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BRIEF ARTICLE

Possible roles of insulin, IGF-1 and IGFBPs in initiation and progression of colorectal cancer

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Abstract

AIM: To investigate the roles of serum insulin, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding proteins (IGFBPs) in the initiation and progression of colorectal cancer.

METHODS: We determined serum insulin, IGF-1 and IGFBPs levels in 615 colorectal cancer patients and 650 control healthy donors by enzyme-linked immunosorbent assay (ELISA). In the meantime, their body mass index (BMI) and waist-to-hip ratio (WHR) were measured.

RESULTS: Serum levels of insulin and IGF-1 as well as IGF-1/IGFBP-3 ratio in pre-operation patients were significantly elevated, but the level of IGFBP-3 was significantly decreased compared with normal controls and post-operation patients ($P < 0.05$ and $P < 0.001$, respectively). There is no significant difference ($P > 0.05$) in the levels of insulin, IGF-1, IGFBP-1, IGFBP-3 and IGF-1/IGFBP-3 between the patients with and without hepatic as well as distal abdominal metastases. WHR and BMI of colon cancer patients were positively and significantly correlated with the levels of insulin and IGF-1/IGFBP-3. In contrast, WHR and BMI were negatively correlated with IGFBP-3 level.

CONCLUSION: The elevation of insulin, IGF-1 as well as IGF-1/IGFBP-3 ratio and the reduction of IGFBP-3 may be related to the initiation of colorectal cancer, but they are not related to the progression and outcome of the disease.

Key words: Colorectal cancer; Insulin; Insulin-like growth factor-1; Insulin-like growth factor binding protein-3; Insulin-like growth factor-1/insulin-like growth factor binding protein-3 ratio

Core tip: A previous study evaluated the effects of insulin, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding proteins (IGFBPs) on cell growth and proliferation, which played important roles in the etiology of colon cancer. The present study aimed to investigate the relationship of changes in serum insulin, IGF-1, IGFBPs, body mass index, waist-to-hip ratio with the initiation and progression of colorectal cancer. We observed that there were no differences in serum levels of leptin, IGF-1, IGFBP-1 and IGFBP-3 as well as IGF-1/IGFBP-3 ratio between pre- and post-operation colorectal cancer patients.

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INTRODUCTION

Reports in recent years showed that the rate of colorectal cancer in North America is 44.60/100 thousand, while in Europe is 42.9/100 thousand[1]. Based on the investigations from the Asian-Pacific colorectal cancer collaborative group, the incidences of colorectal cancer significantly increased in several Asian countries. The rates of colorectal cancer in Japan, South Korea and Singapore are 49.3/100 thousand, 24.7/100 thousand and 35.1/100 thousand, respectively. With the improvement of the quality of life of the Chinese people and changes in their diet, the incidence of colorectal cancer is increasing, especially in large cities[2-4]. The high incidence of colorectal cancer may be associated with genetics, environment, life style and diet. Previous studies showed that both insulin-like growth factor-1 (*IGF-1*) and insulin-like growth factor binding protein-3 (*IGFBP-3*) genes had no association with the occurrence of colon cancer, while insulin receptor substrate-1 (IRS-1) had certain association with colon cancer incidence[5-8]. There are very few reports on the association of biomarkers such as insulin, IGF-1 and IGFBPs with the incidence of colorectal cancer in China. In this study, we investigated risk factors associated with colorectal cancer, and the relationship between IGF-1, IGFBPs and colorectal cancer. Our results may provide insights into the causes of the increased incidence of colorectal cancer in China.

MATERIALS AND METHODS

Study population and recruitment procedure

A total of 615 hospitalized patients or revisited outpatients who were diagnosed with colorectal cancer in the Department of Anorectal Surgery of Shanxi Cancer Hospital from June 2010 to October 2011 were recruited for this study. All participants answered the inquiry questions. The study was approved by the Ethics Committee of Shanxi Cancer Hospital. There were 335 male and 280 female patients with a median age of 53 years old (range, 20 to 80 years old). There were 193 cases of colon cancer (pre-operation 73 cases and post-operation 120 cases), and 410 cases of rectal cancer (pre-operation 199 cases and post-operation 211 cases). There were also 12 cases of colorectal junction cancer. All pre-surgical patients received no treatment, and all post-surgical patients were confirmed with colon or rectal ulcer-cancer, infiltrating cancer or junction cancer by histopathological examination. There were 650 healthy participants as controls, including 368 males and 282 females with a median age of 49 years old (range, 18 to 72 years old). All patients and healthy controls had no history of diabetes. The data for the patients are shown in Table 1.

