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PROTOCOL: Introduction of the largest colorectal cancer survey in China: a nationwide multi-center study

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Introduction of the largest colorectal cancer survey in China: a nationwide multi-center study

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Abstract

Background Colorectal cancer (CRC) is one of the most common cancer in China. Most patients have developed to advanced stage at the time of their first diagnoses, leading to a low 5-year survival rate. To optimize prevention strategies, we planned a survey to evaluate the advanced CRC patients' knowledge on CRC, medical experience, health-related quality of life before and after the treatment of CRC and the associated factors with the change, and costs associated with advanced CRC in China.

Methods and analysis This is a cross-sectional, nationwide, hospital-based, multi-center survey. Nineteen hospitals in seven cities were selected by multi-stage stratified sampling. Mainland China is divided into 7 regions according to the traditional administrative district definition. Two cities of each region were selected through simple random sampling, and then one tertiary cancer hospital and/or one general hospital were selected for each city. More than 4445 CRC patients in the selected hospitals with stage III or IV will be enrolled into this study. The trained interviewers will collect information through patients' self-report and/or medical records, including demographics and medical history; knowledge about CRC high-risk factors, screening procedure and treatment methods; medical experience on CRC screening, diagnosis and treatment; health-related quality of life before and after CRC treatment; and costs associated with advanced CRC. All data will be input by two independent staff and verified using Epidata V.3.1 software. Data validation plan (DVP) will be made to guide data checking. All statistical analyses will be conducted using SAS V.9.4 and SPSS V.24.0 soft-ware.

Ethics and dissemination The study was approved by the ethics committees of all co-participant hospitals. Study findings will be disseminated through peer-reviewed open-access journals, and presented as poster and/or oral sections in national and international conference. Results will be also popularized to the public via media or internet.

Keywords: Nationwide survey, Colorectal cancer, Knowledge, Medical experience, Quality of life, Costs

Strengths and limitations of this study

➢ This is the first geographic representative study with large number of more than 4400 advanced colorectal cancer (CRC) patients in China, to evaluate the patients' knowledge on CRC, medical experience, health-related quality of life before and after the treatment of CRC and the associated factors with the change, and costs associated with advanced CRC

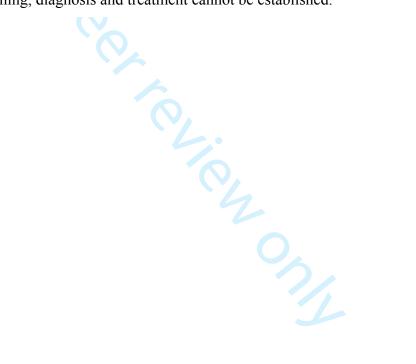➢ The methodology of this study has good replicability and can be applied to the other cancer species.

➢ A lot of data from patients will be collected, allowing to pursue secondary analysis, such as analysis of characteristics of a subgroup.

➢ The self-reported data may be subject to recall biases and social desirability.

➢ As this is a cross-sectional study design, causal relationships between patient characteristics and CRC screening, diagnosis and treatment cannot be established.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated 1.9 million new cases and about 935,000 deaths around 2020 annually[1]. The incidence and mortality of CRC vary among different countries due to differences in lifestyle and socio-economic development[2]. China ranked first worldwide in the number of CRC new cases and CRC-related deaths due to the relatively large population[3]. Furthermore, the country faces a challenge of increasing CRC cases due to a western lifestyle[4, 5]. According to the latest Chinese Cancer Registration Report in 2019, about 110,546 new cases and 53,810 deaths occurred in China, placing it the fourth highest incidence and the fifth mortality among all cancers[6]. Although the overall 5-year survival rate has been increasing in the past decades[7], the rate for patients with advanced CRC is only about 20% while that for patients with early CRC is up to 90%[8]. Even worse, most CRC patients have developed to advanced stage at the time of their first diagnosis[9].

Three-level prevention is the main strategy to reduce incidence and mortality of advanced CRC, includes[10]: primary prevention avoiding high-risk behaviors of CRC, secondary prevention aimed at screening to promote CRC early detection, diagnosis, and treatment, and tertiary prevention adopting appropriate treatment to prolong life and improve the health-related quality of life (HRQOL). To guide the implementation of prevention strategy, patients' knowledge on CRC high-risk factors, screening, and treatment before they were diagnosed should be firstly identified, since knowledge is one of the predisposing factors that may influence patients' motivation to avoid high-risk behaviors and receive some interventions[11]. It is also critical to explore patients' medical experience on CRC screening, diagnosis and treatment, in order to find out potential interventions that could reduce incidence and mortality of advanced CRC[12-15]. Particularly, CRC screening via colonoscopy, and numerous targeted agents which can extend overall survival for advanced CRC have been well developed[16-18], but little is known about the status of and barriers for them. Furthermore, with the advance in treatment, HRQOL has become a significant outcome in advanced CRC patients[19, 20]. In order to choose a preferable treatment modality and inform potential interventions, it is important to assess HRQOL status before and after treatment, as well as the associated factors with the changes[21]. However, no nation-wide representative data of advanced CRC patients in China was reported.

Additionally, substantial costs is also an important issue for the prevention of cancer[22]. In order to guide resource allocation and provide high-quality cancer care, reliable cost estimation is

essential. Although the costs associated with advanced CRC has been evaluated in many countries, such as Iran[23], Vietnam[24], New Zealand[25], and across the European Union[22], the current evidence is limited in China.

Therefore, we launched a national, multi-center survey to comprehensively present the knowledge, medical experience, health-related quality of life and health-care costs among Chinese patients with advanced CRC. This survey will provide unique data to encourage health authorities and policymakers to optimize prevention strategies in China to reduce the burden of advanced CRC. It will also contribute to the methodology of undertaking research on other cancer species. In this paper, we present a detailed methodological description of this survey, hoping that this protocol can be applied to future surveys in other cancers.

