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The National Cohort of Esophageal Cancer-Prospective Cohort Study of Esophageal Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-HRP): rationale and design

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4 The National Cohort of Esophageal Cancer-Pro prospective Cohort Study of Esophageal
5 Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-HRP):
6 rationale and design
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37 **Abstract**

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39 **Introduction:** Esophageal cancer is one of the most common cancers worldwide and about
40 50% of all new cases occurred in China. Population-based screening has been conducted
41 in high risk areas in China since 1970s, however, the difference in screening methods and
42 protocols, inconsistencies in questionnaires for risk factors investigation, lack of standards
43 for sample collection and incomplete follow-up information have limited the integration of
44 the results from previous studies and the sharing of existing resources.
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51 **Methods and analysis:** NCEC-HRP is a prospective cohort study of esophageal cancer
52 screening based on high risk population in China. Eight areas located at eastern, central
53 and western China representing three economical-geographical regions are selected as
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4 screening centers. All local residents aged 40–69 years in the selected areas are invited to
5 take endoscopic examination and risk factors investigation unless they meet the exclusion
6 criteria. A total of 100,000 participants will be enrolled by Dec 2020 and all subjects are
7 to be followed for a long time. This study is designed to be open-ended and has broad
8 research aims. Summary statistics for baseline information will be reported after the
9 recruitment is completed. We will develop a serious of standards and guidelines for
10 esophageal cancer screening during the study. An open and shared research platform linked
11 with epidemiological databases and biobank will be built up for further research.

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19 **Ethics and dissemination:** The study is approved by the Ethics Committee of Cancer
20 Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical
21 College (Approval Number 16-171/1250). The findings of the study will be disseminated
22 through scientific peer-reviewed journals and be provided to the public via the study
23 website (<http://www.ncec-china.cn>).

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29 **Trial registration number:** Chinese Clinical Trial Registry (Registration Number
30 ChiCTR-EOC-17010553).

31 32 33 34 35 **Strengths and limitations of this study**

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37 1. NCEC-HRP is a prospective large sample cohort of esophageal cancer screening, which
38 is expected to enroll more than 100,000 subjects from 8 regions in China.
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40 2. It is an open-ended study with broad research aims, comprehensive exposure data
41 collection and long-term follow-up.
- 42
43 3. A serious of standards on esophageal cancer screening and relevant issues will be
44 developed based on the high quality evidence provide by the study.
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46 4. An open and shared research platform linked with epidemiological databases and
47 biobank will be provided to researchers to conduct studies on esophageal cancer and many
48 other diseases.
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50 5 The study lacks of risk factors information from non-responders and the findings are
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4 limited to high risk areas.

5 6 **Introduction**

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8 Esophageal cancer remains a significant source of morbidity and mortality worldwide.
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10 According to GLOBOCAN report, there are an estimated 572,034 new cases and 508,585
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12 cancer deaths in 2018, with three quarters of the cases occurring in developing countries
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14 and approximately a half of all new cases occurring in China.^{1 2} Esophageal cancer has
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16 been the fifth most common cancer and the fourth most common cause of death in China.³
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18 The two main types of esophageal cancer are squamous cell carcinoma (ESCC) and
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20 adenocarcinoma. ESCC accounts for over 90% of all cases of esophageal cancer in China
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22 and causes the majority burden of it.^{4 5}

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24 Although the exact cause of esophageal cancer is unclear, it is considered as the result of a
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26 multiplicity of demographic factors, diet and lifestyle, environmental and genetic factors.
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28 Esophageal cancer is associated with a poor survival rate, which is mainly due to the late
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30 stage at diagnosis. In China, the survival rate of esophageal cancer is less than 10% when
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32 diagnosed at an advanced stage but is as high as 85% if detected at an earlier stage.⁶

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34 Since the 1970s, several screening programs for esophageal cancer have been performed
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36 in the high-risk areas of China and achieved significant effects in the reduction of its
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38 incidence or mortality.⁷⁻¹² However, the difference in screening methods and protocols,
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40 inconsistencies in questionnaires for risk factors investigation, lack of standards for sample
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42 collection and incomplete follow-up information have limited the integration of the results
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44 from previous studies and the sharing of existing resources.

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46 To this end, we have started the NCEC-HRP cohort, a prospective cohort study of
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48 esophageal cancer and precancerous lesions based on high risk population in China. As an
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50 important part of NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP
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52 cohort focus on populations in rural high-incidence ESCC areas. Given the excellent
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54 experience of existing large cohorts such as the All of US Research Program,¹³ UK
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56 Biobank¹⁴ and China Kadoorie Biobank,¹⁵ NCEC-HRP is designed as a platform without
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4 a specific hypothesis, aiming to provide a foundation for future research.

5 The major objectives of NCEC-HRP cohort are: 1) to establish a screening cohort based
6 on high risk population for esophageal cancer; 2) to develop a serious of standards and
7 guidelines for esophageal cancer screening, early diagnosis and treatment, risk factors
8 investigation, sample collection and follow-up; 3) to build up a biobank with database on
9 epidemiology, diagnosis, treatment and follow-up information; 4) to provide researchers
10 with a platform for data sharing and promote communication and cooperation in
11 esophageal cancer research.
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19 **Methods and analysis**

20 **Study design and site selection**

21 NCEC-HRP is a multi-center prospective cohort study on esophageal cancer screening.
22 The study sites were carefully selected based on the following criteria: 1) located at high
23 risk areas for esophageal cancer; 2) representing different economical-geographical
24 regions in China; 3) relative stability of the target population; 4) reliable local
25 infrastructures including quality of existing cancer registry and death reporting systems,
26 experienced doctors on esophageal cancer screening, and availability of technology and
27 equipment for sample collection and storage; 5) long-term local commitment to the project.
28 A total of eight sites are selected as the study centers (Figure1), including Feicheng of
29 Shandong province, Yangzhong of Jiangsu province, Cixian of Hebei province, Linxian
30 and Huaxian of Henan province, Yangcheng of Shanxi province, Yanting of Sichuan
31 province and Chaoshan of Guangdong province.
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45 **Enrollment of participants**

46 All men and women aged 40-69 who are permanently residents in the selected study
47 areas will be identified and invited to participate unless they met the following exclusion
48 criteria: 1) history of cancer or mental disorder; 2) contraindications for endoscopic
49 examinations; 3) inability to provide informed consent. Participants' enrollment began on
50 Jun 1st, 2017 and a total of 100,000 subjects are expected to be enrolled up to December
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4 31th, 2020.