Table 1 Patient and disease characteristics

Characteristic	*n*
Gender	
Male/female	335/280
Clinical Stage	
T1/T2/T3	60/362/193
Type	
Colon cancer/rectal cancer/colorectal cancer	193/410/12
Colon cancer	
Pre/post-operation	53/140
Rectal cancer	
Pre/post-operation	179/231
Health control	
Male/female	368/282

Data collection

A trained nurse measured the weight (kg), height (cm), and waist and hip circumferences (cm) and collected 10 mL of blood from the pre- and post- operation patients. Information about the risk factors for colorectal cancer was collected by trained interviewers. The investigation questionnaire included age, occupation, education, ethnic group, residence, history of benign colorectal diseases and malignant tumors. Body measurements include height, weight, waist and hip circumferences, and blood pressure.

Analysis of serum insulin, IGF-1, IGFBPs, and leptin

At the time of blood collection, blood constituents were rapidly aliquoted and levels of insulin, IGF-1, IGFBPs and leptin were assayed by ELISA within 48 h. All reagents were provided by American ADL Company and Swedish Mercodi AB Company. Serum leptin levels were assayed by using Human Radioimmunoassay RIA kit (Linco Research, St. Louis, United States). All the procedures were according to the manufacturers' instructions.

Statistical analysis

The survey and the experimental data were statistically analyzed with SPSS13.0 software. The differences between groups were analyzed by *t*-test, χ^2 tests, variances and correlations. Analyzed data are shown as mean ± SD, and the differences were considered significant when $P < 0.05$.

RESULTS

All subjects were local Shanxi residents with 10 or more years of residency and belong to Han ethnic group. The average age of colorectal cancer patients was 53.85 ± 13.99, while the average age was 49.72 ± 9.95 for the healthy control group. There was no statistical difference in age between the two groups. There were also no statistical differences in occupation ($\chi^2 = 10.20$, $P = 0.08$), education ($\chi^2 = 1.588$, $P = 0.66$), residence location ($\chi^2 = 0.37$, $P = 0.59$) or blood pressure ($\chi^2 = 0.20$, $P = 0.78$).

Comparison of serum levels of leptin, insulin, IGF-1, IGFBP1 and IGFBP3 between colorectal patients and healthy controls

The levels of serum leptin, insulin, IGF-1 and IGF-1/IGFBP3 in colorectal cancer patients were significantly

Table 2 Comparisons of pre-operation and post-operation serum levels of biomarkers between colorectal cancer patients and healthy controls (x bar ± s)

Biomarker	Healthy controls (*n* = 650)	Pre-operation (*n* = 284)	Post-operation (*n* = 331)
Insulin (μIU/mL)	6.24 ± 4.70	9.82 ± 4.67[1]	9.971 ± 6.01[1]
IGF-1 (ng/mL)	136.73 ± 63.17	200.16 ± 44.07[1]	209.84 ± 47.82[1]
IGFBP-1 (ng/mL)	10.97 ± 3.58	12.23 ± 4.03	12.34 ± 4.31
IGFBP-3 (μg/mL)	9.24 ± 3.91[2]	6.47 ± 3.05[3]	7.05 ± 2.31
IGF-1/IGFBP-3	29.01 ± 10.00[2]	39.02 ± 16.35[3]	31.98 ± 13.49
Leptin (ng/mL)	9.01 ± 4.97	13.49 ± 8.35[1]	13.79 ± 8.35[1]

[1]Compared to healthy controls, $P < 0.001$ and $P < 0.05$; [2]Healthy controls compared to pre- and post- operation groups, which showed significant differences, $P = 0.015$ and $P = 0.001$; [3]Pre-operation group compared to post-operation group, $P = 0.02$. IGF-1: Insulin-like growth factor-1; IGFBP-1: Insulin-like growth factor binding protein-1.

higher than those in healthy controls, while the IGFBP-3 level was lower than controls ($P < 0.05$ and $P < 0.001$, respectively). There was no significant difference in IGFBP-1 levels between the two groups ($P > 0.05$). IGFBP-3 level was obviously lower in pre-operation patients than in post-operation patients, and the IGF-1/IGFBP-3 ratio was significantly higher in pre-operation patients ($P < 0.05$). The results are shown in Table 2.