Objectives

(1) To evaluate patients' knowledge on CRC high-risk factors, CRC screening, CRC treatment before they were diagnosed, and explore the associated factors.
(2) To investigate patients' medical experience on CRC screening, diagnosis and treatment, and identify status and barriers for CRC screening and targeted agents.
(3) To evaluate patients' health-related quality of life before and after treatment against CRC, and explore the associated factors with the changes.
(4) To estimate the costs associated with advanced CRC.

Methods and Analysis

Study Design

This is a cross-sectional, nationwide, hospital-based, multi-center survey conducted in Mainland China.

Selection of Hospitals

Mainland China is divided into 7 different geographic regions (Northeast, North, Northwest, East, Central, South, and Southwest) according to the traditional administrative district definition[26]. These regions showed different levels of CRC burden[3]. Multi-stage stratified sampling was adopted to choose the participant hospitals. In stage one, two cities of each region were selected by simple random sampling. In stage two, one tertiary cancer hospital and/or one general

hospital were selected in each city with inclusion on the basis that (1) they can provide diagnosis, surgery, radiotherapy, chemotherapy, and routine follow-up care for patients with CRC; (2) visiting patients are from different parts of the region. Finally, a total of 19 hospitals (10 tertiary cancer hospitals and 9 general hospitals) were selected.

Study Population

The study population includes all colorectal cancer patients with stage III or IV via medical chart view and who gives the informed consent in this study (For children under 18 years old, parental consent is required). Patients will be excluded if they had severe physical, cognitive, and/or verbal impairments that would interfere with a patient's ability to complete the questionnaire. Staging of CRC is done according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system[27].

Sample Size

It was estimated that there were about 400,000 advanced CRC patients in China[28, 29]. To ensure that the national survey is geographically representative, it was designed that about 1% patients would be enrolled. Considering the non-response rate of 10%, more than 4445 patients would be enrolled into this survey. Proportional allocation was used to determine the sample size of each region, according to the population density (Table 1).

Study procedures

Preliminary phase

The preliminary study phase in June to August 2019 included preparatory workshops with researchers of the centers to present the study, develop the survey questionnaires, obtain prior agreement to conduct the study, develop principles and manual of the research practice, and train the study staffs. The survey questionnaires were developed through multiple team meetings, and solely included easy-to-answer, single or multiple questions about (1) patients' demographics and medical history; (2) knowledge about CRC high-risk factors, screening procedure and treatment methods; (3) patients' medical experience on CRC screening, diagnosis and treatment; (4) patients' health-related quality of life before and after CRC treatment; (5) costs associated with advanced CRC.

In addition, a pilot survey was conducted in September-October 2019 among 2 hospitals (Henan Cancer Hospital and The First Affiliated Hospital of Baotou Medical College) in order to validate standard operating procedures and the questionnaires. A total of 50 patients were enrolled in the pilot survey and would be not included into the formal research.

Survey implementation

The formal survey has been started since March 2020, after all involved centers received research ethics committee approval. All patients will provide written informed consents prior to participation. The questionnaires take the participants approximately 20 min to complete, and the participants will receive RMB 30 (about 4.2 USD) for their contribution after completion. The trained interviewers carry out this survey. Principles of good research practice is strictly adhered to during the data collection.

Study Measures

Demographics and medical history

Demographic information will be collected through a standardized self-report questionnaire, including birthdate, gender, location, occupational situation, marital status and family members, school education, annual household income, and medical insurance type.

Medical history regarding types of cancer (colon cancer, rectal cancer, and both), disease stage, metastasis at the time of first diagnosis and at present, and cycles of chemotherapy will be linked through medical records.

Knowledge about high-risk factors of CRC, screening procedure and treatment

Patients' knowledge on CRC before they were diagnosed with CRC will be collected using a semi-structured questionnaire (SSQ). The SSQ was developed by the research team based on China guidelines (China guideline for the screening, early detection and early treatment of colorectal cancer (2020, Beijing)[30]; Chinese protocol of diagnosis and treatment of colorectal cancer (2020 edition)[31]). The SSQ consists of 3 multiple choice questions classified in three section: section one (high-risk factors of CRC), section two (CRC screening procedure), section three (CRC treatment). Section one has 10 items, section two has 6 items, and section three has 7 items. If patients answer "I

did not know", score zero will be given; otherwise, score one will be given for each correct choice. Thus, the score ranges from 0 to 20. Table 2 presented the detailed information about the SSQ.

If participants knew any information of CRC before they were diagnosed with CRC, sources of information such as health educational booklets, television, radio, doctors, family and friends, websites and social media would be further collected.

Patients' medical experience on CRC screening, diagnosis and treatment

Another semi-structure questionnaire is used to collect health care information regarding CRC screening, diagnosis and treatment.

i. CRC screening: information on patients' ever cancer screening received as well as the frequency and barriers (Unaware of the need for colonoscopy, Having not enough time for colonoscopy, Fear of side effects, Unaffordable costs, Having a difficulty to make an appointment for colonoscopy, No reimburse for medical insurance, and Others) against cancer screening is collected based on patients' self-report.

ii. CRC diagnosis and treatment: Information regarding (1) the hospital and department where the patients was first diagnosed with CRC, (2) the hospital and department where the patients first received CRC treatment, (3) the initiation of patients seeking medical treatment for the first time, (4) the number of hospitals where patients have visited for CRC, and (5) whether the patients ever changed the visited hospital and the reason for the change is collected based on patients' self-report; information regarding (1) the use of genetic testing, (2) the use of currently available surgery approaches, (3) the use of radiotherapy, (4) the use of chemotherapy including adjuvant and neoadjuvant chemotherapy, (5) the use of targeted agents is collected through medical records; Information on the barriers against targeted cancer agents is collected based on patients' self-report, e.g. Doctors did not inform or recommend molecular targeted agents, Genetic testing results did not meet molecular targeted agents, Not convinced that molecular targeted agents works, Unaffordable medical costs, et al.