5 **Endoscopic examination and therapy**

6 All endoscopic examinations and therapies are conducted by well-trained doctors at local
7 hospitals. The screening procedure follows the recommendation of expert consensus on
8 early esophageal cancer screening and endoscopic diagnosis and treatment in China.¹⁶

9 Briefly, screened participants are provided a standard upper gastrointestinal endoscopy
10 with iodine staining. The entire esophagus and stomach are visually examined and
11 biopsies are taken from all focal lesions. Two pathologists independently read the biopsy
12 slides without knowledge of the visual endoscopic findings. Discordances in the
13 diagnosis are solved by discussion.

14 If early lesions are histologically diagnosed, participants will be recalled to the clinic, and
15 intervention methods appropriate to the lesions' severity would be used. For esophageal
16 severe dysplasia/carcinoma in situ or intramucosal carcinomas, endoscopic mucosal
17 resection and/or endoscopic submucosal dissection treatments will be used as local
18 therapies. For esophageal cancers, therapies include esophagectomy, radical operation,
19 radiotherapy, and other conventional treatments.

20 **Sample collection**

21 Before endoscopy, blood will be collected into an EDTA containing vacutainer from each
22 participant in the fasting state, and a small sample of this is used for routine test for
23 infectious diseases including HBV, HCV, HIV and syphilis. The remaining blood (no less
24 than 5ml) will be dispensed into four pipes after centrifugation, including two pipes of
25 blood cell and two pipes of plasma. All samples will be stored at -80°C freezer for long-
26 term preservation at each local site. Biopsy specimens are fixed in 10% buffered formalin
27 and embedded in paraffin for storage. Pathological specimens and sections are preserved
28 for patients with pathological examination. For each participate, saliva samples are also
29 collected from the oral cavity by drooling and preserved in PreservCyt solution (Hologic,
30 Bedford, MA, United States) at -70°C for use.

Follow up and re-examination

We combine the active and passive follow-ups to ensure accurate collection of outcome information. For participants diagnosed with esophageal cancer or precancerous lesions during the screening, annual interviews through telephone, home visit or other contact methods will be used to collect the outcome information. Meanwhile, a passive follow-up procedure will be carried out in all participants once a year. We will collect data from local clinical settings, cancer registry system, death surveillance system, as well as medical insurance and claim databases to update the follow-up information. All participants are to be followed for at least a decade. Figure 2 shows the enrollment, screening and follow-up procedure.

Re-examinations are required according to the diagnosis. For patients diagnosed with esophageal mild dysplasia, a re-examination is required in three years, and for those with esophagus moderate dysplasia, an annual re-examination is required. For patients with severe dysplasia or in situ cancer, those who refuse treatment should be followed at least once a year.

Data Collection

Although the cohort is based on esophageal cancer screening population, we plan to use a uniform questionnaire based on the modified China Kadoorie Biobank(CKB) questionnaire to collect the exposure information on various outcomes.¹⁵ CKB is one of the largest cohorts in the world for common chronic diseases, involving more than 0.5 million people in 10 regions of China.¹⁷ Information collected through face-to-face interview will cover a broad range of variables (Table 1), including demographic factors, indicators of socioeconomic status, smoking, alcohol and green tea consumption, diet, indoor air pollution, physical activity, reproductive history (women), sleep status, medical and family history. Blood pressure, heart rate, height, weight are also to be measured.

In consideration of the mental health of screening subjects, we will conduct a pilot survey to investigate the impact of screening detected cancer on participants' psychosocial status.

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4 A series of standardized instruments will be used to assess the patients' psychosocial
5 status from multiple aspects, including GAD-7 (General Anxiety Disorder-7) for anxiety,¹⁸
6 PHQ-9 (Patient Health Questionnaire-9) for depression,¹⁹ CD-RISC (The Connor-
7 Davidson Resilience Scale) for resilience,²⁰ LES (Life Event Scale) for life event stress,²¹
8 PSSS (Perceived Social Support Scale) for social support,²² and SWLS (Satisfaction With
9 Life Scale) for life satisfaction.²³
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15 **Data management**

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17 All information collected is entered using a pad-based direct data entry app developed
18 specifically for the project. The survey system has various built-in functions to avoid
19 missing items and minimize logic errors during the interview. All data will be uploaded
20 and stored to the data management platform at National Cancer Center. The platform is
21 designed to be an open and shared platform for professional research on esophageal cancer
22 and other health related issues. It will not only include data from questionnaires, but also
23 include diagnostic images from endoscopy and pathology, and linked with biobank at each
24 center.
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33 **Outcome assessment**

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35 The NCEC-HRP is an open-ended prospective study with very broad research aims. The
36 primary objectives of the study are to investigate the population distribution of esophageal
37 cancer and precancerous lesions in high risk areas and to evaluate the effects of their risk
38 factors in a range of different circumstances. By storing blood, tissue and saliva samples
39 from a large number of participants, the study will allow reliable assessment on genetic
40 factors and related mechanism research in the future. With re-examination and long-term
41 follow-up, dynamic changes in precancerous lesions can be observed and rare outcomes
42 such as incident and death cases will also be accumulated, allowing us to further explore
43 the transformation and progression of precancerous lesions, which will provide evidence
44 for the management of positive cases and optimization of screening programs.
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54 **Sample size calculation**

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4 According to previous studies, the proportion of precancerous lesions in target screening
5 population in high risk areas is about 20-25%. Within the prospective cohort that expected
6 to enroll 100,000 participants, there will be more than 20,000 cases with precancerous
7 lesions. Assuming the detection rate of precancerous lesions is 20%, to achieve a precision
8 of 2% with an α of 0.05, it would need a sample size of 3252 to have 80% power. Since
9 the sample size of our study is significantly larger, we can safely determine that the study
10 has adequate statistical power. In the exploring of risk factors for precancerous lesions, for
11 a factor of 10% exposure level, we will be able to detect a small effect with an odds ratio
12 of 1.1 and 80% power at the 5% level of significance due to the large sample size.
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21 **Data analysis plan**

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23 We will report summary statistics for baseline variables including demographic,
24 socioeconomic and behavioral characteristics, general health related information and
25 family history. The detection rate and the distribution of esophageal cancer and
26 precancerous lesions in different population characteristics (e.g. age group, gender, site,
27 screening year et al) will be reported. Parametric and nonparametric tests such as t test, χ^2
28 test, Fisher's exact test and Wilcoxon rank sum test will be used for univariate analyses to
29 identify risk factors associated with interested outcomes. Multivariable regression analyses,
30 including linear, logistic, Cox proportional hazard and Poisson models will be used to
31 assess the association between risk factors and outcomes after adjusting for potential
32 confounders. The tests will be two sided and $p < 0.05$ will be considered statistically
33 significant. Data analysis will be undertaken using Stata V14.0 (STATA, College Station,
34 Texas, USA).
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46 **Ethics and dissemination**