Comparisons of serum levels of leptin, insulin, IGF-1, IGFBP1, IGFBP3 and IGF-1/IGFBP3 between patients with and without metastatic colorectal cancer

Three hundred and five cases of colorectal cancer patients were involved, who survived one year, three years and more than three years after surgery. Among them, no metastasis was found by color ultrasonic imaging and computed tomography (CT). Another 66 patients were found with hepatic or abdominal metastases by color ultrasonic imaging and CT. We compared the two groups about serum levels of insulin, IGF-1, IGF-1/IGFBP3, IGFBP1, IGFBP3 and leptin. There were no statistical differences ($P > 0.05$) between them. The results are shown in Table 3.

Comparisons of serum levels of leptin, insulin, IGF-1 and IGFBPs between colon cancer and rectal cancer patients

The serum levels of IGF-1, IGFBP1 and IGF-1/IGFBP3 ratio were significantly higher in rectal cancer patients than in colon cancer patients ($P = 0.041$, $P = 0.022$ and $P = 0.033$, respectively). There were no statistical differences in leptin, insulin and IGFBP-3 levels between the two groups ($P > 0.05$). Related data are shown in Table 4.

Comparisons of body mass index and waist-to-hip ratio between colorectal cancer patients and healthy controls

Body mass index (BMI) showed no statistical difference between the two groups ($P > 0.05$), while waist-to-hip ratio (WHR) displayed a significant difference between cancer patients and controls ($P = 0.003$ for colon cancer and $P = 0.035$ for rectal cancer). There was a significant difference in WHR between colon cancer patients and rectal cancer patients ($P = 0.046$), but there was no difference in BMI between the two groups ($P > 0.05$). The comparison data are shown in Table 5.

Table 3 Comparisons of serum levels of biomarkers between patients with and without post-surgical metastasis (x bar ± s)

Biomarker	With metastasis (*n* = 305)	Without metastasis (*n* = 66)	*P* value
Insulin (μIU/mL)	10.95 ± 7.57	10.05 ± 6.36	0.88
IGF-1 (ng/mL)	206.12 ± 22.65	200.64 ± 32.71	0.94
IGFBP-1 (ng/mL)	6.99 ± 2.94	6.91 ± 2.66	0.53
IGFBP-3 (μg/mL)	7.35 ± 3.85	7.01 ± 1.26	0.20
IGF-1/IGFBP-3	31.93 ± 11.91	30.99 ± 12.85	0.89
Leptin (ng/mL)	13.07 ± 4.86	13.43 ± 7.08	0.32

IGF-1: Insulin-like growth factor-1; IGFBP: Insulin-like growth factor binding protein.

Table 4 Comparisons of serum biomarker levels between colon cancer and rectal cancer patients (x bar ± s)

Biomarker	Colon cancer (*n* = 65)	Rectal cancer (*n* = 167)	*P* value
Insulin (μIU/mL)	8.04 ± 3.86	10.01 ± 4.86	0.095
Leptin (ng/mL)	12.80 ± 5.81	13.76 ± 5.69	0.144
IGF-1 (ng/mL)	181.01 ± 38.01	207.39 ± 39.62	0.041
IGFBP-1 (ng/mL)	9.82 ± 1.81	11.99 ± 4.28	0.022
IGFBP-3 (μg/mL)	6.04 ± 2.19	6.31 ± 3.66	0.73
IGF-1/IGFBP-3	30.81 ± 9.64	39.57 ± 15.24	0.033

IGF-1: Insulin-like growth factor-1; IGFBP: Insulin-like growth factor binding protein.