Health-related quality of life

The extensively validated traditional Chinese FACT-C (Functional Assessment of Cancer Therapy-Colorectal) (version 4) and the traditional Chinese version of EORTC (the European

Organization for Research and Treatment of Cancer) QLQ-C30 (version 3) are combined to measure patients' health-related quality of life[32-34]. The traditional Chinese FACT-C (version 4) was translated by the functional assessment of chronic illness therapy translation coordinating team, following a standard procedure and guidelines. It includes 36 items covering five function subscale (physical, social/family, emotional, functional and colorectal cancer subscale). The traditional Chinese version of EORTC QLQ-C30 (version 3) consists of 30 items grouped into five function subscales (physical, role, emotional, cognitive and social), nine symptom subscales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) and a global health/QOL subscale. Further details of the full-scale survey were reported elsewhere[32-34].

In this study, 45 items were selected using experts' opinion to establish a scale named FACT-C-plus-QLQ-C9, consisting of all FACT-C items plus nine items from QLQ-C30. The self-made scale covers six function subscale (physical, social/family, emotional, functional, colorectal cancer subscale and cognitive), and three symptom subscales (fatigue, insomnia and financial difficulties). Each positive item is valued on a 5-point Likert scale (not at all=0, a little bit=1, somewhat=2, quite a bit=3, very much=4), while the negative item is valued reversely (not at all=4, a little bit=3, somewhat=2, quite a bit=1, very much=0). The selected nine items from QLQ-C30 were presented in Table 3.

Patients' quality of life will be collected at two time points, based on patients' self-report:

Point 1: T1 (the first or second day that patients are hospitalized, but before anti-CRC treatment);
Point 2: T2 (the day before discharge, but after anti-CRC treatment).

Individual's rough scores (RS) of total subscale at different points are firstly calculated with a range from 0 to 180, and then linearly converted into a standardized scores (SS) of 0~100. The higher scores indicate better HRQOL. Changes of HRQOL before and after anti-CRC treatment is equal to SS after treatment minus SS before treatment.

Cost estimation

With a social perspective, total direct costs since patients were first diagnosed with advanced CRC will be collected, including direct medical costs and non-medical costs. Direct medical costs include costs of diagnosis, medication, surgery, radiology, medical examinations, registration,

consultation, hospitalization, and etc. Non-medical costs include costs of patients and their families' visit to healthcare centers, nursing and nutrition fees. Direct medical costs will be collected by medical records and/or patients' self-reported, and non-medical will be collected by patients' self-reported.

Data management and quality control of data

A special and trained team is set up to do data management, including data filling, entry, checking and revising, and data locking.

Data filling

Paper-based non-identifiable questionnaire is used to manage individual participant data. Data filled in the questionnaire must be consistent with the patient's self-report and medical records. All completed questionnaires will be checked by the trained interviewers immediately, in order to avoid missing and logic mistakes. Questionnaires with missing items or obvious logical mistakes (e.g. not applicable items are filled in) will be returned to patients to modify.

Data entry

All collected data will be double-entered using Epidata software V.3.1 by two trained research assistants. After the completion of data entry, an independent data administrator will compare the consistency between the two data sets. Any discrepancies will be returned to data entry clerks to be resolved.

Data checking and revising

The rule of data checking includes missing value and logical mistakes checking. Data validation plan (DVP) will be made to guide data checking. One research assistant will use SAS software V.9.4 for data checking, according to the DVP. Any query will be sent to the investigators to be solved. And then, the research assistant will revise the dataset prior to statistical analysis.

Data locking

After the dataset is judged to be accurate and meet the above requirements, it will be locked by the principle investigator and no more changes are allowed. All paper documents will be kept in a

special filing cabinet for reference at any time. Electronic data will be stored on password-protected computer files which can only be accessible to the research team members.

Statistical analysis plan

All statistical analysis will be conducted by the SAS V.9.4 soft-ware.

Descriptive analysis

Descriptive analysis will be used to report patients' demographics, medical history, score of knowledge on CRC, barriers against CRC screening and targeted agents, HRQOL before and after treatment, and costs associated with advanced CRC. Categorical variables will be presented using absolute frequencies and percentage, while normal distributed continuous variables will be presented using mean and standard deviation, and abnormal distributed continuous variables will be presented using median and standard inter-quartile range.

Reliability and validity of the self-made HRQOL scale

The reliability and validity of the self-made HRQOL scale named FACT-C-plus-QLQ-C9 will be tested. Reliability of the scale will be assessed via internal consistency and split-half reliability. Internal consistency of the scale will be determined by Cronbach's α coefficient, using an acceptable cut-off value of 0.70[35]. Split-half reliability will be assessed with intra-class correlation coefficient (ICC) of the scores of two sections, and an adequate value above 0.6 for ICC will be regarded as adequate[36]. Validity of the scale will be tested via construct validity. The confirmed factor analysis (CFA) will be used to test the overall fit of the data to scale model with 45 items and 9 factors. Model fit will be evaluated with comparative fit index (CFI), root mean square error of approximation (RMSEA), and x^2/df. The index criteria for well-fitting models are CFI>0.90, RMSEA<0.08 and $2<x^2$/df<5[35]. The items with lower factor loading less than 0.35 will be removed[37].

Comparative analysis

Paired t-test or Wilcoxon non-parametric tests will be used to compare HRQOL before and after treatment.

Logistic or linear regression model will be used to explore factors associated with CRC knowledge, screening, targeted agents, and the changes of HRQOL before and after anti-CRC

treatment. The ICC will be first calculated to assess the reliability of individual data aggregated at region-level (North East, North, Central, East, South, North West, and South West) in hierarchical models by testing an unconditional or null model, considering the hierarchical structure of the data. If ICC is statistically significant, a multi-level logistic or liner analysis will be conducted, otherwise, one-level regression model will be conducted. Variables with P-value <0.10 in univariate regression model will be entered into the multivariable regression model. Stepwise regression will be performed to determine the statistical significance of each variable in the multivariable regression model, with a P-value <0.05 as the criterion.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

Prevention is an effective strategy to reduce the incidence and mortality of advanced CRC. Exploring patients' knowledge of CRC, medical experience, quality of life, and health care costs, is necessary to identify the weak parts in the prevention of advanced CRC. Although many studies have been done in some countries, such as Armenia[38], Kuwait[39], the United States[19], Iran[23] and New Zealand[25], most of these only focused on the general public or all patients with CRC, which has limited effect on the prevention of advanced CRC. Moreover, the research results of other countries may not be necessarily applicable to China, due to the varied living habits, economic development, and CRC burden.

