< 0.001*
Male	124 (74.25)	55 (49.11)	
Smoking history, *n* (%)	46 (27.54)	15 (13.39)	*< 0.001*
Alcohol consumption, *n* (%)	20 (11.98)	3 (2.68)	*0.002*
Residence			
Shantou	67 (40.12)	58 (51.79)	
Jieyang	29 (17.37)	20 (11.98)	
Chaozhou	18 (10.78)	22 (13.17)	
Other area	43 (25.75)	12 (10.71)	
Cancer location			
Esophageal	70 (41.92)		
Stomach	51 (30.54)		
Intestine	46 (27.54)		
Clinical stages *n* (%)			
I	11 (6.59)		
II	21 (12.57)		
III	57 (33.53)		
IV	33 (20.36)		
T classification, *n* (%)			
T1	10 (5.99)		
T2	17 (10.18)		
T3	34 (20.36)		
T4	52 (31.14)		
N classification, *n* (%)			
N0	39 (23.35)		
N1	29 (17.37)		
N2	25 (14.97)		
N3	20 (11.97)		
M classification, *n* (%)			
M0	76 (45.51)		
M1	37 (22.16)		

$p < 0.05$ was considered statistically significant

Table 2 presented the median with interquartile range (IQR) for blood Cd and Pb levels in cancer patients and controls. Cancer patients had a higher median concentration of blood Cd (2.12 μg/L) than the controls (1.47 μg/L) ($p < 0.001$, Mann-Whitney *U* test), as well as blood Pb (60.03 vs. 53.84 μg/L, $p = 0.027$). Moreover, depending on the type of cancers, blood Cd levels of esophageal and colorectal cancers were significantly higher than the controls ($p < 0.05$), but blood Pb levels were significantly higher than the controls only for esophageal cancer ($p < 0.05$). There was no significant difference of blood Cd/Pb levels between gastric cancer and controls ($p > 0.05$). According to the United States Center for Disease Control and Prevention (CDC) guidelines for blood lead levels, blood lead level ≥ 100 μg/L is considered elevated. Among the cancer cases, 20.86% had blood lead levels ≥ 100 μg/L, whereas only 9.00% of the controls had blood lead levels ≥ 100 μg/L ($p < 0.01$). The threshold value of blood cadmium concentrations that the literature presented as a risk for intoxication is 5 μg/L (Jin et al. 2002; Khassouani et al. 2000). In the study, the percentage of blood cadmium levels ≥ 5 μg/L showed significant differences between cases and controls (13.41 vs. 8.11%, $p < 0.01$).

Effects of Cd and Pb exposure on risk for gastrointestinal cancers and potential confounding variables

Table 3 presented data for comparing means between Cd and Pb concentrations in blood, as well as the major potential confounding in the study population. In the multivariate logistic regression model, the gender, age, current smoking, and alcohol drinking had a significantly elevated OR for gastrointestinal cancers. Among these risk factors, gender and age displayed the highest associations with gastrointestinal cancers (OR = 0.359, $p < 0.001$ vs. OR = 4.069, $p < 0.001$; respectively). Moreover, current smoking and alcohol drinking had a significantly increased odds ratio for gastrointestinal cancers (OR = 2.452, $p = 0.006$ vs. OR = 4.943, $p = 0.011$; respectively). The quartile (P_{25}, P_{50}, and P_{75} division) for blood Cd and Pb levels were used to estimate odds ratios for gastrointestinal cancers. After controlling for related factors, including gender, age, tobacco smoking, and alcohol drinking, blood Cd levels above the P_{50} division demonstrated strong association with gastrointestinal cancers (P_{50}-P_{75}: OR = 2.643, $p = 0.012$; $> P_{75}$: OR = 2.492, $p = 0.020$), when only blood Pb levels above the P_{75} division had association with gastrointestinal cancers (OR = 2.232, $p = 0.048$).

