

Serum homocysteine may related to colorectal adenoma number: a cross-sectional study

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Research article

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Abstract

Background Early detection of high-risk adenomas is crucial for the prevention of colorectal cancer. The aim of the study was to evaluate the usefulness of serum biomarkers in characterizing the histological features of colon adenomas and predicting the progression of high-risk adenomas to colorectal cancer.

Methods Patients diagnosed with colorectal adenoma in Beijing Shijitan Hospital between Jan 2013 and Dec 2015 were recruited to the study. Patients were classified into low-, moderate-, and high-risk according to the adenoma scores. Erythrocyte sedimentation rate (ESR), clinical biochemistry, serum homocysteine (HCY) levels, and serum tumor markers were determined. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. The correlation between the serum biomarkers and basic characteristic of the adenomas was analyzed.

Results The serum levels of HCY (OR=0.06, 95% CI 0.01-1.52), CA724 (OR=0.03, 95% CI 0.00-0.97), and ESR (OR=0.01, 95% CI 0.00-0.44) were positively correlated with the risk of colon adenomas developing into colorectal cancers. High serum level of HCY was related with the development of multiple (>3) adenomas (OR=0.25, 95% CI 0.11-0.56). Higher ESR was related to the occurrence of high-grade intraepithelial neoplasia (OR=0.06, 95% CI 0.00-0.73) and villous adenomas (OR=0.20, 95% CI 0.04-0.98).

Conclusion Serum levels of HCY, ESR and CA724 may be valuable indicators for predicting the risk of colon adenomas, among them, ESR may be more related to specific pathology types, HCY is more related to the number of adenomas and development of colorectal cancer.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the world.¹ In China, CRC causes more than 200,000 deaths annually. CRC often arises from adenomas, therefore early blockade of the adenoma-carcinoma sequence by endoscopic interventions can significantly reduce patient mortality. Colorectal adenoma is classified into low risk and high risk by the endoscopic and pathological findings.² Individualized endoscopic screening may be an effective approach in reducing the risk of colorectal adenoma developing into CRC. In clinical practice, patients with high-risk adenomas often receive more frequent screening with short intervals.

Colonoscopy is considered the gold standard for CRC screening owing to its ability to visualize the entire colon and to remove neoplastic lesions during the procedure. However, endoscopy is an invasive procedure that causes discomfort to patients. As such, non-invasive methods such as faecal occult blood test (FOBT), microRNAs, and serum biomarkers that can assess the risks of the patients with adenoma to develop CRC are much desirable in clinical practice.

Previous studies have found that development of colorectal adenomas may be causally related to alcohol consumption,³ blood lipid concentration,⁴ serum levels of HCY⁵ and folate,⁶ and certain metabolic factors.^{7,8} In clinical settings, elevated serum levels of tumor markers such as CA724 and

carcinoembryonic antigen (CEA) are often indicative of primary colonic tumors and are therefore used as common markers in the diagnosis and differential diagnosis of colorectal tumors. However, the relationship between CA724, CEA and development of colorectal adenomas remain unclear.

Here in this study, we aimed to investigate the relationship between serological markers and the characteristics of colorectal adenomas and the usefulness of serum biomarker in predicting the progression of colorectal adenomas into colorectal cancer.

Study Subjects

Men and women aged 30 years or older with at least one histologically confirmed colorectal adenoma between December 2012 and April 2014 at the Beijing Shijitan Hospital were recruited to the study. Participants with the following conditions were excluded from the study: known colorectal cancer, inflammatory bowel disease, polyposis syndrome, history of surgical intestine resection, incomplete colonoscopy, inadequate bowel preparation, total Boston bowel preparation scale (BBPS) score of <5, and incomplete resection of colorectal polyps, and severe heart disease, defined as New York Heart Association (NYHA) class III-IV.

The study was approved by the Ethics Committee of Beijing Shijitan Hospital Affiliated to Capital Medical University and has been performed in accordance with the Declaration of Helsinki. Informed written consents were obtained from all participants.

Data collection

One hundred ninety out of 399 eligible individuals provided basic demographics (age, gender, and ethnic backgrounds), smoking habits and past history of medication usage. Fasting blood samples were collected for the measurement of full blood count, blood biochemistry, glycometabolic markers, lipid profiles, iron, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumour markers, plasma HCY and the high-sensitivity CRP were collected. Plasma HCY was measured by the enzymatic cycling method. ESR was determined by the Westergren method. Tumour markers were measured by chemiluminescence immunoassay.