Correlations between the BMI/WHR of the patients and their serum leptin, insulin, IGF-1, IGFBP1 and IGFBP3 levels

WHR and BMI of colon cancer patients were positively correlated with serum levels of leptin, insulin and IGF-1/IGFBP3 ratio, and inversely correlated with IGFBP3 level. There is no correlation between the both and IGF-1 and IGFBP1. Data are shown in Table 5. WHR of rectal cancer patients was positively correlated with serum levels of leptin and IGF-1 ($r = 0.213$, $P < 0.05$ and $r = 0.291$, $P = 0.045$), while BMI also positively correlated with serum IGFBP1 level ($r = 0.333$, $P = 0.016$). There was no correlation between BMI and other biomarkers ($P > 0.05$). Table 6 shows the comparison data of colon cancer patients.

Comparisons of serum levels of insulin, IGF-1, IGFBPs and IGF-1/ IGFBP3 between pre- and post-operation cancer patients

There were significant differences between pre- and post-operation stage T2-T3 cancer patients in the levels of serum insulin, IGF-1, IGFBPs and IGF-1/IGFBP3 ratio ($P < 0.05$). Related data are shown in Table 7.

DISCUSSION

Colorectal cancer in Shanghai region of China is positively correlated with the consumptions of red meat, fish and preservative containing food[9-12]. Mao *et al*[13] investigated the association of physical inactivity, energy intake

Table 5 Comparisons of body mass index and waist-to-hip ratio between colorectal cancer patients and healthy controls (x bar ± s)

Group	Body mass index	WHR
Colon cancer	23.99 ± 3.95	0.99 ± 0.061[1,2]
Rectal cancer	24.01 ± 3.62	0.90 ± 0.017[1]
Healthy controls	23.26 ± 2.96	0.81 ± 0.037

[1]Comparison of WHR between colorectal cancer patients and healthy controls, P = 0.003 and P =0.035; [2]Comparison of WHR between colon cancer patients and rectal cancer patients, P = 0.046. WHR: Waist-to-hip ratio.

Table 6 Associations of waist-to-hip ratio and body mass index of colon cancer patients with the levels of leptin, insulin, insulin-like growth factor, insulin-like growth factor binding protein-1, insulin-like growth factor binding protein-3 and insulin-like growth factor-1/insulin-like growth factor binding protein-3 ratio

Biomarker	WHR Pearson correlation	BMI Pearson correlation	*P* value
Insulin	0.519	0.485	< 0.001 0.002
Leptin	0.396	0.448	< 0.001 < 0.001
IGF-1	0.394	0.172	> 0.05 > 0.05
IFGBP-1	-0.259	0.082	> 0.05 > 0.05
IGFBP -3	-0.443	-0.342	0.005 0.018
IGF-1/IGFBP3	0.501	0.296	0.045 0.050

IGF-1: Insulin-like growth factor-1; IFGBP-1: Insulin-like growth factor binding protein-1; WHR: Waist-to-hip ratio; BMI: Body mass index.

and obesity with risk factors for rectal cancer in 1447 rectal cancer patients and 3106 healthy controls from 7 provinces in Canada. Their results showed that the obvious risk factors for rectal cancer are overweight, obesity and BMI $\geqslant$ 30 kg/m^2 with an odds ratio (OR) of 1.44 for females and 1.78 for males. The results also suggest that there is a great increase in risk for the incidence of rectal cancer when high energy intake, high BMI and low physical activity simultaneously exist. Many researchers reached the same conclusion[4,14-17]. In our study, we also found that high BMI and WHR were associated with cancer patients.

Dietary lipids provide a rich source of energy and diets high in lipids, especially animal fat, may increase the risk of colorectal cancer[18,19]. And the obesity is associated with serum levels of insulin, IGF, leptin and lipid, among other factors[4,6]. Insulin-like growth factors include two polypeptides IGF-1 and IGF-2. IGF-1 is an important mitogen in the body, which promotes cell proliferation and inhibits apoptosis[20,21]. There is no report that demonstrated a cause-and-effect relationship between IGF-1 and cancer and no investigator ever suggested that IGF-1 was a causative agent in tumor development. However, it was reported that patients with certain types of tumors had high levels of IGF-1 in their circulation as a manifestation of their disease. The elevated levels of IGF-1 seem to occur very early in tumor development. In our study, we also found high levels of IGF-1 in colorectal cancer patients. It suggested that measurement of IGF-1 in the blood of people may be an early warning indicator that a tumor could be developing in the body.