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48 The study is approved by the independent ethics committee of National Cancer
49 Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical
50 College (Approval Number 16-171/1250). The transmission, storage and analysis of
51 health-related personal data and the storage of biological samples within this project will
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4 strictly follow the legal requirements for data protection and will be performed under the
5 supervision of the ethics committee. Data protection and confidentiality will be guaranteed.
6
7 The findings of the study will be disseminated through scientific peer-reviewed journals
8 and be provided to the public via the NECE study website (<http://www.ncec-china.cn>). The
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10 NCEC study group is committed to making the cohort data available to the scientific
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12 researchers worldwide to advance knowledge about the causes, prevention and treatment
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14 of esophageal cancer and other diseases. Researchers wishing to undertake additional
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16 analyses based on the resources are invited to contact us for further discussion. More
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18 information on data sharing and application will be published online in the future.
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21 **Discussion**

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23 Strengths of the study include the prospectively collected exposure data, an exceptionally
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25 large sample size and the opportunity to follow all participants through various resources.
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27 Based on the high quality evidence provide by the study, a serious of standards and
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29 guidelines on esophageal cancer screening, early diagnosis and treatment, risk factors
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31 investigation, sample collection and follow-up will be developed, which may be
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33 implemented to other high risk areas, especially in developing countries in Central and East
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35 Asia and Eastern Africa. In addition, a biobank containing blood, tissue and saliva samples
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37 are to be established, which lays the foundation for further exploration on the genetic risk
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39 factors and relevant mechanism of esophageal cancer and other diseases. Finally, as an
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41 open-ended prospective study, the exposure measurements of this study are not only for
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43 esophageal cancer, but also for many chronic diseases. With the linkage between
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45 epidemiological databases and the biobank, NCEC-HRP will provide an open and shared
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47 research platform for researchers worldwide to conduct studies on esophageal cancer and
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49 many other diseases.

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51 A major limitation in this study is the lack of risk factors information from non-attenders
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53 since the investigation is for screening subjects. The questionnaire and sampling method
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55 for non-attenders is still under design. Besides, the study sites are limited to high-incidence
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4 areas, so whether the results are applicable to individuals in low-incidence areas remains
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6 to be verified.

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8 Unlike the ongoing randomized controlled trials aiming at evaluating the efficacy of
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10 esophageal cancer screening,^{24 25} our study focuses on the establishment of databases and
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12 biobank to provide sufficient samples and complete data for subsequent multi-omics
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14 researches. NCEC-HRP is part of the NCEC study and, together with other four cohorts
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16 including standardized diagnosis and treatment of clinical cohort, minimally invasive
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18 treatment of early stage and precancerous lesion cohort, genetic lineage cohort and
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20 prospective cohort based on urban community, will provide a comprehensive research
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22 platform for esophageal cancer and precancerous lesions.
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25 **Acknowledgements** We are grateful to all study centers and their staffs whose hard work
26
27 made this study possible.

28
29 **Contributors** RC, SM, CG and WW: study conception and design; SM and SX:
30
31 questionnaire design; GS, SX and DS: sample collection method; RC and WW: manuscript
32
33 draft; All authors have contributed to research platform design and management and
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35 approved the final manuscript.

36
37 **Funding** This study is supported by the National Key R&D Program of China
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39 (2016YFC0901400).

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41 **Competing interests statement** None declared.

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43 **Patient consent** Obtained.

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45 **Ethics approval** The NCEC study has been approved by the Ethics Committee of Cancer
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47 Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical
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49 College (Approval Number 16-171/1250).

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51 **Word Count** 2788

52 53 54 **References**

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Figure legends

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Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

Figure 2 Enrollment, screening and follow-up procedure

Table legends

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Table 1 Summary of questionnaire data collected in the NCEC-HRP

Category	Example variables
Demographic	gender, race, birthday, address, contact number

information

Socioeconomic information marriage, education, occupation, number of house member, house income, insurance type

Behavioral factors alcohol, smoking, green tea, drinking water, hot food/drinking, pickled food, moldy food, spicy food, nutritional supplement, physical activity

General health related information self-rated health status, current medication, history of cancer, history of digestive disease, history of chronic disease, exposure to indoor air pollution from cooking/heating fuel, exposure to passive smoking, sleep situation

Family history parental age/or age of death, number of siblings, number of children, family history of cancer, family history of chronic disease

Reproductive history (for women) age of first menstrual period, menopause status, history of contraceptive pills use, history of hysterectomy and of ovary/breast surgery

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Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China

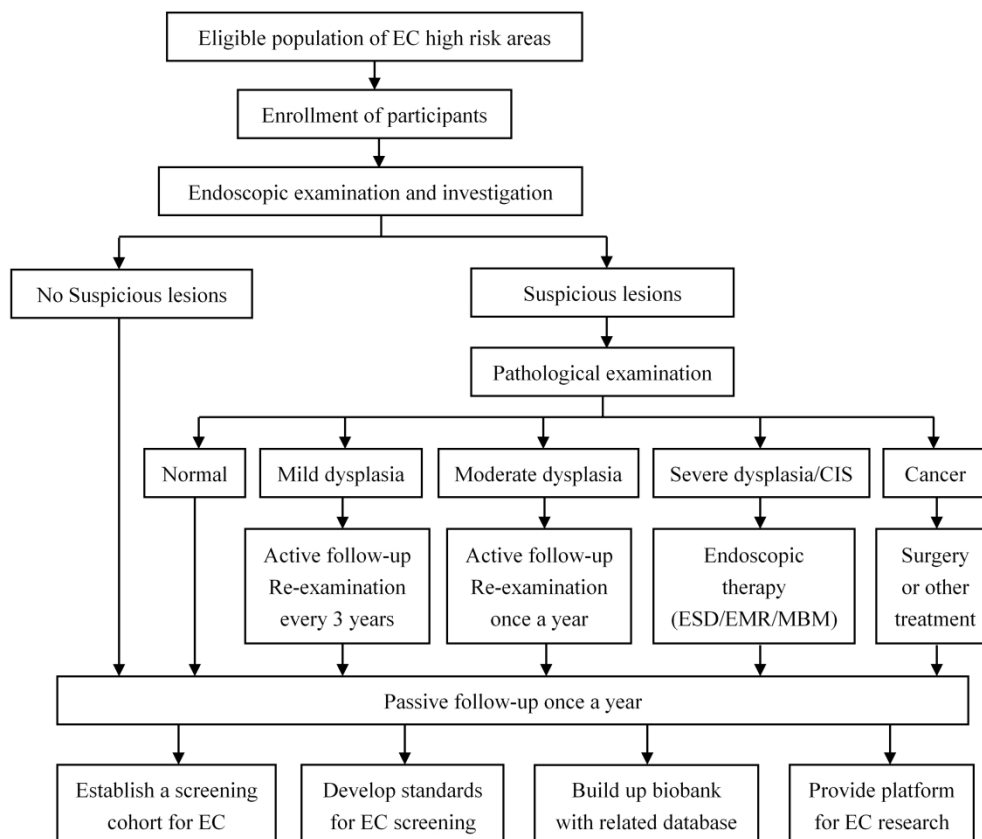


Figure 2 Enrollment, screening and follow-up procedure. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