Collection for the macroscopic data for adenomas

Colonoscopy is performed in the afternoon of the same day of blood sample collection. Characteristics of adenomas observed during colonoscopy were recorded in a complete colonoscopy report. Key information included whether the scope reached ileocecal junction; size, location and gross morphology of the lesions; methods of adenoma resection; and quality of bowel preparation. The adenoma is considered proximal if the lesion is located proximal to the splenic flexure, or if the colonic segment was not specified but colonoscope insertion was ≥ 60 cm.

Pathological classification and scoring of adenomas, patient grouping

All biopsied colonic tissues were examined by routine *hematoxylin-eosin* (H&E) staining. The pathological diagnosis and classifications were made using the 2019 edition of World Health Organization (WHO) Digestive System Pathological Diagnostic Criteria^{9,10}. The lesions were divided into adenomas, hyperplastic polyp, tubular adenoma, villous adenoma, chorionic tubular adenoma, serrated adenoma, low grade glandular intraepithelial neoplasms, high grade glandular intraepithelial neoplasms and cancer.

Adenomatous lesions were scored by their pathological features which include adenomas with villous histology; high grade dysplasia; ≥ 10 mm in size; and ≥ 3 adenomas. Each of these components worths one point, and the final scores were calculated by the sum of all scores. If the patient has more than one adenoma, the score will be decided by the adenoma with the highest risk.

Based on these scores, patients were classified into low-, moderate-, and high-risk groups. Hence, patients with 0 point lesions were classified into low-risk group; those with 1 point lesions were classified into moderate-risk groups; and those with ≥ 2 points were classified into high-risk groups.

All pathological diagnosis and classifications were based on independent diagnoses made by two experienced pathologists.

Statistic analysis

The data analysis was performed using SPSS statistical software version 22.0. Continuous variables were reported as means \pm standard deviation (SD). Categorical variables were presented as percentages of the total. Study subjects were first classified into low-risk, moderate-risk, and high-risk based on the colonoscopic findings. The Kolmogorov-Smirnov test was used to verify if the data fitted normal distribution. Summary and groping data for baseline characteristics (the laboratory results) were compared using variance analysis and rank-sum test (for continuous variables) or Fisher's exact test (for categorical variables). To investigate the relationship between the serum biomarkers and the risk of adenomas, multivariate-adjusted odds ratios and 95% confidence intervals were calculated using logistic regression among the three subgroups. Models for evaluating the efficiency of potential serum biomarker were created using logistic regression, with the following possible variables: HCY, CEA, CA724, total cholesterol (TC), triglyceride (TG), glucose and ESR. The normal reference values for each serum biomarker analyzed in the model were used as the grouping criteria. In another model, the correlation between the serum biomarkers and the characteristics of the colorectal adenomas (including number of lesions, lesion size, lesion location, presence or absence of villous pathology, presence/absence of high-grade intraepithelial neoplasia or dysplasia) were analyzed by the logistic regression. In all analyses, age and sex were adjusted as a confounder. A p value of <0.05 was considered statistically significant.

All statistical methodologies and results were reviewed by Dr. Qingkun Song from the Department of Science and Technology, Beijing Shijitan Hospital.

Results

Data analysis was performed in 192 patients (age range: 34-91, mean age 70.49 ± 11.60 , 63.9% were males) who have undergone at least one adenoma resection in the Beijing Shijitan Hospital. The baseline characteristics of these patients are shown in Table 1. Among all study subjects, 111 were in the low-risk group (mean age: 69.42 ± 11.11 , 53.1% were males), 48 in the moderate-risk group (mean age: 70.67 ± 12.04 , 74.6% were males), and 33 in the high-risk group (mean age: 73.94 ± 12.26 , 63.5% were males).

As shown in Table 1, serum levels of HCY ($F=4.320$ $^aP=0.015$) and ESR ($F=6.828$ $^aP=0.002$) were significantly different across the low-, moderate-, and high-risk groups. Most of the patients were males in the three groups. Through inter-group comparison, significant difference in ESR was observed between the low- and high-risk groups ($p=0.02$), and between the moderate- and high-risk groups ($p=0.042$). HCY was significantly different only between the low-risk and moderate-risk groups.