Blood Cd levels, blood Pb levels, and possible related factors

We evaluated the associations between Cd, Pb exposure, and related factors (Table 4). Males had a tendency to obtain higher concentrations of blood Cd compared to females (2.00 vs. 1.60 μg/L, $p = 0.011$). Blood Cd levels at ages > 50 years were higher than blood Cd levels at ages < 50 years (2.11 vs. 1.56 μg/L, $p = 0.019$), indicating that Cd accumulates in the human body with age. However, no association was found between blood Pb levels and age or gender. Blood levels of Cd and Pb associated with tobacco and alcohol drinking habits were also studied. Blood Cd levels of the tobacco consumers were higher than that of non-tobacco consumers (2.34 vs. 1.63 μg/L, $p = 0.006$).

Table 2 Levels of Cd and Pb for controls and cases (μg/L)

	Cd			Pb		
	n	Median (P_{25}, P_{75})	≥ 5 μg/L	n	Median (P_{25}, p_{75})	≥ 100 μg/L
Controls	112	1.47 (0.95, 2.80)	9 (8.11)	111	53.84 (39.51, 76.27)	10 (9.00)
Total cases	164	2.12 (1.28, 3.80)**	22 (13.41)***	163	60.03 (41.90, 90.86)*	34 (20.86)***
Esophageal cancer	68	2.17 (1.44, 3.85)**		70	64.23 (48.32, 99.70)**	
Gastric cancer	51	1.62 (1.12, 3.12)		50	59.58 (40.30, 85.51)	
Colorectal cancer	45	2.42 (1.52, 4.22)**		43	56.45 (37.88, 87.30)	

3 Cd and 4 Pb data loss in cases; 1Pb data loss in controls

* Compared with controls, Mann-Whitney U test, $p < 0.05$

** Compared with controls, Mann-Whitney U test, $p < 0.01$

*** Compared with controls, chi-square test, $p < 0.01$

Blood Pb levels of smokers (82.14 μg/L) were also higher than the non-smokers (61.65 μg/L) ($p < 0.05$). Alcohol consumption had no effect on the levels of either Cd or Pb ($p > 0.05$).

Table 3 Logistic regression of metal exposures and potential related factors on the risk of gastrointestinal cancers

Characteristics	Controls/cases	OR (95% CI)	p
Gender			
Male	57/124	1.00	
Female	55/43	0.359 (0.216, 0.597)	*< 0.001*
Age			
~ 50	59/35	1.00	
51–60	24/62	4.069 (2.229, 7.428)	*< 0.001*
61–90	29/70	0.934 (0.493, 1.772)	0.835
Current smoking, n (%)			
No	107/121	1.00	
Yes	15/46	2.452 (1.295, 4.667)	*0.006*
Alcohol drinking, n (%)			
No	109/147	1.00	
Yes	3/20	4.943 (1.433, 17.057)	*0.011*
BCLs (μg/L)			
$< P_{25}$	39/28	1.00	
P_{25}-P_{50}	31/41	1.657 (0.801, 3.428)	0.173*
P_{50}-P_{75}	22/47	2.643 (1.240, 5.633)	*0.012**
$> P_{75}$	20/48	2.492 (1.155, 5.377)	*0.020**
BLLs (μg/L)			
$< P_{25}$	29/36	1.00	
P_{25}-P_{50}	36/36	0.683 (0.328, 1.423)	0.309*
P_{50}-P_{75}	29/39	0.865 (0.410, 1.822)	0.702*
$> P_{75}$	17/52	2.232 (1.009, 4.940)	*0.048**

$p < 0.05$ was considered statistically significant

BCLs blood Cd levels, *BLLs* blood Pb levels

*Adjusted with the gender, age, tobacco smoking, and alcohol drinking variable

Blood Cd, Pb levels, and clinical characteristics

The P_{75} percentiles of the blood Cd levels and Pb levels of the cancer patients were used as cutoffs to assign the study subjects into either the low- or high-level group, in order to estimate the odds ratios for the gastrointestinal cancers (Table 5). Logistic regression analysis with all ORs adjusted by gender, age, smoking history, and alcohol drinking showed that the T3 + T4 stage cases possessed high levels of Cd (OR = 4.476, $p < 0.05$) compared with T1 + T2 stage patients, and M1 stage cases possessed a higher level of Cd compared to M0 stage patients (OR = 10.959, $p < 0.05$). Moreover, there was a significantly higher level of Pb between T3 + T4 stage and T1 + T2 stage patients (OR = 4.752, $p < 0.05$), but we did not find any relationships between blood Pb levels and M or N stage.