BMJ Open

The National Cohort of Esophageal Cancer-Prospective Cohort Study of Esophageal Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-HRP): study protocol

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4 The National Cohort of Esophageal Cancer-Pro prospective Cohort Study of Esophageal
5 Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-
6 HRP): study protocol
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39 **Abstract**

40
41 **Introduction:** Esophageal cancer is one of the most common cancers worldwide and
42 about 50% of all new cases occurred in China. Population-based screening has been
43 conducted in high risk areas in China since 1970s, however, the difference in screening
44 methods and protocols, inconsistencies in questionnaires for risk factors investigation,
45 lack of standards for sample collection and incomplete follow-up information have
46 limited the integration of the results from previous studies and the sharing of existing
47 resources.
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55 **Methods and analysis:** NCEC-HRP is a prospective cohort study of esophageal cancer
56 screening based on high risk population in China supported by the National Key R&D
57 Program. Eight areas located at eastern, central and western China representing three
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4 economical-geographical regions are selected as screening centers. All local residents
5 aged 40–69 years in the selected areas are invited to take endoscopic examination and
6 risk factors investigation unless they meet the exclusion criteria. The recruitment began
7 on Jun 2017 and a total of 100,000 participants will be enrolled by Dec 2020 and all
8 subjects are to be followed for a long time. This study is designed to be open-ended and
9 has broad research aims. Summary statistics for baseline information will be reported
10 after the recruitment is completed. We will develop a serious of standards and
11 guidelines for esophageal cancer screening during the study. An open and shared
12 research platform linked with epidemiological databases and biobank will be built up
13 for further research.

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23 **Ethics and dissemination:** The study is approved by the Ethics Committee of Cancer
24 Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union
25 Medical College (Approval Number 16-171/1250). The findings of the study will be
26 disseminated through scientific peer-reviewed journals and be provided to the public
27 via the study website (<http://www.ncec-china.cn>).

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33 **Trial registration number:** Chinese Clinical Trial Registry (Registration Number
34 ChiCTR-EOC-17010553).

35 36 37 38 39 **Strengths and limitations of this study**

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42 1. NCEC-HRP is a prospective large sample cohort of esophageal cancer screening,
43 which is expected to enroll more than 100,000 subjects from 8 regions in China.
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45 2. It is an open-ended study with broad research aims, comprehensive exposure data
46 collection and long-term follow-up.
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48 3. A serious of standards on esophageal cancer screening and relevant issues will be
49 developed based on the high quality evidence provide by the study.
- 50
51 4. An open and shared research platform linked with epidemiological databases and
52 biobank will be provided to researchers to conduct studies on esophageal cancer and
53 many other diseases.
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55 5 The study lacks of risk factors information from non-responders and the findings are
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4 limited to high risk areas.
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6 **Introduction**

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8 Esophageal cancer remains a significant source of morbidity and mortality worldwide.
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10 According to GLOBOCAN report, there are an estimated 572,034 new cases and
11
12 508,585 cancer deaths in 2018, with three quarters of the cases occurring in developing
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14 countries and approximately a half of all new cases occurring in China.^{1 2} Esophageal
15
16 cancer has been the fifth most common cancer and the fourth most common cause of
17
18 death in China.³ The incidence rate and mortality of esophageal cancer were
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20 18.85/100,000 and 14.11/100,000 respectively in China in 2014.³ The two main types
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22 of esophageal cancer are squamous cell carcinoma (ESCC) and adenocarcinoma. ESCC
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24 accounts for over 90% of all cases of esophageal cancer in China and causes the
25
26 majority burden of it.^{4 5}

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28 Although the exact cause of esophageal cancer is unclear, it is considered as the result
29
30 of a multiplicity of demographic factors, diet and lifestyle, environmental and genetic
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32 factors. Esophageal cancer is associated with a poor survival rate, which is mainly due
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34 to the late stage at diagnosis. In China, the survival rate of esophageal cancer is less
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36 than 10% when diagnosed at an advanced stage but is as high as 85% if detected at an
37
38 earlier stage.⁶

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40 Since the 1970s, several screening programs for esophageal cancer have been
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42 performed in the high-risk areas of China and achieved significant effects in the
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44 reduction of its incidence or mortality.⁷⁻¹² For example, Wei et al. reported that the
45
46 endoscopic screening and intervention significantly reduced mortality caused by
47
48 esophageal cancer during 10 year follow-up¹². And there are two ongoing high-quality
49
50 randomized controlled trials in evaluating the efficacy of endoscopic screening for
51
52 esophageal cancer in China.^{13 14} However, the difference in screening methods and
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54 protocols, inconsistencies in questionnaires for risk factors investigation, lack of
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56 standards for sample collection and incomplete follow-up information have limited the
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58 integration of the results from previous studies and the sharing of existing resources.

59 To this end, we have started the NCEC-HRP cohort, a prospective cohort study of
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4 esophageal cancer and precancerous lesions based on high risk population in China. As
5 an important part of NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP
6 cohort focus on populations in rural high-incidence ESCC areas. Given the excellent
7 experience of existing large cohorts such as the All of US Research Program,¹⁵ UK
8 Biobank¹⁶ and China Kadoorie Biobank,¹⁷ NCEC-HRP is designed as a platform
9 without a specific hypothesis, aiming to provide a foundation for future research.

10
11 Unlike previous cohorts or trails aiming at evaluation the efficacy of screening, NCEC
12 is a platform project designed to provide the basis for subsequent research. The major
13 objectives of NCEC-HRP cohort are: 1) to establish a screening cohort based on high
14 risk population for esophageal cancer; 2) to develop a serious of standards and
15 guidelines for esophageal cancer screening, early diagnosis and treatment, risk factors
16 investigation, sample collection and follow-up; 3) to build up a biobank with database
17 on epidemiology, diagnosis, treatment and follow-up information; 4) to provide
18 researchers with a platform for data sharing and promote communication and
19 cooperation in esophageal cancer research. Through standardized processes, NCEC-
20 HRP can take advantage of resource integration, make rational use of samples and data,
21 and provide scientific evidence for prevention and control of esophageal cancer.

