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

Yin Liu, Hui-Fang Xu, Xi Zhang, Yan-Qin Yu, Yu-Qian Zhao, Shao-Kai Zhang, You-Lin Qiao

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 optimise prevention strategies, we planned a survey to evaluate the disease knowledge, medical experience and health-related quality of life (HRQOL) before and after the treatment of CRC, and healthcare costs among patients with advanced CRC in China.

Methods and analysis This is a nationwide, hospital-based, multicentre survey. Nineteen hospitals in seven cities were selected by multistage 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 one general hospital were selected for each city. More than 4445 patients with CRC 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; HRQOL 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 will be made to guide data checking. All statistical analyses will be conducted using SAS V.9.4 and SPSS V.24.0 software.

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 popularised to the public via media or the internet.

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. The incidence and mortality of CRC vary among different countries due to differences in lifestyle and socioeconomic development. China ranks first worldwide in the number of CRC new cases and CRC-related deaths due to the relatively large population. Furthermore, the country faces a challenge of increasing CRC cases due to a Western lifestyle. According to the latest Chinese Cancer Registration Report in 2019, about 110 546 new cases and 53 810 deaths occurred in China, placing it as having the fourth highest incidence and the fifth mortality among all cancers. Although the overall 5-year survival rate has been increasing in the past decades, the rate for patients with advanced CRC is only about 20%, while that for patients with early CRC is up to 90%. Even worse, about 56% of patients with CRC have developed advanced stage at diagnosis.

Three-level prevention is the main strategy to reduce incidence and mortality of advanced CRC, including primary prevention, avoiding high-risk behaviours 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 first identified, since knowledge is one of the predisposing factors that may influence patients’ motivation to avoid high-risk behaviours and receive some interventions. 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. Particularly, CRC screening via colonoscopy and numerous targeted agents which can extend overall survival for advanced CRC have been well developed, 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 patients with advanced CRC. 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. However, no nationwide representative data of patients with advanced CRC 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. Costs of CRC have been assessed in many countries, such as Iran, Vietnam, New Zealand and across the European Union, and all studies have demonstrated high costs of CRC and substantial burden on the healthcare 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 patient with CRC was 37 902 Chinese yuan (CNY) in 2011 value. 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, multicentre survey to comprehensively present the knowledge, medical experience, HRQOL and healthcare costs among patients with advanced CRC in China. This survey will provide unique data to encourage health authorities and policymakers to optimise prevention strategies to 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
- To evaluate patients’ knowledge about CRC high-risk factors, CRC screening and CRC treatment before they were diagnosed and to explore the associated factors.
- To investigate patients’ medical experience on CRC screening, diagnosis and treatment, and to identify status of and barriers for colonoscopy screening and targeted agents.
- To evaluate patients’ HRQOL before and after treatment against CRC and to explore the associated factors with the changes.
- To estimate the costs of CRC.

METHODS AND ANALYSIS

Study design
This is a nationwide, hospital-based, multicentre survey conducted in Mainland China.

Selection of hospitals
Mainland China is divided into seven different geographical regions (Northeast, North, Northwest, East, Central, South and Southwest) according to the traditional administrative district definition. These regions showed different levels of CRC burden. Multistage stratified sampling was adopted to choose the participant hospitals. In stage 1, two cities of each region were selected by simple random sampling. In stage 2, 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; and (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 and (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 eighth edition of the American Joint Committee on Cancer tumor, node, metastasis staging system.

Sample size
It was estimated that there were about 400 000 patients with advanced CRC in China. For a targeted population with a large sample (more than 150 000), a sampling ratio of 1% is enough to ensure the representativeness of the sample. Therefore, it is designed that 1% (about 4000) of the eligible patients with advanced CRC 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 4445 or 347.

Study procedures

Preliminary phase

The preliminary study phase performed in June–August 2019 included preparatory workshops with researchers of the centres 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’ HRQOL before and after CRC treatment; and (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 questionnaires. Fifty patients were enrolled in the pilot survey and 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 30 renminbi (about US$4.2) 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 standardised 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 semistructured 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 CRC (2020, Beijing)33 and Chinese protocol of diagnosis and treatment of CRC (2020 edition).34 The SSQ consists of three multiple choice questions classified in three sections: section 1 (high-risk factors of CRC), section 2 (CRC screening procedure) and section 3 (CRC treatment methods). Section 1 has 11 items; section 2 has 6 items; and section 3 has 7 items. If patients answer ‘I did not know’, a score of 0 will be given; otherwise, a score of 1 will be given for each correct choice. Thus, the score ranges from 0 to 21. Detailed information about the SSQ is presented in Box 1.

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 SSQ is used to collect healthcare information regarding CRC screening, diagnosis and treatment.

► CRC screening: information on patients’ screening history will be collected, including data on whether the patients been screened, the methods (ie, faecal immunological test, colonoscopy, sigmoidoscopy, etc) 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.