The nationwide survey is expected to generate important indicators about Chinese advanced CRC patients' knowledge of CRC, medical experience, HRQOL status before and after anti-CRC treatment, and costs associated with advanced CRC. The indicators will help to visualize the overall situation of China, which can facilitate further updates of the prevention strategy and policy development. The information generated by this survey can be used by the team members and other concerned bodies to advocate for the mobilization of policy changes and extra resources aimed at supporting prevention efforts across China. Moreover, results of the survey can be used to identify levels of unmet medical need, and determine the subgroup of patients who need more interventions, and the regions which need extra resources in guiding prevention system.

This study has several strengths. First, this is the first geographic representative study with large number of more than 4400 patients in China. Burden of CRC varied in different regions in China. We select patients from the 7 geographic regions through multi-stage stratified sampling, which not only ensure geographic representativeness and generalization, but also make it possible to compare different regions. Second, the methodology of this study has good replicability and can be applied to the other cancer species. Additionally, we will collect a lot of data from patients, allowing to pursue secondary analysis, such as analysis of characteristics of a subgroup.

The study has also several limitations. First, the self-reported data may be subject to recall biases and social desirability. Second, since the participants are all voluntary, their characteristics may be different from those who do not participate in this study. Finally, as this is a cross-sectional study design, causal relationships between patient characteristics and CRC screening, diagnosis and treatment cannot be established.

Ethics and Dissemination

Before starting the study, agreements were made by all co-participant hospitals, and the survey protocol was reviewed and approved by their corresponding ethics committees. All individuals must voluntarily agree to participant this survey and provide informed consent form.

Study findings will be disseminated through peer-reviewed open-access journals, and presented as poster and/or oral sections in national and international conference. Results will also be popularized to the public via media or internet.

Authors' contributions

YL, SKZ and YLQ: conception and design. YL: drafting of the article. HFX, XZ, YQY, and YQZ have made substantial contribution to the study protocol. All authors: revised the manuscript and approved the final version of the manuscript.

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Competing interests statement

None declared.

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Table 1 Sample distribution by population density and geographic regions

Geographic Regions	Number* (10,000)	Population Proportion	Sample distribution
Northeast	10836	7.8%	347
North	17522	12.5%	556
Northwest	10279	7.4%	329
East	36477	26.1%	1160
Central	27069	19.4%	862
South	17206	12.3%	547
Southwest	20217	14.5%	645
Total	**139606**	**100%**	**4445**

*Roughly sample allocation, according to China Statistical Yearbook 2018.

Table 2 Semi-structured questionnaire on colorectal cancer knowledge

1. **Before you were diagnosed with colorectal cancer, did you think which of the following was/were the high-risk factors of colorectal cancer?**

A.   Aged 50~74

B.   A history of colorectal adenoma

C.   A history of chronic diarrhea, chronic constipation or bloody stool

D.   A history of chronic appendicitis or appendectomy

E.   A history of chronic cholecystitis or cholecystectomy

F.   Lack of physical exercise

G.   Unhealthy habits such as heavy smoking or drinking

H.   Unhealthy diet such as excessive intake of red meat, or less intake of vegetables and cellulose

I.   Others, please specify_____

J.   I did not know

2. **Before you were diagnosed with colorectal cancer, did you think which of the following was/were the procedure of colorectal cancer screening?**

A.　For the general population aged 50~74, questionnaire survey is needed for the first screening, then decide whether colonoscopy is necessary

B.　For the general population aged 50~74, fecal occult blood test should be done at least once a year. If it is positive, colonoscopy is required

C.　For the general population aged 50~74, colonoscopy screening should be done at least once every five years

D.　For high-risk population, colonoscopy screening should be done at least once every year

E.　Others, please specify_____

F.　I did not know

3.　Before you were diagnosed with colorectal cancer, did you think which of the following was/were the treatment methods of colorectal cancer?

A.　Endoscopic treatment (endoscopic mucosal resection)

B.　Surgical treatment (colectomy + regional lymphadenectomy)

C.　Radiotherapy

D.　Chemotherapy

E.　Targeted therapy

F.　Traditional Chinese medicine treatment

G.　I did not know

Table 3 The selected nine items from QLQ-C30

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Physical Function					
Do you need help with eating, dressing, washing yourself or using the toilet?	4	3	2	1	0
Insomnia Function					
Have you had trouble sleeping?	4	3	2	1	0
Fatigue Function					
Were you tired?	4	3	2	1	0

Emotional Function

Did you feel irritable?	4	3	2	1	0
Did you feel depressed?	4	3	2	1	0

Cognitive Function

Have you had difficulty remembering things?	4	3	2	1	0

Social Function

Has your physical condition or medical treatment interfered with your family life?	4	3	2	1	0
Has your physical condition or medical treatment interfered with your social activities?	4	3	2	1	0

Financial Difficulties

Has your physical condition or medical treatment interfered with your financial difficulties?	4	3	2	1	0

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A

		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion

Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Disease knowledge, medical experience, health-related quality of life, and health-care costs among patients with advanced colorectal cancer in China: protocol for a nationwide multi-center survey

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Disease knowledge, medical experience, health-related quality of life, and health-care costs among patients with advanced colorectal cancer in China: protocol for a nationwide multi-center survey

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Abstract

Background Colorectal cancer (CRC) is one of the most common cancers in China. Most patients have developed advanced stage at diagnosis, leading to a low 5-year survival rate. To optimize prevention strategies, we planned a survey to evaluate the disease knowledge, medical experience, health-related quality of life before and after the treatment of CRC, and health-care costs among patients with advanced CRC in China.

