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Trace Element and Heavy Metal Levels in Colorectal Cancer: Comparison Between Cancerous and Non-cancerous Tissues

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Abstract Cases of colorectal cancer (CRC) have increased dramatically in Middle Eastern and other Asian countries. Many studies indicate an important role of environmental factors, including trace elements as an etiology of cancer. This study aims to assess the concentration of eight trace elements in cancerous and adjacent non-cancerous tissues in case of CRC. In a cross-sectional study, conducted between March 2015 and February 2016, zinc (Zn), chromium (Cr), manganese (Mn), tin (Sn), copper (Cu), aluminum (Al), lead (Pb), and iron (Fe) levels were evaluated among patients suffering from CRC. All the patients underwent a full colonoscopy. Multiple samples were taken from cancerous lesions and adjacent healthy tissues that kept a minimum distance of 10 cm from the lesions. These specimens were kept at −80 °C. The classic flame atomic absorption spectroscopy (FAAS) method was applied in this study. The mean age of the study population was 55.6 ± 12.8. The median of Zn, Cr, Cu, Al, and Pb in cancerous tissues was significantly higher than that of healthy tissues ($P < 0.05$). Nevertheless, the median of Mn, Sn, and Fe was significantly lower than that of non-cancerous tissues ($P < 0.05$). Between colon and rectal specimens, we did not find a difference between Cr and Al levels and Zn, Sn, and Cu levels in cancerous and healthy tissues, respectively. We revealed that gender and history of smoking may influence the level of some trace elements. We revealed that the levels of eight elements were significantly different for cancerous and healthy tissues. This may play a role in developing CRC. These findings reflect the importance of environmental pollution in this setting.

Keywords Colorectal cancer · Trace elements · Gender · Tissue

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Introduction

The rate of colorectal cancer (CRC) has dramatically increased in Middle Eastern and other Asian countries in the recent decades [1], and its incidence is estimated to be more than 1% [2, 3]. The etiology of this disease is not clearly understood. However, many studies have emphasized the role of diet and environmental pollutions. The role of trace elements has been put in this category [4–6].

Trace elements (TEs) play a key role in cell stabilization and enzymatic and hormonal activities; they also reduce the impact of other toxic TEs such as heavy metals like aluminum (Al) and lead (Pb) [7, 8]. Angiogenesis and oxidative stress

have been proposed as major factors in the pathogenesis of colorectal cancer. The amounts of superoxide dismutase (SOD), glutathione reductase, glutathione peroxidase, as well as lipid peroxidation products in cancerous tissues were shown to be associated with concentrations of TEs [9, 10]. Therefore, any variation in their concentrations may lead to cell damage, DNA injuries, and consequently, mutagenesis. In line with this, the carcinogenesis may affect TE levels. Moreover, a single TE may have different roles in different types of cancer [11]. Although the interaction among TEs is not fully understood, some studies suggest that variable concentrations of essential trace elements, such as zinc (Zn), iron (Fe), and copper (Cu), may play a role in the pathogenesis of some types of cancers including colon cancer [11–13]. As Zn may be involved in telomerase enzyme activity, it may act as an inhibitor of NADPH oxidase and Cu, Zn-SOD. Cu integrates in many pro-angiogenesis pathways that may be important for carcinogenesis. However, there is not sufficient data concerning the levels of TEs in tissues of CRC patients. Furthermore, many previous studies have used serum for measuring TEs, but not tissues. In this study, we assess the concentrations of eight trace elements in both malignant and normal colon tissues in CRC patients.

Methods and Materials

Type of the Study

The study was designed as a cross-sectional study of tissue levels of TEs including Zn, chromium (Cr), manganese (Mn), tin (Sn), Cu, Al, Pb, and Fe. These were analyzed in patients with CRC, who had been referred to the Firoozgar University Hospital between March 2015 and February 2016.

Subjects and Samples

Fifty patients with confirmed diagnosis of CRC by documented pathology reports were enrolled. Demographic, clinical, and lab data were recorded for each patient. The exclusion criteria were patients' reluctance, history of non-CRC malignancies, metabolic or nutritional disorders, use of vitamin supplementations, hormones, chelators, and being on chemotherapy or radiations.