► CRC diagnosis and treatment: information regarding (1) the hospital and department where the patients were first diagnosed with CRC, (2) the hospital and department where the patients first received CRC treatment, (3) reasons for the patient’s first visit, (4)
Box 1 Semistructured questionnaire on CRC knowledge

1. Before you were diagnosed with CRC, did you think which of the following was/were the high-risk factors of CRC?
   A. Aged 50–74.
   B. A history of colorectal adenoma.
   C. A history of chronic diarrhoea, 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 CRC.
   J. Others, please specify: ______.
   K. I did not know.

2. Before you were diagnosed with CRC, did you think which of the following was/were the procedure of CRC 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, faecal 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 5 years.
   D. For a 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 CRC, did you think which of the following was/were the treatment methods of CRC?
   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.

CRC, colorectal cancer.

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, and (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; for example, 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, etc.

Health-related quality of life

The extensively validated traditional Chinese Functional Assessment of Cancer Therapy-Colorectal (FACT-C) V.4 and the traditional Chinese version of EORTC (the European Organisation for Research and Treatment of Cancer) QLQ-C30 V.3 are combined to measure patients’ HRQOL. The traditional Chinese FACT-C V.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 subscales (physical, social/family, emotional, functional and colorectal cancer subscale). The traditional Chinese version of EORTC QLQ-C30 V.3 consists of 30 items grouped into five function subscales (physical, role, emotional, cognitive and social), nine symptom subscales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea 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 and very much=4), while the negative item is valued reversely (not at all=4, a little bit=3, somewhat=2, quite a bit=1 and very much=0). The selected nine items from QLQ-C30 are presented in table 2.

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 hospitalised, 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 first calculated with a range from 0 to 180, and then linearly converted into standardised 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 time frame 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 hospitalisation. Non-medical costs include costs of patients and their families’ transportation to and from healthcare centres, 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 3.

**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.

### Table 2 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 3 Details of the costs**

|                           | First year* | Second year | Third year | Fourth year | … | Total costs (CNY) |
|---------------------------|-------------|-------------|------------|-------------|----|------------------|
| **Direct medical costs (CNY)** |             |             |            |             |    |                  |
| Registration cost         |             |             |            |             |    |                  |
| Diagnosis cost            |             |             |            |             |    |                  |
| Medical examinations cost |             |             |            |             |    |                  |
| Medication cost           |             |             |            |             |    |                  |
| Surgery cost              |             |             |            |             |    |                  |
| Radiology cost            |             |             |            |             |    |                  |
| Hospitalisation cost      |             |             |            |             |    |                  |
| **Non-medical costs (CNY)** |             |             |            |             |    |                  |
| Transportation cost       |             |             |            |             |    |                  |
| Nursing cost              |             |             |            |             |    |                  |
| Nutrition cost            |             |             |            |             |    |                  |
| **Total costs (CNY)**     |             |             |            |             |    |                  |

*Year of diagnosis of CRC.

CNY, Chinese yuan; CRC, colorectal cancer.

**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 (eg, 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 datasets. 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. 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 aforementioned requirements, it will be locked by the principal 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 software.

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 SD, and abnormal distributed continuous variables will be presented using median and standard IQR.

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 intracllass 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 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 χ²/df. The index criteria for well-fitting models are CFI >0.90, RMSEA <0.08 and 2<χ²/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 multilevel logistic or linear analysis will be conducted; otherwise, one-level regression model will be conducted. Variables with p value of <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 of <0.05 as the criterion.

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 healthcare 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 USA,20 Iran24 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 patients with advanced CRC in China. The indicators will help to visualise the overall situation in China, which can facilitate further updates of the prevention strategy and policy development. The information generated from this survey can

Liu Y, et al. BMJ Open 2022;12:e054403. doi:10.1136/bmjopen-2021-054403
be used by the team members and other concerned bodies to advocate for the mobilisation 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 geographical representative study with a large number of more than 4400 patients in China. The burden of CRC varies in different regions in China. We selected patients from the seven geographical regions through multistage stratified sampling, which not only ensured geographical representativeness and generalisation but also made it possible to compare different regions. Second, this is a comprehensive research programme, which will provide detailed information of disease knowledge, medical experience, HRQOL and healthcare costs among patients with advanced CRC, and guidance for the prevention and control of advanced CRC in China. Additionally, we will collect large amount of data from patients, allowing pursuance of 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 healthcare 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 cannot be well established. Fourth, all participants enrolled in this study are under treatment for 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 the economic burden of CRC.

**Acknowledgements** We are grateful to the patients, their family and all the investigators who are participating in the study.

**Collaborators** China Working Group On Colorectal Cancer Survey

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

**Funding** This study is funded by Beijing Love Book Cancer Foundation and Merck Serono Co. (grant number: not applicable).