Methods and analysis This is a nationwide, hospital-based, multi-center survey. Nineteen hospitals in seven cities were selected by multi-stage stratified sampling. Mainland China is divided into seven regions according to the traditional administrative district definition; two cities of each region were selected through simple random sampling, and then one tertiary cancer hospital and/or one general hospital were selected for each city. More than 4445 CRC patients in the selected hospitals with stage III or IV will be enrolled in this study. The trained interviewers will collect information through patients' self-report and/or medical records, including demographics and medical history; knowledge about CRC high-risk factors, screening procedure and treatment methods; medical experience on CRC screening, diagnosis and treatment; health-related quality of life before and after CRC treatment; and costs of CRC. All data will be input by two independent staff and verified using Epidata V.3.1 software. Data validation plan (DVP) will be made to guide data checking. All statistical analyses will be conducted using SAS V.9.4 and SPSS V.24.0 soft-ware.

Ethics and dissemination The study was approved by the ethics committees of Henan cancer hospital, the leading participant hospital. Findings of this study will be disseminated through peer-reviewed open-access journals, and presented as posters and/or oral sections in national and international conferences. Results will also be popularized to the public via media or the internet.

Keywords: Nationwide survey, Colorectal cancer, Knowledge, Medical experience, Quality of life, Costs

Strengths and limitations of this study

➢ This is the first survey with a large number of advanced CRC patients in China.

➢ This is a nationwide, multi-center study, including 19 hospitals from 7 regions.

➢ This comprehensive research will provide detailed and important information for prevention and control measures for advanced CRC.

➢ Large amount of data from patients will be collected, allowing to pursue secondary analysis.

➢ The self-reported data may be subject to recall biases and social desirability.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated 1.9 million new cases and about 935,000 deaths around 2020 annually[1]. The incidence and mortality of CRC vary among different countries due to differences in lifestyle and socio-economic development[2]. China ranks first worldwide in the number of CRC new cases and CRC-related deaths due to the relatively large population[3]. Furthermore, the country faces a challenge of increasing CRC cases due to a western lifestyle[4 5]. According to the latest Chinese Cancer Registration Report in 2019, about 110,546 new cases and 53,810 deaths occurred in China, placing it the fourth highest incidence and the fifth mortality among all cancers[6]. Although the overall 5-year survival rate has been increasing in the past decades[7], the rate for patients with advanced CRC is only about 20% while that for patients with early CRC is up to 90%[8]. Even worse, about 56% of CRC patients have developed advanced stage at diagnosis[9 10].

Three-level prevention is the main strategy to reduce incidence and mortality of advanced CRC, including[11]: primary prevention avoiding high-risk behaviors of CRC; secondary prevention aimed at screening to promote CRC early detection, diagnosis and treatment; and tertiary prevention adopting appropriate treatment to prolong life and improve the health-related quality of life (HRQOL). To guide the implementation of prevention strategies, patients' knowledge on CRC high-risk factors, screening, and treatment before they were diagnosed should be firstly identified, since knowledge is one of the predisposing factors that may influence patients' motivation to avoid high-risk behaviors and receive some interventions[12]. It is also critical to explore patients' medical experience on CRC screening, diagnosis and treatment, to find out potential interventions that could reduce incidence and mortality of advanced CRC[13-16]. Particularly, CRC screening via colonoscopy, and numerous targeted agents which can extend overall survival for advanced CRC have been well developed[17-19], but little is known about the status of and barriers for them. Furthermore, with the advance in treatment, HRQOL has become a significant outcome in advanced CRC patients[20 21]. In order to choose a preferred treatment modality and inform potential interventions, it is essential to assess HRQOL status before and after treatment, as well as the associated factors with the changes[22]. However, no nationwide representative data of advanced CRC patients in China has been reported.

Additionally, cost-of-illness studies are critical to informing policy decisions on cancer prevention and control, cost-effectiveness evaluations, and improving public health[23]. Costs of CRC have been assessed in many countries, such as Iran[24], Vietnam[25], New Zealand[26], and across the European

Union[23], and all studies have demonstrated high costs of CRC and substantial burden on the health-care system. However, evidence on costs of CRC in China is limited. A retrospective survey in China revealed that the annual average medical expenditure increased rapidly from 2002 to 2011, and the average medical expenditure per CRC patient was 37,902 Chinese Yuan (CNY) in 2011 value[27]. However, with the development of diagnosis and treatment methods, previous results are no longer representative of the current situation. In order to provide timely data for future related evaluations of the cost-effectiveness of CRC-related screening, diagnosis and treatment, and guiding prevention and control of advanced CRC, a nationwide survey on current costs of CRC is needed in China.

Therefore, we launched a national, hospital-based, multi-center survey to comprehensively present the knowledge, medical experience, health-related quality of life, and health-care costs among advanced CRC patients in China. This survey will provide unique data to encourage health authorities and policymakers to optimize prevention strategiesto reduce the burden of advanced CRC. It will also contribute to the methodology of undertaking research on other cancer types. This paper presents a detailed methodological description of this survey, hoping that this protocol can be applied to future surveys in other cancers.

Objectives

(1) To evaluate patients' knowledge about CRC high-risk factors, CRC screening, CRC treatment before they were diagnosed, and explore the associated factors.

(2) To investigate patients' medical experience on CRC screening, diagnosis and treatment, and identify status of and barriers for colonoscopy screening and targeted agents.

(3) To evaluate patients' health-related quality of life before and after treatment against CRC, and explore the associated factors with the changes.

(4) To estimate the costs of CRC.

Methods and Analysis

Study Design

This is a nationwide, hospital-based, multi-center survey conducted in Mainland China.

Selection of Hospitals

Mainland China is divided into seven different geographic regions (Northeast, North, Northwest, East, Central, South, and Southwest) according to the traditional administrative district definition[28]. These regions showed different levels of CRC burden[3]. Multi-stage stratified sampling was adopted to choose the participant hospitals. In stage one, two cities of each region were selected by simple random sampling. In stage two, one tertiary cancer hospital and/or one general hospital were selected in each city with inclusion on the basis that (1) they can provide diagnosis, surgery, radiotherapy, chemotherapy, and routine follow-up care for patients with CRC; (2) visiting patients are from different parts of the region. Finally, a total of 19 hospitals (10 tertiary cancer hospitals and 9 general hospitals) were selected.