32 **Methods and analysis**

33 **Study design and site selection**

34 NCEC-HRP is a multi-center prospective cohort study on esophageal cancer screening.
35 The study sites were carefully selected based on the following criteria: 1) located at
36 high risk areas for esophageal cancer; 2) representing different economical-
37 geographical regions in China; 3) relative stability of the target population; 4) reliable
38 local infrastructures including quality of existing cancer registry and death reporting
39 systems, experienced doctors on esophageal cancer screening, and availability of
40 technology and equipment for sample collection and storage; 5) long-term local
41 commitment to the project.

42 A total of eight sites are selected as the study centers (Figure1), including Feicheng of
43 Shandong province, Yangzhong of Jiangsu province, Cixian of Hebei province, Linxian
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3 and Huaxian of Henan province, Yangcheng of Shanxi province, Yanting of Sichuan
4 province and Chaoshan of Guangdong province. The incidence rates among selected
5 areas ranged between 35.52/100,000 to 81.23/100,000.
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8 9 **Enrollment of participants**

10 All men and women aged 40-69 who are permanently residents in the selected study
11 areas will be identified and invited to participate unless they met the following
12 exclusion criteria: 1) history of cancer or mental disorder; 2) contraindications for
13 endoscopic examinations; 3) inability to provide informed consent. The recruitment is
14 based on the village. While promoting the benefits of screening and early diagnosis,
15 village doctors and local staff will notify all target groups according to household
16 registration to go to designated hospitals for endoscopic examination. Those who are
17 willing to participate in the study will be registered and scheduled for screening. If the
18 hospital is far from the village, the vehicle will be arranged to pick up the participants
19 to ensure the response rate. If the response rate in a village is too low, a second
20 notification and screening will be conducted to ensure that the response rate maintains
21 at a steady rate. Participants' enrollment began on Jun 1st, 2017 and a total of 100,000
22 subjects are expected to be enrolled up to December 31th, 2020.
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36 **Endoscopic examination and therapy**

37 All endoscopic examinations and therapies are conducted by well-trained doctors at
38 local hospitals. The screening procedure follows the recommendation of expert
39 consensus on early esophageal cancer screening and endoscopic diagnosis and
40 treatment in China.¹⁸ Briefly, screened participants are provided a standard upper
41 gastrointestinal endoscopy with iodine staining. The entire esophagus and stomach are
42 visually examined and biopsies are taken from all focal lesions. Two pathologists
43 independently read the biopsy slides without knowledge of the visual endoscopic
44 findings. Discordances in the diagnosis are solved by discussion.
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54 If early lesions are histologically diagnosed, participants will be recalled to the clinic,
55 and intervention methods appropriate to the lesions' severity would be used. For
56 esophageal severe dysplasia/carcinoma in situ or intramucosal carcinomas, endoscopic
57 mucosal resection and/or endoscopic submucosal dissection treatments will be used as
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4 local therapies. For esophageal cancers, therapies include esophagectomy, radical
5 operation, radiotherapy, and other conventional treatments.

6 7 **Sample collection**

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9 Before endoscopy, blood will be collected into an EDTA containing vacutainer from
10 each participant in the fasting state, and a small sample of this is used for routine test
11 for infectious diseases including HBV, HCV, HIV and syphilis. The remaining blood
12 (no less than 5ml) will be dispensed into four pipes after centrifugation, including two
13 pipes of blood cell and two pipes of plasma. All samples will be stored at -80°C freezer
14 for long-term preservation at each local site. Biopsy specimens are fixed in 10%
15 buffered formalin and embedded in paraffin for storage. Pathological specimens and
16 sections are preserved for patients with pathological examination. For each participate,
17 saliva samples are also collected from the oral cavity by drooling and preserved in
18 PreservCyt solution (Hologic, Bedford, MA, United States) at -70°C for use.

19 20 **Follow up and re-examination**

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22 We combine the active and passive follow-ups to ensure accurate collection of
23 outcome information. For participants diagnosed with esophageal cancer or
24 precancerous lesions during the screening, annual interviews through telephone, home
25 visit or other contact methods will be used to collect the outcome information.

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27 Meanwhile, a passive follow-up procedure will be carried out in all participants once
28 a year. We will collect data from local clinical settings, cancer registry system, death
29 surveillance system, as well as medical insurance and claim databases to update the
30 follow-up information. All participants are to be followed for at least a decade. Figure
31 2 shows the enrollment, screening and follow-up procedure.

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33 Re-examinations are required according to the diagnosis. For patients diagnosed with
34 esophageal mild dysplasia, a re-examination is required in three years, and for those
35 with esophagus moderate dysplasia, an annual re-examination is required. For patients
36 with severe dysplasia or in situ cancer, those who refuse treatment should be followed
37 at least once a year.

38 39 **Data Collection**

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41 Although the cohort is based on esophageal cancer screening population, we plan to use
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4 a uniform questionnaire based on the modified China Kadoorie Biobank(CKB)
5 questionnaire to collect the exposure information on various outcomes.¹⁷ CKB is one
6 of the largest cohorts in the world for common chronic diseases, involving more than
7 0.5 million people in 10 regions of China.¹⁹ Information collected through face-to-face
8 interview will cover a broad range of variables (Table 1), including demographic factors,
9 indicators of socioeconomic status, smoking, alcohol and green tea consumption, diet,
10 indoor air pollution, physical activity, reproductive history (women), sleep status,
11 medical and family history. We have also developed some specific questionnaire based
12 on the characteristics of esophageal cancer, such as the history of digestive diseases,
13 family history of cancer, drinking water, dietary habits (hot food, softness of food,
14 eating speed), and oral hygiene and so on. Blood pressure, heart rate, height, weight are
15 also to be measured.

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27 In consideration of the mental health of screening subjects, we will conduct a pilot
28 survey to investigate the impact of screening detected cancer on participants'
29 psychosocial status. A series of standardized instruments will be used to assess the
30 patients' psychosocial status from multiple aspects, including GAD-7(General Anxiety
31 Disorder-7) for anxiety,²⁰ PHQ-9(Patient Health Questionnaire-9) for depression,²¹
32 CD-RISC (The Connor-Davidson Resilience Scale) for resilience,²² LES (Life Event
33 Scale) for life event stress,²³ PSSS (Perceived Social Support Scale) for social
34 support,²⁴ and SWLS (Satisfaction With Life Scale) for life satisfaction.²⁵

42 **Data management**

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44 All information collected is entered using a pad-based direct data entry app developed
45 specifically for the project. The survey system has various built-in functions to avoid
46 missing items and minimize logic errors during the interview. All data will be uploaded
47 and stored to the data management platform at National Cancer Center. The platform
48 is designed to be an open and shared platform for professional research on esophageal
49 cancer and other health related issues. It will not only include data from questionnaires,
50 but also include diagnostic images from endoscopy and pathology, and linked with
51 biobank at each center.