IGFBP-3 is an apoptosis inducing factor and exerts its roles through competing with IGF-1 for receptor binding and through regulating local concentration of IGF-1. It was shown with increasing evidence that IGFBP-3 could also independently inhibit cell proliferation and induce apoptosis without involving IGFs. Hyperglycemia, hyperinsulinemia, and increased IGF-1 level have already been etiologically proven as risk factors for colorectal cancer[22,23]. IGFBPs were also considered as regulators of insulin level[7]. Slattery *et al*[3] evaluated the effects of insulin, IGF-1 and IGFBPs on cell growth and proliferation, which played important roles in the etiology of colon cancer and breast cancer. They also analyzed the relationship of genetic polymorphisms of IRS-1, 2, IGF-1 and IGFBP-3 with colon cancer by genotyping using data collected in a case-control study of 1346 colon cancer cases paired with 1544 controls and 952 rectal cancer cases paired with 1205 controls. The results implied that IRS-1 and the R allele of G927R are risk factors for colon cancer with an OR of 1.4; in the meantime IRS2 and G927R heterozygote GD genotype significantly reduced the colon cancer risk with an OR of 0.8. Wei *et al*[4] believed that hyperinsulinemia, IGF-1 and IGFBP-3 are involved in the pathogenic mechanism of colon cancer and increased colon cancer risk. They also reported that Western style of life and diet may be the major reasons for increased risk of cancer, especially colon cancer[7-10]. Xuan *et al*[24] also found that insulin level could increase the risk of breast cancer. The main mechanisms may involve reduced plasma and tissue levels of IGFBPs by elevated insulin level (hyperinsulinemia and insulin resistance). Therefore, a subsequently increased IGF-1 activity inhibited cell apoptosis and stimulated cell proliferation activity, and finally induced the rapid growth of tumor cells.

Our results showed that the levels of serum leptin, insulin, IGF-1 and IGF-1/IGFBP3 in colorectal cancer patients were significantly higher than those in healthy controls, while the IGFBP-3 level was lower than controls.

Leptin is the product of the *OB* gene, and its biological effects are regulating the body weight, maintaining metabolism and keeping energy balance. Leptin promoted colon cell proliferation and cancer initiation[25]. Investigations from Stattin *et al*[17] also suggest that leptin may be directly involved in the initiation of colon cancer and may serve as a sensitive biomarker for obesity induced adverse endocrine environment. Liu *et al*[6] postulated that a high-fat diet enhances colon cell proliferation and carcinogenesis by elevating serum leptin. In their experiments, colon cell proliferation, c-fos protein expression and aberrant crypt foci (ACF) were elevated following increased dietary fat. There was a significant correlation between serum leptin and colon cell proliferation and ACF[6]. Our results also

Table 7 Analysis of serum insulin, insulin-like growth factor-1, insulin-like growth factor binding proteins, and insulin-like growth factor-1/insulin-like growth factor binding protein-3 ratio

Stage	*n*	Insulin (mU/L)	IGF-1 (μg/L)	IGFBP-1 (μg/L)	IGFBP-3 (μg/L)	IGF-1/IGFBP-3
T1	60					
Pre-operation		7.85 ± 4.87	153.52 ± 32.65	8.25 ± 1.24	8.25 ± 3.25	18.61 ± 10.01
Post-operation		7.68 ± 5.07	151.46 ± 39.19	7.91 ± 4.66	9.65 ± 4.06	15.70 ± 9.65
P value		$P > 0.05$	$P > 0.05$	$P > 0.05$	$P < 0.05$	$P < 0.05$
T2	362					
Pre-operation		10.51 ± 6.03	200.37 ± 52.45	11.95 ± 2.69	5.95 ± 3.26	33.68 ± 16.08
Post-operation		8.78 ± 8.07	148.58 ± 45.63	9.06 ± 4.31	8.84 ± 4.06	16.81 ± 11.01
P value		$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$
T3	193					
Pre-operation		11.25 ± 6.57	209.69 ± 48.11	12.25 ± 3.01	5.75 ± 3.86	36.47 ± 12.46
Post-operation		8.83 ± 8.07	150.78 ± 35.21	9.85 ± 3.66	8.63 ± 3.33	17.48 ± 10.57
P value		$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$

IGF-1: Insulin-like growth factor-1; IFGBP-1: Insulin-like growth factor binding protein-1.

demonstrated that serum leptin level in colorectal cancer patients was significantly higher than that in controls.