Discussion

The GI tract including the esophagus, stomach, and intestine has the highest cancer incidence and cancer-related mortality in the body. Esophageal cancer is the eighth most common cancer by incidence and the sixth most common cause of cancer death worldwide (Tettey et al. 2012). Chaoshan is one of the major geographic regions in China known for their high incidence of esophageal cancer. The high occurrence rate of esophagus cancer in Chaoshan contained risk factors as genetic predisposition, living habit, and environmental pollution (Lin et al. 2015). Gastric cancer was the fourth most common cancer and the second cause of cancer mortality worldwide (Ferlay et al. 2010). Gastric cancer is a multifactorial disease with environmental and lifestyle factors as major contributors. Recognized risk factors include *Helicobacter pylori* infection, dietary factors, smoking, obesity, radiation, pernicious anemia, and partial gastrectomy (Krejs 2010). Colorectal cancer was the second cause of both death and incidence in developed countries and fifth in developing

Table 4 Comparisons of blood Cd and Pb levels by related factors (μg/L)

	n	Median (P_{25}, P_{75})	Statistic	*p*
Cd				
Gender			$U = 7080.50$[a]	*0.011*
Male	179	2.00 (1.22, 3.62)		
Female	97	1.60 (1.01, 2.82)		
Age			$\chi^2 = 7.96$[b]	*0.019*
~50	94	1.56 (0.86, 2.91)		
51–60	85	2.11 (1.27, 3.46)		
61~90	97	2.08 (1.25, 3.56)		
Smoking history			$U = 4989.50$[a]	*0.006*
Yes	60	2.34 (1.50, 3.75)		
No	216	1.63 (1.07, 3.13)		
Alcohol consumption			$U = 2423.00$[a]	
Yes	23	2.15 (1.13, 4.42)		0.184
No	253	1.70 (1.20, 3.19)		
Pb				
Gender			$U = 8128.00$[a]	0.467
Male	177	58.74 (40.66, 84.71)		
Female	97	54.01 (39.85, 80.18)		
Age			$\chi^2 = 1.670$[b]	
~50	92	54.94 (38.68, 80.69)		0.434
51–60	84	54.96 (40.77, 85.64)		
61–90	98	58.51 (47.22, 82.29)		
Smoking history			$U = 5008.50$[a]	*0.019*
Yes	58	63.04 (46.29, 112.55)		
No	216	54.70 (39.68, 78.93)		
Alcohol consumption			$U = 2377.50$[a]	0.268
Yes	22	60.82 (45.93, 97.61)		
No	252	56.54 (40.30, 80.90)		

$p < 0.05$ was considered statistically significant

[a] Value of *U* for Mann-Whitney *U* test

[b] Kruskal-Wallis *H* test

Table 5 Odds ratio (OR) and 95% confidence internal (95% CI) for blood Cd levels greater than 3.80 μg/L (P_{75}) and blood Pb levels greater than 90.86 μg/L (P_{75}) from regression modeling by clinical characteristics of cases

Investigated or clinical factors	BCLs < 3.80 μg/L	BCLs ≥ 3.80 μg/L	OR (95%CI)	*p*	BLLs < 90.86 μg/L	BLLs ≥ 90.86 μg/L	OR (95%CI)	*p*
Clinical stages								
I	8	3	1.00		6	4	1.00	
II	14	7	1.101 (0.229, 5.295)	0.904	14	7	2.099 (0.451,9.759)	0.344
III	43	11	1.460 (0.423, 5.036)	0.549	47	10	1.458 (0.419, 5.074)	0.553
IV	25	8	0.801 (0.280, 2.288)	0.618	23	8	0.613 (0.210, 1.789)	0.370
T classification								
T1 + T2	20	10	1.00		15	11	1.00	
T3 + T4	66	17	4.476 (1.186, 16.893)	*0.027*	68	16	4.752 (1.299, 17.389)	*0.019*
N classification								
N0	28	10	1.00		23	13	1.00	
(N1+ N2 + N3)	55	17	2.462 (0.626, 9.678)	0.197	59	14	3.000 (0.822, 10.945)	0.096
M classification								
M0	54	20	1.00		56	19	1.00	
M1	29	17	10.959 (1.029, 116.711)	*0.047*	27	8	4.546 (0.757, 27.317)	0.098