Study Population

Patients at the selected hospitals will be enrolled if they (1) are diagnosed with stage III or IV CRC; (2) are aged >=18 years old; (3) are inpatients; (4) provide the informed consent. Patients will be excluded if they had severe physical, cognitive, and/or verbal impairments that would interfere with a patient's ability to complete the questionnaire. Staging of CRC is done according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system[29].

Sample Size

It was estimated that there were about 400,000 advanced CRC patients in China[30 31]. For a targeted population with large sample (more than 150,000), a sampling ratio of 1% is enough to ensure the representativeness of the sample[32]. Therefore, it is designed that 1% (about 4,000) of the eligible advanced CRC patients in China are included. Considering the non-response rate of 10%, more than 4445 patients would be enrolled into this survey. Proportional allocation was used to determine the sample size of each region, according to the population density (Table 1). For example, the proportion of population in Northeast China is 7.8% (10,836/139,606), therefore, the sample size in Northeast China is equal to 7.8% times 4,445, or 347.

Study procedures

Preliminary phase

The preliminary study phase performed in June to August 2019 included preparatory workshops with researchers of the centers to present the study, develop the survey questionnaires, obtain prior agreement to conduct the study, develop principles and a manual of the research practice, and train the

study staff. The survey questionnaires were developed through multiple team meetings and solely included easy-to-answer, single or multiple questions about (1) patients' demographics and medical history; (2) knowledge about CRC high-risk factors, screening procedure and treatment methods; (3) patients' medical experience on CRC screening, diagnosis and treatment; (4) patients' health-related quality of life before and after CRC treatment; (5) costs of CRC.

In addition, a pilot survey was conducted from September to October 2019 in two Chinese hospitals (Henan Cancer Hospital and The First Affiliated Hospital of Baotou Medical College) to validate standard operating procedures and the questionnaires. Fifty patients were enrolled in the pilot survey and they were not included in the formal research.

Survey implementation

The formal survey was started in March 2020, and is expected to be completed by July 2022. All patients will provide written informed consents prior to participation. The questionnaires take approximately 20 min to be completed, and the participants will receive RMB 30 (about 4.2 USD) for their contribution after completion. Trained interviewers will carry out this survey. Principles of good research practice are strictly adhered to during the data collection.

Study Measures

Demographics and medical history

Demographic information will be collected through a standardized self-report questionnaire, including birth date, gender, location, occupational situation, marital status, family members, school education, annual household income, and medical insurance type.

Medical history including date of diagnosis, types of cancer (colon cancer, rectal cancer, and both), disease stage at diagnosis and at present, metastasis at diagnosis and at present, and cycles of chemotherapy will be linked through medical records.

Knowledge about high-risk factors of CRC, screening procedure, and treatment methods

Patients' knowledge about CRC before they were diagnosed will be collected using a semi-structured questionnaire (SSQ). The SSQ was developed by the research team based on China guidelines (China guideline for the screening, early detection, and early treatment of colorectal cancer

(2020, Beijing)[33]; Chinese protocol of diagnosis and treatment of colorectal cancer (2020 edition)[34]). The SSQ consists of 3 multiple choice questions classified in three sections: section one (high-risk factors of CRC), section two (CRC screening procedure), section three (CRC treatment methods). Section one has 11 items, section two has 6 items, and section three has 7 items. If patients answer "I did not know", a score of zero will be given; otherwise, a score of one will be given for each correct choice. Thus, the score ranges from 0 to 21. The detailed information about the SSQ is presented in Table 2.

If participants knew any information about CRC before they were diagnosed, sources of information such as health educational booklets, television, radio, doctors, family and friends, websites, and social media would be further collected.

Patients' medical experience on CRC screening, diagnosis, and treatment

Another semi-structured questionnaire is used to collect health care information regarding CRC screening, diagnosis, and treatment.

i. CRC screening: information on patients' screening history will be collected, including: have the patients been screened, the methods (i.e. faecal immunological test (FIT), colonoscopy, sigmoidoscopy, et al) and frequency of screening. Given that colonoscopy is the standard screening method with the highest performance, barriers (unaware of the need for colonoscopy, having not enough time for colonoscopy, fear of side effects, unaffordable costs, having difficulties making an appointment for colonoscopy, and others) against colonoscopy are also collected based on patients' self-report.

ii. CRC diagnosis and treatment: Information regarding (1) the hospital and department where the patients were firstly diagnosed with CRC, (2) the hospital and department where the patients first received CRC treatment, (3) reasons for the patient's first visit, (4) the number of hospitals where patients have visited for CRC, and (5) whether the patients ever changed the visited hospital and the reason for the change is collected based on patients' self-report; information regarding (1) the use of genetic testing, (2) the use of currently available surgery approaches, (3) the use of radiotherapy, (4) the use of chemotherapy including adjuvant and neoadjuvant chemotherapy, (5) the use of targeted agents is collected through medical records; Information on the barriers against targeted agents is collected based on patients' self-report, e.g. Doctors did not inform or recommend molecular targeted agents,

Genetic testing results did not meet molecular targeted agents, Not convinced that molecular targeted agents works, Unaffordable medical costs, et al.

Health-related quality of life

The extensively validated traditional Chinese FACT-C (Functional Assessment of Cancer Therapy-Colorectal) (version 4) and the traditional Chinese version of EORTC (the European Organization for Research and Treatment of Cancer) QLQ-C30 (version 3) are combined to measure patients' health-related quality of life[35-37]. The traditional Chinese FACT-C (version 4) was translated by the functional assessment of chronic illness therapy translation coordinating team, following a standard procedure and guidelines. It includes 36 items covering five function subscale (physical, social/family, emotional, functional and colorectal cancer subscale). The traditional Chinese version of EORTC QLQ-C30 (version 3) consists of 30 items grouped into five function subscales (physical, role, emotional, cognitive and social), nine symptom subscales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) and a global health/QOL subscale. Further details of the full-scale survey were reported elsewhere[35-37].