Colonoscopy

All the patients underwent a colonoscopy. They were sedated by a certified registered nurse anesthetist (CRNA), under the supervision of an anesthetist, by using midazolam and propofol. Patient preparation was administered according to the standard protocol of the hospital by taking polyethylene glycol (PEG) orally 24 h before colonoscopy and diet restrictions. The procedure was performed by using the Fujinon colonoscope 2200 (Japan). Multiple biopsies were obtained from cancerous tissues and normal mucosa at least 10 cm away from the cancerous lesions. These specimens were immediately transferred into an −80 °C environment and stored until use.

Assessment of TEs

Instrument

Assessment of TEs was performed using the flame atomic absorption spectroscopy (FAAS) method with the Varian Spectra AA240 (Mulgrave, Victoria, 3170, Australia). An Alpha silver heater and Mettler College 150 balances were used. The instrument parameters were set for each element based on the manufacturer's instruction.

Reagents

All reagents and solvents were obtained from Merck Company (Darmstadt, Germany). The glassware was washed by 65% nitric acid and double-distilled water as needed. For digestion procedures, 65% nitric acid and 30% hydrogen peroxide (Darmstadt, Germany) were used. In the next step, standard solutions for each trace element were prepared as follows: copper (0.05–3.5 μg/ml), aluminum (1–49.0 μg/ml), lead (0.05–3 μg/ml), iron (0.05–21.0 μg/ml), chromium (0.05–3.0 μg/ml), manganese (0.05–4.0 μg/ml), zinc (1.0–8.0 μg/ml), and Sn (0.05–20.0 μg/ml). These solutions were used for obtaining the calibration curves of such elements at different concentrations.

Tissue Preparation

The tissue samples were dried at 80 °C for an hour. Also, 65% nitric acid (15 ml) and 30% hydrogen peroxide (7.5 ml) were added to the tissue for chemical digestion and stored at lab temperature (25 °C) for 24 h. Afterward, the solution was heated until it became gloomy, and 2 ml of 65% nitric acid and 1 ml of 30% hydrogen peroxide were added. The solution was then heated again for about 4 h at 50 °C. As many as 50 ml of distilled water was then added to it. The final solution was then injected into FAAS.

Statistical Analysis

The data was analyzed using descriptive statistics [including frequencies, ranges, means, and standard deviations (SDs) through SPSS software, version 20 (IBM SPSS Statistics)]. The Shapiro–Wilk test was used to determine the normality of the data relating to TEs. The paired *t* test was used for

normally distributed variables, while the Wilcoxon test was used for variables without normal distribution. As many as 95% confidence interval (CI) was reported, and a significant level was considered to be $P < 0.05$.

Results

The mean age of patients was 55.6 ± 12.8 (32–85) years. Table 1 represents the characteristics of the study population. Table 2 shows the concentrations of TEs in cancerous tissues and non-cancerous tissues. Median concentrations of Zn, Cr, Cu, Al, and Pb in cancerous tissues were significantly higher than those of control tissues. However, the median concentrations of Sn and Fe were significantly lower in cancerous tissues than in non-cancerous tissues ($P < 0.05$) (Table 3).

As shown in Table 3, based on the location, the median concentrations of TEs were not the same. In colon cancer, there was no difference between concentrations of Cr and Al in cancerous and control tissues. The same was found in the concentrations of Zn, Sn, and Cu in rectal samples. Table 4 represents the median concentrations of TEs in cancerous and normal tissues in accordance with the gender. Table 5 illustrates the differences of our findings regarding the history of smoking.

Table 1 Characteristics of the study population ($n = 50$)

Variables	Number	Percent
Gender		
Male	25	50
Female	25	50
Type of cancer		
Colon	34	68
Rectal	16	32
History of smoking		
No	25	50
Yes	25	50
Job category		
Administrative	21	42
Self-employed	29	58
Age (mean ± SD)	55.6 ± 12.8	

Discussion

Based on previous studies, the variations in levels of TEs in normal and cancerous tissues may play a causative role in the development of cancers [14]. This study showed the differences between concentrations of eight trace elements in cancerous tissues compared to adjacent normal tissues in patients with CRC (Tables 3, 4, and 5).