$p < 0.05$ was considered statistically significant

BCLs blood Cd levels, *BLLs* blood Pb levels countries (Kleihues & Stewart 2003). It continues to be the second highest cause of cancer-related death in the world (Ferrández & Lanas 2006). Recent studies reveal that exposure to Cd or Pb is associated with an increased risk of total cancer (Absalon & Ślesak 2010; Nawrot et al. 2015). Zheng assessed the potential public health risk associated with the heavy metal composition of PM2.5 and showed that Cd has a potential cancer risk in females (Zheng 2016). Also, a region with a high prevalence of gastrointestinal cancers has been found to be related to excessive levels of Cd and Pb in soil (Mohajer et al. 2013). These findings suggested that environmental factors might also cause the unusual high rate of gastrointestinal cancers. In the present study, we provided further direct evidence of the possible association between Cd/Pb exposure and gastrointestinal cancers by determining blood Cd and Pb level in the GI cancer cases and controls and interacting with other possible influence factors such as gender, age, tobacco smoking, and alcohol drinking.

In the present study, blood levels of Cd and Pb in gastrointestinal cancer patients are significantly higher than those of controls (Table 2), suggesting that high blood Cd or Pb concentration might be a risk factor for gastrointestinal cancers. These results are consistent with previous studies in respect to cadmium and the digestive tract tumors (Brown & Devesa 2002; Chen et al. 2014; Liu et al. 2013). Furthermore, Mao et al. conducted an ecologic study in a multi-metal sulfide mine from Guangdong province in China and found significant associations between long-term environmental exposure to both Cd and Pb and an increased risk of mortality from all cancer, in which GI cancers were included (Mao et al. 2011). Compared to available data, we found that blood Cd and Pb concentrations in the study were higher than the general Chinese population (0.62 and 42.27 μg/L) (Zhang et al. 2015). Chaoshan terrain, tilting from northwest to southeast, borders with mountains in the west, north, and east with hills in the center and Hanjiang River, Rongjiang River, Lianjiang River, and Feng jiang River, etc., flowing to coastal south, formed several alluvial plains. Unfortunately, the "capital of electronic-waste" in China is in the Chaoshan area. Meanwhile, Lianjiang River has become the most polluted river among the five major rivers in eastern Guangdong. The river is polluted by heavy metal, especially lead and cadmium (Wong et al. 2007; Yan et al. 2007; Yang et al. 2013). As the only island county in Guangdong, Nanao Island is also polluted by heavy metals (Qiao et al. 2010; Zhou et al. 2011). Our previous studies have shown that the relationship between cadmium and nasopharyngeal carcinoma as well as breast cancer is evident based on the population of Chaoshan (Peng et al. 2015a, b). In the logistic regression analyses, it shows a strong association between GI cancers and blood Cd levels of high concentration (above the P_{50} division). In addition, higher blood Pb levels (above the P_{75} division) also display an association with GI cancers.

In this study, reference values were established for the risk of gastrointestinal cancers, stratified according to age, gender, smoking, and alcohol use for the cases and controls. Gastrointestinal cancers have a high incidence in males and the most frequent age is about 50 years old. Our research shows that the median age of the case group is older than that of the control group (59.065 ± 10.43 vs. 47.09 ± 19.81 years, $p < 0.001$). Previous studies have shown that cigarette smoking and alcohol drinking are risk factors for gastrointestinal cancers (Kira et al. 2015; Tallberg et al. 2014). The present study demonstrates that cigarette smoking and alcohol drinking are risk factors for gastrointestinal cancers.