In this study, 45 items were selected using experts' opinion to establish a scale named FACT-C-plus-QLQ-C9, consisting of all FACT-C items plus nine items from QLQ-C30. The self-made scale covers six function subscales (physical, social/family, emotional, functional, colorectal cancer subscale, and cognitive), and three symptom subscales (fatigue, insomnia, and financial difficulties). Each positive item is valued on a 5-point Likert scale (not at all=0, a little bit=1, somewhat=2, quite a bit=3, very much=4), while the negative item is valued reversely (not at all=4, a little bit=3, somewhat=2, quite a bit=1, very much=0). The selected nine items from QLQ-C30 are presented in Table 3.

Patients' quality of life will be collected at two-time points, based on patients' self-report:

Point 1: T1 (the first or second day that patients are hospitalized, but before anti-CRC treatment);
Point 2: T2 (the day before discharge, but after anti-CRC treatment).

Individual's rough scores (RS) of total subscale at different points are firstly calculated with a range from 0 to 180, and then linearly converted into standardized scores (SS) of 0~100. The higher scores indicate better HRQOL. Changes of HRQOL before and after anti-CRC treatment is equal to SS after treatment minus SS before treatment.

Cost estimation

The costs of CRC will be estimated from a societal perspective, including direct medical costs and direct non-medical costs. We will use an annual timeframe to retrospectively collect all costs since the time of diagnosis. Direct medical costs are defined as all expenditures related to the diagnosis and treatment of CRC, which include costs of registration, diagnosis, medical examinations, medication, surgery, radiology, and hospitalization. Non-medical costs include costs of patients and their families' transportation to and from healthcare centers, nursing and nutrition fees. The costs will be collected through medical records or patients' self-report if medical records are not available. All costs will be converted to 2021 CNY using a discount rate of 3%, and summed over each year for each patient. Annual direct costs per patient will be calculated to present the costs of CRC. Details of the costs are presented in Table 4.

Data management and quality control of data

A special and trained team is set up to manage data, including data filling, entry, checking and revising, and data locking.

Data filling

Paper-based non-identifiable questionnaire is used to manage individual participant data. Data filled in the questionnaire must be consistent with the patient's self-report and medical records. All completed questionnaires will be checked by the trained interviewers immediately to avoid missing and logical mistakes. Questionnaires with missing items or obvious logical mistakes (e.g. not applicable items are filled in) will be returned to patients to modify.

Data entry

All collected data will be double-entered using Epidata software V.3.1 by two trained research assistants. After completing data entry, an independent data administrator will compare the consistency between the two data sets. Any discrepancies will be returned to data entry clerks to be resolved.

Data checking and revising

The rule of data checking includes missing values and logical mistakes checking. Data validation plan (DVP) will be made to guide data checking. One research assistant will use SAS software V.9.4

for data checking, according to the DVP. Any query will be sent to the investigators to be solved. And then, the research assistant will revise the dataset prior to statistical analysis.

Data locking

After the dataset is judged to be accurate and meet the above requirements, it will be locked by the principle investigator, and no more changes are allowed. All paper documents will be kept in a special filing cabinet for reference at any time. Electronic data will be stored on password-protected computer files, which can only be accessible to the research team members.

Statistical analysis plan

All statistical analyses will be conducted by the SAS V.9.4 soft-ware.

Descriptive analysis will be used to report patients' demographics, medical history, score of knowledge on CRC, barriers against CRC screening and targeted agents, HRQOL before and after treatment, and annual costs of CRC. Categorical variables will be presented using absolute frequencies and percentages, while normal distributed continuous variables will be presented using mean and standard deviation (SD), and abnormal distributed continuous variables will be presented using median and standard inter-quartile range.

The reliability and validity of the self-made HRQOL scale named FACT-C-plus-QLQ-C9 will be tested. The reliability of the scale will be assessed via internal consistency and split-half reliability. Internal consistency of the scale will be determined by Cronbach's α coefficient, using an acceptable cut-off value of 0.70[38]. Split-half reliability will be assessed with intra-class correlation coefficient (ICC) of the scores of two sections, and an adequate value above 0.6 for ICC will be regarded as adequate[39]. The validity of the scale will be tested via construct validity. The confirmed factor analysis (CFA) will be used to test the overall fit of the data to scale the model with 45 items and 9 factors. Model fit will be evaluated with comparative fit index (CFI), root mean square error of approximation (RMSEA), and x^2/df. The index criteria for well-fitting models are CFI>0.90, RMSEA<0.08 and $2<x^2$/df<5[38]. The items with lower factor loading less than 0.35 will be removed[40].

Subgroup analyses will be performed according to gender, median age, region, disease stages and so on. Logistic or linear regression model will be used to explore factors associated with CRC knowledge, colonoscopy screening, targeted agents, and the changes of HRQOL before and after anti-CRC treatment. The ICC will be first calculated to assess the reliability of individual data aggregated

at region-level (North East, North, Central, East, South, North West, and South West) in hierarchical models by testing an unconditional or null model, considering the hierarchical structure of the data. If ICC is statistically significant, a multi-level logistic or linear analysis will be conducted; otherwise, one-level regression model will be conducted. Variables with *P*-value <0.10 in the univariate regression model will be entered into the multivariable regression model. Stepwise regression will be performed to determine the statistical significance of each variable in the multivariable regression model, with a *P*-value <0.05 as the criterion.

Patient and Public Involvement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and Dissemination

Before starting the study, agreements were made by all co-participant hospitals, and the survey protocol was reviewed and approved by the leading participating hospital (Henan cancer hospital) (reference number: 2019273). All individuals must voluntarily agree to participant this survey and provide informed consent form.

Study findings will be disseminated through peer-reviewed open-access journals, and presented as posters and/or oral sections in national and international conferences. Results will also be popularized to the public via media or the internet.

Discussion

Prevention is an effective strategy to reduce the incidence and mortality of advanced CRC. Exploring patients' knowledge about CRC, medical experience, quality of life, and health care costs, is necessary to identify the weak parts in the prevention of advanced CRC. Although many studies have been done in some countries, such as Armenia[41], Kuwait[42], the United States[20], Iran[24] and New Zealand[26], most of these only focused on the general public or all patients with CRC, which has limited effect on the prevention of advanced CRC. Moreover, the results of studies conducted in other countries may not be necessarily applicable to China, due to the varied living habits, economic development, and CRC burden.