Trace elements are not homogenously distributed across human tissues. A few studies have so far addressed the differences in concentrations of TEs between non-cancerous and cancerous tissues in patients with CRC. Most studies have focused on plasma levels or cancerous tissues without possessing a control tissue. Nevertheless, in a study on tumoral and non-tumoral specimens of 38 CRC patients, the concentrations of Mn, Sn, Cu, Al, Fe, Mg, Ca, K, P, and S were significantly elevated in cancerous sites of colorectal tissues, while the cadmium level was significantly lower in tumoral tissues as compared to non-tumoral tissues [14]. In this regard, Hornik et al. have demonstrated that the levels of Cu, Fe, and Sn were significantly higher in cancerous tissues than in the control samples [15]. Rinaldi et al. similarly showed that magnesium, chromium, zinc, and silicon were statistically elevated in colorectal tumor specimens compared to adjacent healthy tissues [13].

Gender may have influenced the concentrations of trace elements in our study. The effect of gender cannot be explained correctly by current knowledge, but it may be related to exposure to some types of pollution, variations in defense mechanisms between two genders, and the number of subjects or assessment techniques.

Smoking can be considered as an important source of TE that may cause genetic mutation via DNA damage. In fact, there are many environmental factors involved in manufacturing of cigarettes that may influence TE levels consequently exposed to smokers. Table 5 illustrates TE levels among smokers and non-smokers. Noticeably, Zn, Mn, Cu, and Al levels among smokers were not significant. This finding was not comparable to other corresponding studies, even though there is not enough data in this regard [16, 17].

Iron is a vital element in cell proliferation and oxidative activities. In the present study, iron levels significantly decreased in cancerous tissues, which is consistent with the findings in similar studies [18–20]. Studies have shown that high serum levels of iron may be associated with CRC. This might be related to biochemical alteration and inflammatory status in which a variation in iron metabolism exists as initiators [18, 21]. Furthermore, inflammation may play an important role in developing cancer. Hence, the role of iron in the inflammation process, along with a higher metabolism rate in cancer cells, may induce inflammation. Alteration levels of iron in cancerous tissues can be expected [22].

We found that Mn and Sn levels were lower in cancerous tissues compared to non-cancerous tissues [13]. One possible explanation is the over-expression of Mn-related enzymes. Mn is part of vital enzymes such as manganese-superoxide dismutase (Mn-SOD). It is also considered a neurotoxin substance, but its role in some types of cancer and carcinogenesis pathways is somehow illustrated [23, 24]. The Mn concentration in patients with cancer has been shown to be higher than

Table 2 Descriptive statistics of TEs in cancerous and healthy tissues (μg/ml)

TEs	Number	Median	Mean	SD	Minimum	Maximum
Zn in cancerous tissue	50	1.51	1.51	1.79	0.04	11.43
Zn in healthy tissue	50	0.61	1.05	1.41	0.00	6.83
Cr in cancerous tissue	50	0.18	0.17	0.12	0.00	0.80
Cr in healthy tissue	50	0.09	0.12	0.08	0.00	0.40
Mn in cancerous tissue	50	0.005	0.008	0.008	0.00	0.02
Mn in healthy tissue	50	0.006	0.03	0.06	0.00	0.25
Sn in cancerous tissue	50	0.00	0.27	0.42	0.00	1.50
Sn in healthy tissue	50	0.56	1.70	1.86	0.00	5.45
Cu in cancerous tissue	50	0.14	0.17	0.08	0.08	0.45
Cu in healthy tissue	50	0.11	0.12	0.05	0.02	0.29
Al in cancerous tissue	50	8.90	7.95	4.71	0.00	15.40
Al in healthy tissue	50	4.00	5.61	4.36	0.00	17.10
Pb in cancerous tissue	50	0.05	0.09	0.14	0.01	0.63
Pb in healthy tissue	50	0.04	0.04	0.04	0.00	0.10
Fe in cancerous tissue	50	0.44	2.17	4.45	0.00	18.59
Fe in healthy tissue	50	3.34	6.59	6.02	0.13	19.86

the control group [25]. Mn-related enzymes play a role in the maintenance of reactive oxygen species, which is involved in the development of CRC. Mn-SOD may induce p53-dependent pathways in CRC [9, 26, 27]. In addition, Sn is

Table 3 Comparison of TEs (μg/ml) in cancerous and healthy tissues with the use of Wilcoxon signed-ranks test according to the site of cancer