The relationship between the serum biomarkers and the risk of adenomas are presented in Table 2. The levels of HCY (OR=0.349, 95% CI 0.128, 0.947, $p=0.039$), and ESR (OR=0.113, 95% CI 0.025, 0.507, $p=0.004$) were positively correlated with colorectal adenoma occurrence in different risk groups.

The relationship between the characteristics of colorectal adenomas and potential serum biomarkers was also analyzed (Table 3). Our data showed that serum level of HCY was associated with the number of adenomas ≥ 3 , and the serum level of ESR was associated with the occurrence of villous tubular adenomas (VTA) and high-grade intraepithelial neoplasia (HGIN).

Discussion

The plasma HCY is a reflection of the folate level in the body because it is involved in the folate metabolism. A diet includes consistency low consumption of vegetable and high fat and meat may lead to low level of folate as well as high level of plasma HCY¹¹. Researches have proved that excessive intake of red meats, saturated/animal fats and cholesterol is positively correlated with increased risk of CRC development, and inversely, sufficient consumption of vegetables, fruit, and fibers that are rich in cruciferous, vitamins and minerals may protect against CRC risk¹². Folate is an essential co-factor in DNA methylation and production of antioxidants. Insufficient folate intake has been shown to be related to increased risk of adenoma occurrence and recurrence¹³⁻¹⁵. However the level of folate is difficult to evaluated because it's not only affected by the ingested food but also the BMI, vitamin B-12 and so on¹⁶. Therefore, homocysteine was used as a new marker which is accurately and repeatable and has been confirmed may be used as a predictor of adenoma occurrence and recurrence^{13, 17, 18}.

Homocysteine has been paid more attention by researchers because it participates in one carbon unit reaction, regulates the appropriate level of S-adenosylmethionine and participates in the normal methylation level of DNA which may account for the formation of colorectal adenoma and CRC¹⁵. In our study, we found that HCY is strongly related to the risk of adenomas which is supported by the previous article that it's elevated in cancer¹⁹. And we believe that it may provide information for clinicians to set up examination intervals for patients and screening for high-risk adenomas as early as possible in combination with other indicators. Moreover, our study has found that there is a significant difference

between the serum HCY and the colorectal adenomas characteristic of having more than 3 adenomas, which indicates that HCY may be related to the recurrence. And this result was verified by many assays as well^{18, 20}.

ESR is a sensitive yet nonspecific marker of systemic inflammation that is elevated in association with inflammation condition, hyperglobulinemia. The existing literature on this topic is inconsistent. A few assays contribute part of the significant result to subclinical inflammatory bowel disease²¹. Some studies have reported no significant association between ESR and adenomas. And the other supported the idea that activation of inflammatory response in CRC and other tumors, leading to an increase in ESR¹⁹. And in our research, there is a significant difference between the ESR and the risk of adenomas which shown that advanced risk of adenomas was led to the increasing of chronic inflammation markers. What's more after analyzed the relationship between the ESR and the colorectal adenomas characteristic we found that ESR is related to high-grade intraepithelial neoplasia and villous adenomas, which may demonstrated that high-risk adenoma would lead to increase of abnormal inflammation factor released to the plasma from the dysplasia cell, however this is only our suppose, which needs more evidence and studies to support the idea.

Colonoscopy is regarded as the gold standard of CRC screening because it can show the state of intestinal cavity morphology and resect the lesion directly. However, colonoscopy as an invasive procedure, may cause discomfort in patient. In clinic, doctors are looking for a non-invasive method to screen lesions. Some researches use c²², microRNAs²³, serum biomarkers and other related indicators to predict the nature and extent of colorectal lesions. In this study, we aimed to search for a sensitive, specific serum marker for early detection of high-risk colorectal adenomas. In a recent study involving 64,422 patient data from 21 medical centers, high-risk adenomas were more likely to develop into CRC and were associated with increased mortality rate, as compared with the non-adenoma group¹⁰, which supported that high-risk adenomas require close monitoring and intervention. In this aspect, our current study may open a new avenue for screening high-risk adenoma patients with serological tests.