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the ethics committee of Henan Cancer Hospital (number 2019273). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing is not applicable as no datasets were generated and/or analysed for this study.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**

Yin Liu http://orcid.org/0000-0003-0961-2276

Xi Zhang http://orcid.org/0000-0001-7402-6981

Yu-Qian Zhao http://orcid.org/0000-0002-2736-4766

Shao-Kai Zhang http://orcid.org/0000-0002-0154-7126

**REFERENCES**

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.

2. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Sut* 2017;66:683–91.

3. Yang Y, Han Z, Li X, et al. Epidemiology and risk factors of colorectal cancer in China. *Chin J Cancer Res* 2020;32:729–41.

4. Sun D, Cao M, Li H, et al. Cancer burden and trends in China: a review and comparison with Japan and South Korea. *Chin J Cancer Res* 2020;32:129–39.

5. Yin J, Bai Z, Zhang J, et al. Burden of colorectal cancer in China, 1990–2017: Findings from the Global Burden of Disease Study 2017. *Chin J Cancer Res* 2019;31:489–98.

6. Center NC. China cancer registry annual report 2019. Beijing: People’s Medical Publishing House, 2021.

7. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health* 2018;6:e655–67.

8. Shen L, Li Q, Wang W, et al. Treatment patterns and direct medical costs of metastatic colorectal cancer patients: a retrospective study of electronic medical records from urban China. *J Med Econ* 2020;23:456–63.

9. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017;67:177–93.

10. Millas SG, Alawadi ZM, Wray CJ, et al. Treatment delays of colon cancer in a safety-net hospital system. *J Surg Res* 2015;198:311–6.

11. Roncucci L, Mariani F. Prevention of colorectal cancer: how many tools do we have in our basket? *Eur J Intern Med* 2015;26:752–6.

12. Di Giuseppe G, Pelullo CP, Mitidieri M, et al. Cancer prevention: knowledge, attitudes and lifestyle cancer-related behaviors among adolescents in Italy. *Int J Environ Res Public Health* 2020;17. doi:10.3390/ijerph17222894. [Epub ahead of print: 10 11 2020].

13. Sawicki T, Ruszkowska M, Daniewicz A, et al. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. *Cancers* 2021;13. doi:10.3390/cancers13092025. [Epub ahead of print: 22 04 2021].

14. Shah R, Chan KKW. The impact of socioeconomic status on stage at presentation, receipt of diagnostic imaging, receipt of treatment and overall survival in colorectal cancer patients. *Int J Cancer* 2021;149:1031–43.
15 Lim KT, Ng CH, Decruz GM, et al. Barriers and facilitators towards colonoscopy: a qualitative systematic review. Eur J Cancer Prev 2021;30:232–8.
16 Wolbert T, Barry R, Gress T, et al. Assessing colorectal cancer screening barriers in rural Appalachia. South Med J 2021;114:293–8.
17 Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637–49.
18 Ciombor KK, Bekaii-Saab T. A comprehensive review of sequencing and combination strategies of targeted agents in metastatic colorectal cancer. Oncologist 2018;23:25–34.
19 Xie Y-H, Chen Y-X, Fang J-Y. Comprehensive review of targeted therapy for colorectal cancer. Signal Transduct Target Ther 2020;5:22.
20 Pate A, Löwyer J, Kilbourn K, et al. Quality of life and the negative impact of comorbidities in long-term colorectal cancer survivors: a population-based comparison. J Cancer Surviv 2020;14:653–9.
21 Ratjen I, Schaftmayer C, Enderle J, et al. Health-Related quality of life in long-term survivors of colorectal cancer and its association with all-cause mortality: a German cohort study. BMC Cancer 2018;18:1156.
22 Johansson A-C, Brink E, Cliftordson C, et al. The function of fatigue and illness perceptions as mediators between self-efficacy and health-related quality of life during the first year after surgery in persons treated for colorectal cancer. J Clin Nurs 2018;27:e1537–48.
23 Luengo-Fernandez R, Leal J, Gray A, et al. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol 2013;14:1165–74.
24 Vahdatimanesh Z, Zandehdel K, Kbari Sari AA, et al. Economic burden of colorectal cancer in Iran in 2012. Med J Islam Repub Iran 2017;31:768–73.
25 Tran BT, Choi KS, Nguyen TX, et al. The direct and indirect costs of colorectal cancer in Vietnam: an economic analysis from a social perspective. Int J Environ Res Public Health 2020;18. doi:10.3390/ijerph18010012. [Epub ahead of print: 22 12 2020].
26 Dunn JP. The economic burden of colorectal cancer in New Zealand. NZ Med J 2015;128:100.
27 Shi J, Liu G, Wang H, et al. Medical expenditures for colorectal cancer diagnosis and treatment: A 10-year high-level-hospital-based multicenter retrospective survey in China, 2002-2011. Chin J Cancer Res 2019;31:825–37.
28 NOICPaGNoCMo H. National survey on cancer mortality in China-the third sample survey on mortality. Beijing: The People’s Health Press, 2010.