Site of cancer	TEs	Cancerous tissue	Healthy tissue	Wilcoxon Z test	*P* value
Total	Zn	1.51	0.61	−2.29[a]	0.022
	Cr	0.18	0.09	−3.12[a]	0.002
	Mn	0.005	0.006	−1.51[b]	0.130
	Sn	0.00	0.56	−3.61[b]	<0.001
	Cu	0.14	0.11	−3.15[b]	0.002
	Al	8.90	4.00	−2.39[b]	0.017
	Pb	0.05	0.04	−2.58[b]	0.010
	Fe	0.44	3.34	−3.76[a]	<0.001
Colon	Zn	0.12	0.00	−3.36[a]	0.001
	Cr	0.17	0.16	−1.13[a]	0.259
	Mn	0.00	0.02	−3.68[b]	<0.001
	Sn	0.00	2.87	−3.11[b]	0.002
	Cu	0.14	0.14	−1.74[b]	0.083
	Al	3.6	4.2	–	0.99
	Pb	0.09	0.04	−3.63[b]	<0.001
	Fe	0.6	2.86	−1.80[a]	0.072
Rectum	Zn	1.61	1.85	−0.88[b]	0.379
	Cr	0.19	0.08	−3.52[a]	<0.001
	Mn	0.02	0.004	−3.23[a]	0.001
	Sn	0.00	0.00	−1.01[a]	0.314
	Cu	0.14	0.13	−1.02[b]	0.307
	Al	10	2.9	−3.48[b]	0.001
	Pb	0.0	0.06	−2.33[a]	0.0
	Fe	0.15	13.06	−3.26[a]	0.001

[a] Based on negative ranks

[b] Based on positive ranks

Table 4 Comparison of TEs (μg/ml) in cancerous and healthy tissues with the use of Wilcoxon signed-ranks test according to the gender of patients

Gender	TEs	Cancerous tissue	Healthy tissue	Wilcoxon *Z* test	*P* value
Male	Zn	1.54	0.76	−2.09[a]	0.037
	Cr	0.18	0.079	−2.01[a]	0.045
	Mn	0.005	0.005	−1.25[b]	0.211
	Sn	0.10	0.40	−1.53[b]	0.126
	Cu	0.15	0.11	−3.16[b]	0.002
	Al	10	3.60	−1.72[b]	0.085
	Pb	0.06	0.04	−2.25[b]	0.025
	Fe	0.59	8.57	−3.32[a]	0.001
Female	Zn	1.46	0.25	−1.31[a]	0.192
	Cr	0.19	0.13	−2.38[a]	0.017
	Mn	0.008	0.007	−0.94[b]	0.346
	Sn	0.00	2.87	−3.25[b]	0.001
	Cu	0.14	0.14	−1.20[b]	0.230
	Al	6.90	4.00	−1.50[b]	0.135
	Pb	0.039	0.039	−1.50[b]	0.135
	Fe	0.28	2.37	−1.90[a]	0.058

[a] Based on negative ranks

[b] Based on positive ranks

mainly found in extra-intestinal organs such as the lung, liver, and kidney. There is insufficient data regarding this element and its role in colon cancer. In our study, we showed a considerable difference in concentrations of Sn in two sets of specimens. Also, the concentration of Sn in colonic tissues was higher in women—in fact, whether the affinity of Sn to colonic tissue in female patients is higher than male patients needs further investigation. Although tin is not usually considered as a carcinogenic element, previous studies demonstrated that the incidence of lung cancer increased in patients who were exposed to the tin element [28, 29].

On the other hand, we showed that cancer tissues have significantly higher contents of Zn, Cr, Cu, Al, and Pb ($P < 0.005$). There is limited data regarding these elements

Table 5 Comparison of TEs (μg/ml) in cancerous and healthy tissues with the use of Wilcoxon signed-ranks test according to the history of smoking of patients

Gender	TEs	Cancerous tissue	Healthy tissue	Wilcoxon *Z* test	*P* value
Smoker	Zn	1.57	0.65	−1.22[a]	0.221
	Cr	0.18	0.13	−2.38[a]	0.017
	Mn	0.00	0.007	−1.49[b]	0.139
	Sn	0.00	0.42	−2.37[b]	0.018
	Cu	0.14	0.13	−1.53[b]	0.126
	Al	8.9	4.00	−1.48[b]	0.139
	Pb	0.05	0.04	−2.07[b]	0.038
	Fe	0.059	7.9	−2.30[a]	0.021
Non-smoker	Zn	1.46	0.38/	−2.11[a]	0.035
	Cr	0.19	0.08	−1.87[a]	0.061
	Mn	0.01	0.005	−0.71[b]	0.480
	Sn	0.00	1.47	−2.71[b]	0.007
	Cu	0.14	0.10	−2.86[b]	0.004
	Al	8.90	2.90	−2.04[b]	0.041
	Pb	0.05	0.04	−1.54[b]	0.122
	Fe	0.28	2.86	−3.30[a]	0.001