Better risk classification example has been shown in the following: A patient with 4 small colorectal adenomas(risk score 1) and B patient with 4 high-grade intraepithelial neoplasia adenomas(risk score 2), both patient should be high-risk patient judged by the latest guidance². However, in our opinion, A patient should be considered as moderate-group and B patient should be included in high-risk group and these two patient should be attached different attention and have different endoscopic detection period. Moreover, both the current data and previous studies have verified that due to multiple risk factors, the risk for patient B is much higher than patient A. The adenoma risk classification takes all these factors into account, resulting in better discrimination ability for different risk levels.

The necessity of more detail colorectal adenomas risk classification which is universally accepted has been supported by a pooled analysis of 4 prospective studies²⁴. This study compared the risk for advanced colorectal neoplasia at 1-year colonoscopy among patients cross-classified by U.S. and U.K. surveillance guidelines. The study finds a high discrimination ability of UK guideline compared with USA

guideline. And the US guideline was superior in discriminating between low- and intermediate-risk patients, whereas the UK guideline was superior in discriminating between intermediate- and high-risk patients. These data suggest that combining the 2 risk stratification schemes might result in better discrimination than either guidance alone. Both guidelines call for a more detailed classification which is the same as our study.

Expect the virtue we have achieved; our study had several limitations. First, not all risk factors for adenoma risk factor were considered, including smoking, obesity, and diabetes. Second, the sample size of our data is not large enough, and the study populations only include the patients from Beijing shijitan hospital and might have confounding factors because of the difference in the distribution of hospital patients. Third, the patients were all Chinese and the findings might not be generalizable to other ethnic population. In addition, our study is a cross-sectional one and thus cannot provide enough evidence for the causal relationship between colorectal adenomas and the potential biomarkers.

Using the potential serum biomarker to assess the patient risks for adenoma will be more convenient, more cost-effective, and less invasive than colonoscopy

In summary, our study finds that HCY, CA724, ESR seems to be a strong independent correlation factor with high-risk adenomas in colorectal. HCY may be related to the number of colorectal adenomas and ESR may have a connection with specific histology type. We would conduct perspective articles to further verify the repeatability of this result.

Abbreviations

Colorectal cancer (CRC); faecal occult blood test (FOBT); carcinoembryonic antigen (CEA); Boston bowel preparation scale (BBPS); New York Heart Association (NYHA); erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); hematoxylin-eosin (H&E); World Health Organization (WHO); standard deviation (SD); total cholesterol (TC); triglyceride (TG); high-grade intraepithelial neoplasia (HGIN); villous tubular adenomas (VTA);

Declarations

Ethics approval

All the ethics approval have been given by the ethics committee of Beijing shijitan hospital affiliated to capital medical university and have been performed in accordance with the Declaration of Helsinki. And all the patients have given their permission orally.

Consent for publication

Verbal consent has been obtained from all participants

Availability of data and material

All the data have been collected in Beijing shijitan hospital from December 2012 to April 2014. All data generated or analysed during this study are included in this published article.

Competing interests

Not applicable

Funding

Not applicable

Authors' contributions

Hong Liu designed the research; Ya-Dan Wang collected the data. Lin Lin performed the endoscopy; Feng-Xiao Dong analyzed the data; Jing-Wei Wang wrote the paper and Jing Wu critically revised the manuscript for important intellectual content.

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Tables

Table 1 Baseline Characteristics of the patients according to the risk stratification