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60 We treated all data as protected health information and stored it securely in an encrypted

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4 and password protected database at the management center. The raw data is backed up
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6 in both the pad-based survey system and the platform servers built for the study. The
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8 collection, shipping and receipt of data carriers were tracked by the management center.

9 10 **Outcome assessment**

11 The NCEC-HRP is an open-ended prospective study with very broad research aims.
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13 The primary objectives of the study are to investigate the population distribution of
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15 esophageal cancer and precancerous lesions in high risk areas and to evaluate the effects
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17 of their risk factors in a range of different circumstances. By storing blood, tissue and
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19 saliva samples from a large number of participants, the study will allow reliable
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21 assessment on genetic factors and related mechanism research in the future. With re-
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23 examination and long-term follow-up, dynamic changes in precancerous lesions can be
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25 observed and rare outcomes such as incident and death cases will also be accumulated,
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27 allowing us to further explore the transformation and progression of precancerous
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29 lesions, which will provide evidence for the management of positive cases and
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31 optimization of screening programs.

32 33 **Quality control**

34 All investigators in the study are trained and assessed for consistency by investigating
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36 the same object with an experienced investigator. Ten percent of the participants will
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38 be randomly selected from the same village with repeat questionnaire and measures on
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40 selected items for quality control. During the course of the survey, the management
41
42 center will regular monitor the recruitment rate, the distribution of certain key variables
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44 and the sample collection through the system.

45 46 47 **Sample size calculation**

48 According to previous studies, the proportion of precancerous lesions in target
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50 screening population in high risk areas is about 20-25%. Within the prospective cohort
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52 that expected to enroll 100,000 participants, there will be more than 20,000 cases with
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54 precancerous lesions. Assuming the detection rate of precancerous lesions is 20%, to
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56 achieve a precision of 2% with an α of 0.05, it would need a sample size of 3252 to
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58 have 80% power. Since the sample size of our study is significantly larger, it will has
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60 adequate statistical power for all type of precancerous lesions. In the exploring of risk

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3 factors for precancerous lesions, for a factor of 10% exposure level, we will be able to
4 detect a small effect with an odds ratio of 1.1 and 80% power at the 5% level of
5 significance due to the large sample size.
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8 9 **Data analysis plan**

10 We will report summary statistics for baseline variables including demographic,
11 socioeconomic and behavioral characteristics, general health related information and
12 family history. The detection rate and the distribution of esophageal cancer and
13 precancerous lesions in different population characteristics (e.g. age group, gender, site,
14 screening year et al) will be reported. Parametric and nonparametric tests such as t test,
15 χ^2 test, Fisher's exact test and Wilcoxon rank sum test will be used for univariate
16 analyses to identify risk factors associated with interested outcomes. Multivariable
17 regression analyses, including linear, logistic, Cox proportional hazard and Poisson
18 models will be used to assess the association between risk factors and outcomes after
19 adjusting for potential confounders. The tests will be two sided and $p < 0.05$ will be
20 considered statistically significant. Data analysis will be undertaken using Stata V14.0
21 (STATA, College Station, Texas, USA).
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35 **Ethics and dissemination**

36 The study is approved by the independent ethics committee of National Cancer
37 Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union
38 Medical College (Approval Number 16-171/1250). The transmission, storage and
39 analysis of health-related personal data and the storage of biological samples within
40 this project will strictly follow the legal requirements for data protection and will be
41 performed under the supervision of the ethics committee. Data protection and
42 confidentiality will be guaranteed.
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50 The findings of the study will be disseminated through scientific peer-reviewed journals
51 and be provided to the public via the NECE study website (<http://www.ncec-china.cn>).
52 The NCEC study group is committed to making the cohort data available to the
53 scientific researchers worldwide to advance knowledge about the causes, prevention
54 and treatment of esophageal cancer and other diseases. Researchers wishing to
55 undertake additional analyses based on the resources are invited to contact us for further
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4 discussion. More information on data sharing and application will be published online
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6 in the future.

7 **Patient and Public Involvement**

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9 The protocol of this study was discussed and developed by a multidisciplinary team of
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11 experts including epidemiologists, clinicians, statisticians, and computer engineers as
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13 well as field investigators, but no patients or public were involved in the design phase.
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15 **Discussion**

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17 Strengths of the study include the prospectively collected exposure data, an
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19 exceptionally large sample size and the opportunity to follow all participants through
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21 various resources. Based on the high quality evidence provide by the study, a serious
22
23 of standards and guidelines on esophageal cancer screening, early diagnosis and
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25 treatment, risk factors investigation, sample collection and follow-up will be developed,
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27 which may be implemented to other high risk areas, especially in developing countries
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29 in Central and East Asia and Eastern Africa. In addition, a biobank containing blood,
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31 tissue and saliva samples are to be established, which lays the foundation for further
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33 exploration on the genetic risk factors and relevant mechanism of esophageal cancer
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35 and other diseases. Finally, as an open-ended prospective study, the exposure
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37 measurements of this study are not only for esophageal cancer, but also for many
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39 chronic diseases. With the linkage between epidemiological databases and the biobank,
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41 NCEC-HRP will provide an open and shared research platform for researchers
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43 worldwide to conduct studies on esophageal cancer and many other diseases.

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45 A major limitation in this study is the lack of risk factors information from non-
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47 attenders since the investigation is for screening subjects. The questionnaire and
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49 sampling method for non-attenders is still under design. Even though we can also obtain
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51 the baseline and outcome information of non-participants by referring to various data
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53 sources to ensure the feasibility of the research and the accuracy of the research results.
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55 Besides, the study sites are limited to high-incidence areas, so whether the results are
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57 applicable to individuals in low-incidence areas remains to be verified.