Furthermore, in this study, we also observed that there was no difference in serum levels of leptin, IGF-1, IGFBP-1 and IGFBP-3 as well as IGF-1/IGFBP-3 ratio between pre- and post-operation colorectal cancer patients or between patients with and without post-surgical metastasis ($P > 0.05$). We believed that high serum levels of insulin, IGF-1 and IGFBP-3 have no correlation with the disease's outcome and tumor stage classification in colorectal cancer patients. The underlying mechanisms need to be further investigated. This study also showed that the WHR of colorectal cancer patients were significantly higher than that of healthy controls and it positively correlated with leptin and insulin levels as well as IGF-1/IGFBP3 ratio. This suggests that central obesity is an important risk factor for the initiation of colorectal cancer. The results from MacInnis *et al*[7] implied that the occurrence of colon cancer and human level of obesity are mainly determined by two factors, FFM and WHR, while the data from Moore *et al*[8] showed that BMI ⩾ 30 increased the risks of colon cancer by 50% in 30-54-year-old adults and by 2.4-fold in 55-79-year-old adults. Larger waist size was associated with a two-fold increase in the risk of colon cancer. There was a linear increase in risk with the waist size for both proximal and distal colon cancer[8]. Mao *et al*[13] believed that obesity induced BMI increase is the major risk factor for colon cancer death. Hou *et al*[26] also reported a positive correlation between BMI and the incidence of colon cancer in Shanghai residents. In this study, we revealed that BMI of colorectal cancer patients showed no statistical difference from that of healthy controls and the relationship of increasing BMI with the initiation of colorectal cancer is of interest for further investigations.

COMMENTS

Background

Insulin-like growth factor-1 (IGF-1) is an important mitogen in the body, which promotes cell proliferation and inhibits apoptosis. Insulin-like growth factor binding protein-3 (IGFBP-3) is an apoptosis inducing cell growth factor and plays its roles through competing with IGF-1 for receptor binding and through regulating local concentration of IGF-1. Increased IGF-1 level has already been etiologically proved as a risk factor for colorectal cancer. IGFBPs were also considered as regulators of insulin level. But there is no further evidence for them.

Research frontiers

A previous study evaluated the effects of insulin, IGF-1 and IGFBPs on cell growth and proliferation, which played important roles in the etiology of colon cancer. Wei *et al* believed that hyperinsulinemia, IGF-1 and IGFBP-3 are involved in the pathogenic mechanism of colon cancer and increased colon cancer risk.

Innovations and breakthroughs

A previous study evaluated the effects of insulin, IGF-1 and IGFBPs on cell growth and proliferation, which played important roles in the etiology of colon cancer. The present study aimed to investigate the relationship of changes in serum insulin, IGF-1, IGFBPs, body mass index, waist-to-hip ratio (WHR) with the initiation and progression of colorectal cancer. The authors observed that there were no differences in serum levels of leptin, IGF-1, IGFBP-1 and IGFBP-3 as well as IGF-1/IGFBP-3 ratio between pre-operation and post-operation colorectal cancer patients or between patients with and without post-surgical metastasis.

Applications

The study results suggest that the WHR of colorectal cancer patients was significantly higher than that of healthy controls and it positively correlated with leptin and insulin levels as well as IGF-1/IGFBP3 ratio. This suggests that central obesity is an important risk factor for the initiation of colorectal cancer.

Peer review

This paper "Association of Insulin, IGF-1 and IGFBPs with the Risk of Colorectal Cancers" wrote by Bo Jiang *et al* is good. The investigation is interesting.

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