Characteristic	Low risks	Moderate risk	High risks	total	P-value
Age	69.51±11.185	70.67±12.041	73.94±12.255	70.49±11.60	0.159
Sex	Male	63.7%	68.8%	57.6%	63.9% 0.583
	Female	36.3%	31.3%	42.4%	36.1%
CEA(ng/ml)	3.532±6.649	2.804±1.828	3.908±2.479	3.429±5.175	0.610
CA724(U/ml)	4.412±8.069	3.869±7.860	1.714±1.268	3.755±7.251	0.221
GHb(%)	6.350±1.528	6.139±0.900	6.359±1.204	6.292±1.318	0.746
Insulin(U/ml)	10.910±10.344	11.478±12.513	13.290±11.410	11.294±11.041	0.689
ESR(mm/h)	7.25±7.340	8.07±7.943	15.46±12.339	8.87±9.005	^a 0.000
NLR	2.234±1.082	2.277±1.110	3.285±2.908	2.426±1.591	^a 0.003
RDW(%)	13.130±1.157	12.842±0.733	13.494±1.630	13.129±1.181	^a 0.049
TC(mmol/L)	4.562±1.071	4.379±0.825	4.462±1.158	4.499±1.031	0.579
TG (mmol/L)	1.463±0.933	1.388±0.825	1.712±1.323	1.491±0.987	0.323
Ca(mmol/L)	2.318±0.127	2.311±0.114	2.320±0.113	2.317±0.121	0.940
Glucose(mmol/L)	5.930±1.716	5.899±1.784	5.724±1.260	5.884±1.650	0.822
CRP (mg/L)	7.905±28.350	5.527±16.308	12.380±36.504	7.994±27.024	0.672
hs-CRP(mg/L)	2.44±1.132	2.59±1.064	2.50±1.286	2.50±1.126	0.913
HCY(μmol/L)	14.073±4.604	16.293±4.959	16.173±5.820	15.384±6.261	^a 0.015

CRP, C-reactive protein; Ghb, glycosylated hemoglobin; ESR, erythrocyte sedimentation rate

NLR, neutrophil lymphocyte rate; RDW, red blood cell distribution width; TC, total cholesterol; TG, triglyceride; Ca, calcium; HCY, homocysteine;

P were calculated by variance analysis and rank-sum test for continuous variables and Fisher's exact test for categorical variable; Superscripted alphabetical lettering indicates statistically significant values.

Table 2 Multivariable analysis for serum markers and colorectal adenoma risks

	OR	95%CI	P
HCY(μmol/L)			
Q1 6.3-14.9 ^a	0.349	0.128, 0.947	^b 0.039
Q2 15.1-52.7 ^a	0	0	
CEA(ng/ml)			
Q1 (0.5-4.9)	0.346	0.097,1.239	0.103
Q2 (5.0-65.9)	0	0	
CA724(U/ml)			
Q1 (0.48-5.60)	1.293	0.327, 5.119	0.714
Q2 (6.9-71.8)	0	0	
Ghb(%)			
Q1 (4.8-6.0)	1.198	0.457, 3.146	0.713
Q2 (6.1-15.2)	0	0	
TC(mmol/L)			
Q1(0-1.70)	1.011	0.334,3.059	0.984
Q2(1.71-8.01)	0	0	0
TG (mmol/L)			
Q1(0-5.20)	2.270	0.647,7.973	0.201
Q2(5.21-7.54)	0	0	0
Glucose(mmol/L)			
Q1 0-6.10 ^a	2.151	0.696 ^a 6.659	0.184
Q2 6.11-15.93 ^a	0	0	0
ESR(mm/h)			
Q1(0-20)	0.113	0.025, 0.507	^b 0.004
Q2(>20)	0	0	

Abbreviations as in Table 1; OR, odds ratio;

Superscripted alphabetical lettering indicates statistically significant values.

Table 3 Multivariable analysis for colorectal adenomas characteristics and potential serum biomarkers

	HCY			ESR		
	OR	95%CI	P-value	OR	95%CI	P-value
number \geq 3	0.288	0.125, 0.662	^c 0.003	3.963	0.422, 37.151	0.228
number \geq 5	1.565	0.575 \pm 4.259	0.381	0.832	0.055, 12.667	0.895
number \geq 10	1.587	0.396, 6.373	0.514	0.181	0.014, 2.354	0.191
size \geq 30mm	0.569	0.089, 3.640	0.552	0.610	0.038, 9.816	0.727
PC/DC	1.861	0.957, 3.615	0.067	2.134	0.543, 8.398	0.278
VTA	1.412	0.506, 3.943	0.511	0.200	0.040, 1.002	0.050
Size \geq 10mm	0.579	0.267, 1.257	0.167	0.434	0.103, 1.833	0.256
· HGIN	0.102	0.010, 1.034	0.053	0.078	0.006, 0.990	^c 0.049
· dysplasia	1.028	0.291, 3.633	0.965	8.628	0.575, 129.412	0.119

HGIN, high-grade intraepithelial neoplasia;PC, proximal colon;DC, distal colon;VTA, villous tubular adenomas

Superscripted alphabetical lettering indicates statistically significant values.