Studies suggest that age range, gender, smoking, and intake of distilled beverages are associated with blood Cd and Pb concentrations (Ikeda et al. 2011; Madeddu et al. 2011). Even in the children, the blood Pb levels increase with age (Huo et al. 2007). In the present study, blood Cd levels at age > 50 years are higher than blood Cd levels in the age < 50 years, suggesting that Cd accumulates in the human body with gender and age. We also concluded that the age range at 50 to 60 has the highest risk for gastrointestinal cancers, and the number of afflicted males is three times that of afflicted women (Table 1). Study also showed that females are under a relatively higher level of Cd accumulation (Yang et al. 2005). One possible reason may be the improper hobby selection for males was twofold higher than the females, and males had a higher incidence of smoking. Exposure to Cd via smoking has been estimated based on the measurements of their concentrations in the blood of smokers vs. non-smokers (Afridi et al. 2010; Matsunaga et al. 2014). We found no associations between Pb and gender, age, and alcohol consumption. In addition, except for smoking and contaminated rice, inhalation, and ingestion are equal pathways of Cd and Pb exposure. Therefore, further epidemiological studies and researches on mechanism are needed to confirm the findings and to explore the mechanisms.

Some studies revealed that advanced stage cancer patients are under a higher risk of high Cd load (Chen et al. 2009; Peng et al., 2015a, b). Cd and Pb exposure also affects the clinical stages of gastrointestinal cancers. In our present study, M1 stage cases display a higher level of Cd compared to patients at the M0 stage (OR = 10.959, $p < 0.05$), and T3 + T4 stage cases show higher levels of Cd, as well as Pb (OR = 4.476, $p < 0.05$ vs. OR = 4.752, $p < 0.05$), compared with T1 + T2 stage cases. These results suggest that Cd concentrations are linked to tumor size, and that cancers with distant metastases have higher Cd and Pb levels compared with cancer without metastasis. This indicates that Cd/Pb exposure may encourage the development of gastrointestinal cancers and metastases.

Furthermore, anemia has been analyzed as a risk factor for a high load of heavy metal. Anemia is a frequent complication of various malignant tumors. It can influence the treatment of the tumor. Cancer anemia causes include cancer-related anemia, treatment-related anemia, and lack of nutrition. A retrospective study suggested that anemia is an important predictor of packed red blood cell (PRBC) transfusion during radical nephrectomy for renal cell carcinoma, and transfusion is linked to poor postoperative outcome (Kim et al. 2014). Our present study shows that anemia is a risk factor for high Cd load (OR = 5.602, $p < 0.05$), but has no association with Pb (OR = 0.579, $p > 0.05$). Cd has the ability to replace iron, causing iron deficiency which is a frequent cause of anemia (Wu et al. 2016). The gastrointestinal tract absorbs Cd and in turn results in low iron storage (Jarup and Akesson, 2009). It is also indicated in another report that blood Pb levels did not affect the hemoglobin levels (Huo et al. 2007).

Since the roles of these two noxious elements in the mechanism of cancer development remain unclear, further detailed and comprehensive investigations are necessary for risk assessment. The potential limitations may lie in non-random sampling of the subjects due to insufficient cases, and for that reason we cannot match a control per case. In the future work, we will try to collect more control samples, and detect several other heavy metals, so that we can have a better understanding of heavy metal exposure in the area.

Conclusions

Our results may provide further evidence of the possible association between Cd/Pb exposure and gastrointestinal cancers. Blood Cd or Pb at a certain high concentration might be a risk factor for gastrointestinal cancers. Patients with high blood Cd and Pb were more likely to be in more advanced clinical stages. Cd or Pb exposure may encourage the development of gastrointestinal cancers and metastases.

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Compliance with ethical standards

Ethics approval and consent to participate This study was performed with the approval of the Human Ethical Committee of the Cancer Hospital of Shantou University Medical College. All participants signed informed consent.

Competing interests The authors declare that they have no competing interests.

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