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59 Although the existing cohorts and ongoing trials may bring new insights into
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61 esophageal cancer, the lack of standardization and sharing will limit the promotion and

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4 application of results. Therefore, there is an urgent need for a large cohort to be
5 established with uniform standards on esophageal cancer screening, early diagnosis and
6 treatment, risk factors investigation, sample collection and follow-up. This study
7 focuses on the establishment of databases and biobank to provide sufficient samples
8 and complete data for subsequent multi-omics researches. With large sample size and
9 long-term follow-up, we can have a more comprehensive understanding of the
10 epidemiology of esophageal cancer and precancerous lesions, including the incidence
11 and mortality, risk factors, progress and survival et al. NCEC-HRP is part of the NCEC
12 study and, together with other four cohorts including standardized diagnosis and
13 treatment of clinical cohort, minimally invasive treatment of early stage and
14 precancerous lesion cohort, genetic lineage cohort and prospective cohort based on
15 urban community, will provide a comprehensive research platform for esophageal
16 cancer and precancerous lesions.
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31 **Acknowledgements** We are grateful to all study centers and their staffs whose hard
32 work made this study possible.
33

34 **Contributors** Ru Chen, Shanrui Ma, Chentao Guan and Wenqiang Wei: study
35 conception and design; Shanrui Ma: questionnaire for psychosocial status; Shuanghua
36 Xie: questionnaire for baseline risk factors investigation; Guohui Song: biobank
37 establishment; Guohui Song, Shuanghua Xie and Dantong Shao: sample collection
38 method; Chentao Guan, Qing Ma and Meng Wang: screening procedure; Ru Chen: data
39 management and analysis; Xinqing Li: quality control; Ru Chen and Wenqiang Wei:
40 manuscript draft. All authors have contributed to research platform design and
41 management and approved the final manuscript.
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51 (2016YFC0901400).
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54 **Competing interests statement** None declared.
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56 **Patient consent** Obtained.
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58 **Ethics approval** The NCEC study has been approved by the Ethics Committee of
59 Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking
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4 Union Medical College (Approval Number 16-171/1250).

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6 **Word Count 2788**

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Figure legends

Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

Figure 2 Enrollment, screening and follow-up procedure

Table legends

Table 1 Summary of questionnaire data collected in the NCEC-HRP

Category	Example variables
Demographic	gender, race, birthday, address, contact number

1	information	
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4	Socioeconomic	marriage, education, occupation, number of house member,
5	information	house income, insurance type
6		
7	Behavioral factors	alcohol, smoking, green tea, drinking water, hot
8		food/drinking, pickled food, moldy food, spicy food,
9		nutritional supplement, physical activity
10		
11	General health	self-rated health status, current medication, history of cancer,
12	related information	history of digestive disease, history of chronic disease,
13		exposure to indoor air pollution from cooking/heating fuel,
14		exposure to passive smoking, sleep situation
15		
16	Family history	parental age/or age of death, number of siblings, number of
17		children, family history of cancer, family history of chronic
18		disease
19		
20	Reproductive history	age of first menstrual period, menopause status, history of
21	(for women)	contraceptive pills use, history of hysterectomy and of
22		ovary/breast surgery



Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China

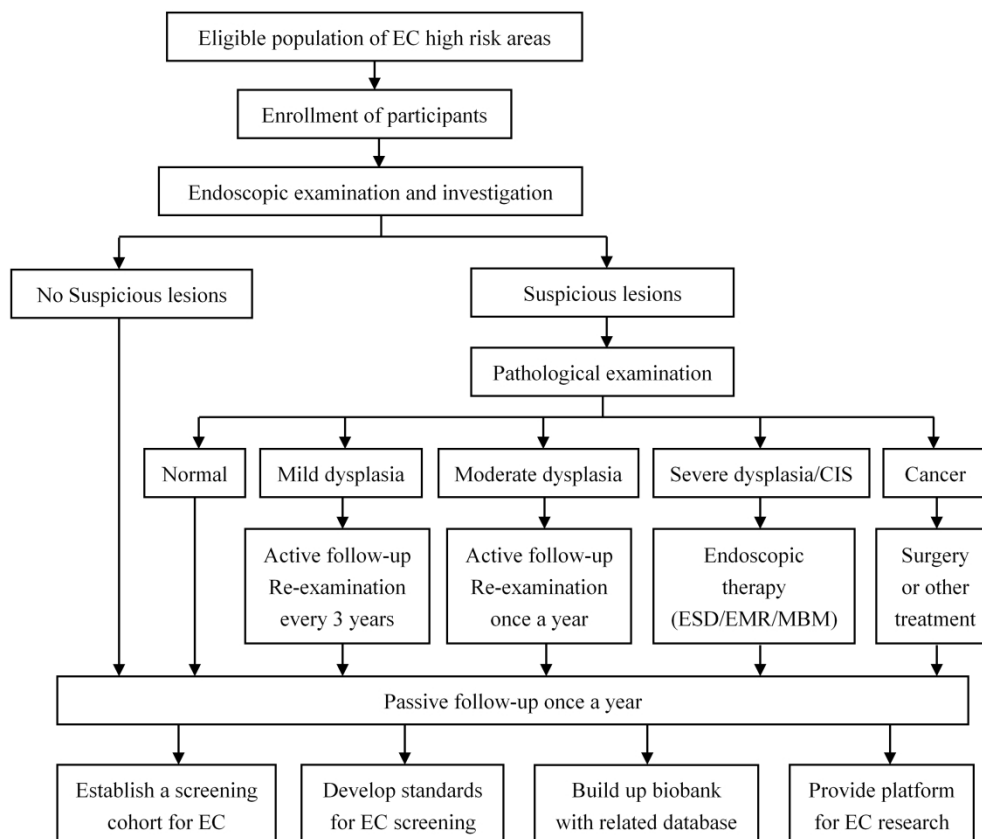


Figure 2 Enrollment, screening and follow-up procedure. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

BMJ Open

The National Cohort of Esophageal Cancer-Prospective Cohort Study of Esophageal Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-HRP): study protocol

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology
Keywords:	Epidemiology < ONCOLOGY, EPIDEMIOLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

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4 The National Cohort of Esophageal Cancer-Prospective Cohort Study of Esophageal
5 Cancer and Precancerous Lesions based on High Risk Population in China(NCEC-
6 HRP): study protocol
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39 **Abstract**

40
41 **Introduction:** Esophageal cancer is one of the most common cancers worldwide and
42 about 50% of all new cases occurred in China. Population-based screening has been
43 conducted in high risk areas in China since 1970s, however, a few factors have limited
44 the integration of the results from previous studies and the sharing of existing resources,
45 such as the difference in screening methods and protocols, inconsistencies in
46 questionnaires for risk factors investigation, lack of standards for sample collection and
47 incomplete follow-up information.
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54 **Methods and analysis:** NCEC-HRP is a prospective cohort study of esophageal cancer
55 screening based on high risk population in China supported by the National Key R&D
56 Program. Eight areas located at eastern, central and western China are selected as
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4 screening centers to represent three economical-geographical regions. All local
5 residents aged 40–69 years in the selected areas are invited to take endoscopic
6 examination and risk factors investigation unless they meet the exclusion criteria. The
7 recruitment began on Jun 2017 and a total of 100,000 participants will be enrolled by
8 Dec 2020 and all subjects will be followed for a long time. This study is designed as
9 open-ended and has broad research aims. Summary statistics for baseline information
10 will be reported after the completion of recruitment. We will develop a serious of
11 standards and guidelines for esophageal cancer screening during the study. An open
12 and shared research platform linked with epidemiological databases and biobank will
13 be built up for further research.