The nationwide survey is expected to generate important indicators about disease knowledge, medical experience, HRQOL status before and after anti-CRC treatment, and costs of CRC among advanced CRC patients in China. The indicators will help to visualize the overall situation of China, which can facilitate further updates of the prevention strategy and policy development. The information generated from this survey can be used by the team members and other concerned bodies to advocate for the mobilization of policy changes and extra resources to support prevention efforts across China. Moreover, results of this survey can be used to identify levels of unmet medical need and determine the subgroup of patients who need more interventions and the regions which need extra resources in guiding the prevention system.

This study has several strengths. First, this is the first geographic representative study with large number of more than 4400 patients in China. The burden of CRC varies in different regions in China. We select patients from the 7 geographic regions through multi-stage stratified sampling, which not only ensure geographic representativeness and generalization, but also make it possible to compare different regions. Second, this is a comprehensive research program, which will provide detailed information of disease knowledge, medical experience, health-related quality of life, and health-care costs among advanced CRC patients, and provide guidance for the prevention and control of advanced CRC in China. Additionally, we will collect large amount of data from patients, allowing to pursue secondary analysis, such as analysis of characteristics of a subgroup.

The study also has several limitations. First, some elements of the study design are retrospective in nature, and some data will be collected by patients' self-report when medical records are not available, such as disease knowledge, CRC screening, HRQOL, and health-care costs, these may be subject to recall biases and social desirability. Second, since the participants are all voluntary, their characteristics may differ from those who do not participate in this study. Third, we are using a cross-sectional study to explore the associated factors with disease knowledge, colonoscopy screening, and targeted agents, the causal relationships can not be well established. Fourth, all participants enrolled in this study are in the treatment of CRC, and the treatment is still continuing, which will lead to an underestimation of the number of hospitals where patients have visited for CRC, and proportions of initiating genetic testing, surgery, radiotherapy, chemotherapy, and targeted agents. Finally, we only include direct costs of CRC, which will result in an underestimation of economic burden of CRC.

Authors' contributions

YL, SKZ and YLQ: conception and design. YL: drafting of the article. HFX, XZ, YQY, and YQZ have made substantial contribution to the study protocol. All authors: revised the manuscript and approved the final version of the manuscript.

Competing interests statement

None declared.

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Table 1 Sample distribution by population density and geographic regions

Geographic Regions	Number* (10,000)	Population Proportion	Sample distribution
Northeast	10,836	7.8%	347
North	17,522	12.5%	556
Northwest	10,279	7.4%	329
East	36,477	26.1%	1160
Central	27,069	19.4%	862
South	17,206	12.3%	547
Southwest	20,217	14.5%	645
Total	**139,606**	**100%**	**4,445**

*Roughly sample allocation, according to China Statistical Yearbook 2018.

Table 2 Semi-structured questionnaire on colorectal cancer knowledge

1. **Before you were diagnosed with colorectal cancer, did you think which of the following was/were the high-risk factors of colorectal cancer?**

A.   Aged 50~74

B.   A history of colorectal adenoma

C.   A history of chronic diarrhea, chronic constipation or bloody stool

D.   A history of chronic appendicitis or appendectomy

E.   A history of chronic cholecystitis or cholecystectomy

F.   Lack of physical exercise

G.   Unhealthy habits such as heavy smoking or drinking

H.   Unhealthy diet such as excessive intake of red meat, or less intake of vegetables and cellulose

I.   A first-degree family history of colorectal cancer

J.   Others, please specify_____

K.   I did not know

2. **Before you were diagnosed with colorectal cancer, did you think which of the following was/were the procedure of colorectal cancer screening?**

A.   For the general population aged 50~74, questionnaire survey is needed for the first screening, then decide whether colonoscopy is necessary

B.   For the general population aged 50~74, fecal occult blood test should be done at least once a year. If it is positive, colonoscopy is required

C.   For the general population aged 50~74, colonoscopy screening should be done at least once every five years

D.   For high-risk population, colonoscopy screening should be done at least once every year

E.   Others, please specify_____

F.   I did not know

3. Before you were diagnosed with colorectal cancer, did you think which of the following was/were the treatment methods of colorectal cancer?

A.   Endoscopic treatment (endoscopic mucosal resection)

B.   Surgical treatment (colectomy + regional lymphadenectomy)

C.   Radiotherapy

D.   Chemotherapy

E.   Targeted therapy

F.   Traditional Chinese medicine treatment

G.   I did not know

Table 3 The selected nine items from QLQ-C30

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Physical Function					
Do you need help with eating, dressing, washing yourself or using the toilet?	4	3	2	1	0
Insomnia Function					
Have you had trouble sleeping?	4	3	2	1	0
Fatigue Function					
Were you tired?	4	3	2	1	0
Emotional Function					

Did you feel irritable?	4	3	2	1	0
Did you feel depressed?	4	3	2	1	0
Cognitive Function					
Have you had difficulty remembering things?	4	3	2	1	0
Social Function					
Has your physical condition or medical treatment interfered with your family life?	4	3	2	1	0
Has your physical condition or medical treatment interfered with your social activities?	4	3	2	1	0
Financial Difficulties					
Has your physical condition or medical treatment interfered with your financial difficulties?	4	3	2	1	0

Table 4   Details of CRC Costs

	1st Year*	2nd Year	3rd Year	4th Year	…	Total costs(CNY)
Direct medical costs (CNY)						
Registration cost						
Diagnosis cost						
Medical examinations cost						
Medication cost						
Surgery cost						
Radiology cost						
Hospitalization cost						
Non-medical costs (CNY)						
Transportation cost						
Nursing cost						
Nutrition cost						
Total costs (CNY)						

*Year of diagnosis of CRC.

CNY: Chinese Yuan.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A

		(*b*) Report category boundaries when continuous variables were categorized		N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives		N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		13
Generalisability	21	Discuss the generalisability (external validity) of the study results		13
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.