[a] Based on negative ranks

[b] Based on positive ranks

in CRC. It was reported that Cu and Zn are cofactors of SODs and involved in some enzymes that protect the cells against the free radicals. The elevated level of copper in cancerous tissues in our study is consistent with findings from the previous studies [14, 30]. An excessive level of Cu can directly, or through ROS, damage DNA. In addition, these metallic ions play an important role in angiogenesis as well as in the proliferation and migration of endothelium—all these are important in carcinogenesis [31–36].

Zinc is an essential element in cell growth, differentiation, and apoptosis and immune functions. Zinc deficiency may be secondary to agriculture, as it has been estimated that more than 7% of the general population in our region suffer from zinc deficiency. It is also associated with some problems such as weight loss and hypogonadism. This ion has an effect on mitogenic and antioxidant activities [37, 38]. Studies have shown that a low zinc diet may increase the rate of the development of adenoma and that rich-zinc diet is associated with lower susceptibility to cancer [13, 14, 39–41]. It was previously reported that some conditions, such as obesity and hypothyroidism, may be associated with low Zn levels [42, 43]. In this setting, Baltaci et al. revealed that serum and tissue levels of zinc among patients with thyroid cancer were lower than those in the control group—this could be associated with cancer development [44]. In the present study, the accumulation of zinc in cancerous tissues was observed. We cannot offer an exact explanation, but this discrepancy might be related to the number of subjects, the method of analysis, and the real difference between target populations. It may be related to the irregular distribution of Zn in the cancerous status. Therefore, the etiologic correlation between Zn levels and CRC needs more investigation.

In our study, the concentration of aluminum was notably elevated in cancerous tissues, which is consistent with other reports [13, 45]. We also showed increased levels of Al in female patients and in recto sigmoid tissues. Further investigation is required to explore the significance of such findings. Even though aluminum is a contributor in oxidative stress in animal studies, it has a biologically toxic effect on human tissues [46, 47].

We also showed a high level of Cr in cancer tissues. There is a discrepancy in the literature discussing the concentration of Cr in cancer tissues. Some studies have shown similar results, but some others have revealed lower concentrations of Cr in cancerous tissues as compared to non-cancer tissues [13, 14, 48]. The importance of Cr can be attributed to its role in angiogenesis as well as in producing ROS in the body and the consequent DNA damage. These events happen via different signaling pathways, such as NF-κB, p53, GADD45, G proteins, and Src kinase, involved in cell proliferation and differentiation [49, 50].

Pb has been the subject of many studies. Although the role of lead in carcinogenesis is highly suspected, there is no consensus regarding its concentration and role in colorectal cancer. In our study, Pb concentration was higher in cancerous tissues as compared to the non-cancerous ones. This finding was in contrast to other corresponding studies [13, 14, 40]. Pb has been shown to have several roles including oxidation and inhibition of DNA repair; it also induces cellular inflammatory response by increasing IL-8, which enhances the angiogenesis [51, 52].

In general, the concentration of trace elements in colon and CRC tissues may reflect endogenous and/or exogenous sources and may be eventually involved in cellular activities. Several studies have shown the association between environmental pollution, such as Pb, Zn, Fe, and Mn, and gastrointestinal diseases and cancers [23, 53, 54]. In addition, we cannot rule out the effects of cancer on concentrations of these elements.

Conclusion

There is limited data regarding concentrations of trace elements in cancer and non-cancer tissues in CRC patients. We showed different concentrations of eight elements in cancer and healthy tissues from the same patients, which might have avoided the risk of bias due to environmental factors. Larger studies are warranted to explore the role of each element in the carcinogenesis of CRC. Our findings suggest that any alteration in concentrations of trace elements may play a role in the malignant transformation of normal colonic mucosa.

Compliance with Ethical Standards This study was approved by the Ethics Committee of Iran University of Medical Sciences with ID IR.IUMS.REC.1395-25881. All subjects signed their informed consents before participation. The researchers were committed to the principles of the Declaration of Helsinki.

Conflict of Interest The authors declare that they no conflict of interest.

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