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23 **Ethics and dissemination:** The study is approved by the Ethics Committee of Cancer
24 Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union
25 Medical College (Approval Number 16-171/1250). The findings of the study will be
26 disseminated through scientific peer-reviewed journals as well as the public via the
27 study website (<http://www.ncec-china.cn>).

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33 **Trial registration number:** Chinese Clinical Trial Registry (Registration Number
34 ChiCTR-EOC-17010553).

35 36 37 38 39 **Strengths and limitations of this study**

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41 1. NCEC-HRP is a prospective cohort of esophageal cancer screening with large sample
42 size, which is expected to enroll more than 100,000 subjects from 8 regions in China.
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44 2. It is an open-ended study with broad research aims, comprehensive exposure data
45 collection and long-term follow-up.
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47 3. A serious of standards on esophageal cancer screening and relevant issues will be
48 developed based on the high quality evidence provided by this study.
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50 4. An open and shared research platform linked with epidemiological databases and
51 biobank will be offered to researchers to conduct studies on esophageal cancer and
52 many other diseases.
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54 5 The study lacks of risk factors information from non-responders and the findings are
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4 limited to high risk areas in China.

5 6 **Introduction**

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8 Esophageal cancer remains a significant source of morbidity and mortality worldwide.
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10 According to GLOBOCAN report, there are an estimated 572,034 new cases and
11
12 508,585 cancer deaths in 2018, with approximately a half of all new cases occurring in
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14 China.^{1,2} Esophageal cancer has been the fifth most common cancer and the fourth most
15
16 common cause of death in China.³ The incidence rate and mortality of esophageal
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18 cancer were 18.85/100,000 and 14.11/100,000 respectively in China in 2014.³ The two
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20 main types of esophageal cancer are squamous cell carcinoma (ESCC) and
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22 adenocarcinoma, with ESCC accounting for over 90% of all cases of esophageal cancer
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24 in^{4,5}

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26 Although the exact cause of esophageal cancer is unclear, it is considered as the result
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28 of a multiplicity of demographic factors, diet and lifestyle, environmental and genetic
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30 factors. Esophageal cancer has a poor survival rate mainly result from the late stage at
31
32 diagnosis. In China, its survival rate is less than 10% if diagnosed at an advanced stage
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34 but is as high as 85% if detected at an earlier stage.⁶

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36 Since the 1970s, several screening programs for esophageal cancer have been
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38 conducted in the high-risk areas of China and achieved significant effects in the
39
40 reduction of its incidence or mortality.⁷⁻¹² For example, Wei et al. reported that the
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42 endoscopic screening and intervention significantly reduced mortality caused by
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44 esophageal cancer during 10 year follow-up¹². Two more high-quality randomized
45
46 controlled trials are ongoing to evaluate the efficacy of endoscopic screening for
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48 esophageal cancer in China.^{13,14} However, a few factors have limited the integration of
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50 the results from previous studies and the sharing of existing resources, such as the
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52 difference in screening methods and protocols, inconsistencies in questionnaires for
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54 risk factors investigation, lack of standards for sample collection and incomplete
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56 follow-up information.

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58 To this end, we started the National Cohort of Esophageal Cancer-Pro prospective Cohort
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60 Study of Esophageal Cancer and Precancerous Lesions based on High Risk Population

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4 in China(NCEC-HRP) cohort, a prospective cohort study of esophageal cancer and
5 precancerous lesions based on high risk population in China. As an important part of
6 NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP cohort focuses on
7 populations in rural areas with high-incidence of ESCC. Learning from existing large
8 cohorts such as the All of US Research Program,¹⁵ UK Biobank¹⁶ and China Kadoorie
9 Biobank,¹⁷ NCEC-HRP is designed as a platform without a specific hypothesis in order
10 to facilitate future research.

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17 The major objectives of NCEC-HRP cohort are: 1) to establish a screening cohort based
18 on high risk population for esophageal cancer; 2) to develop a series of standards and
19 guidelines for esophageal cancer screening, early diagnosis and treatment, risk factors
20 investigation, sample collection and follow-up; 3) to build up a biobank with database
21 on epidemiology, diagnosis, treatment and follow-up information; 4) to provide
22 researchers with a platform for data sharing and promote communication and
23 cooperation in esophageal cancer research. Through standardized processes, NCEC-
24 HRP could take advantage of resource integration, make rational use of samples and
25 data, and provide scientific evidence for prevention and control of esophageal cancer.

35 **Methods and analysis**

36 **Study design and site selection**

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38 NCEC-HRP is a multi-center prospective cohort about esophageal cancer screening.
39 The study sites were carefully selected with the following criteria: 1) located at high
40 risk areas for esophageal cancer; 2) representing different economical-geographical
41 regions in China; 3) relative stability of the target population; 4) reliable local
42 infrastructures including quality of existing cancer registry and death reporting systems,
43 experienced doctors on esophageal cancer screening, and availability of technology and
44 equipment for sample collection and storage; 5) long-term local commitment to the
45 project.

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55 A total of eight sites are selected as the study centers (Figure1), including Feicheng of
56 Shandong province, Yangzhong of Jiangsu province, Cixian of Hebei province, Linxian
57 and Huaxian of Henan province, Yangcheng of Shanxi province, Yanting of Sichuan
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4 province and Chaoshan of Guangdong province. The incidence rates among selected
5 areas ranged from 35.52/100,000 to 81.23/100,000.

6 7 **Enrollment of participants**

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9 All men and women aged 40-69 who are permanently residents in the selected study
10 sites will be identified and invited to participate unless they met the following
11 exclusion criteria: 1) history of cancer or mental disorder; 2) contraindications for
12 endoscopic examinations; 3) inability to provide informed consent. The recruitment is
13 conducted village by village. While propagandizing the benefits of screening and
14 early diagnosis, village doctors and local staff will also notify all target groups to go
15 to designated hospitals for endoscopic examination. Those who are willing to do will
16 be registered and scheduled for screening. If the hospital is far from the village, the
17 vehicle will be arranged to pick up the participants to ensure the response rate. If the
18 response rate of a village is too low (under 30%), a second mobilization will be
19 conducted to improve response rate. Participants' enrollment began on Jun 1st, 2017
20 and a total of 100,000 subjects are expected to be included up to December 31th,
21 2020.

22 23 **Endoscopic examination and therapy**

24 All endoscopic examinations and therapies are conducted by well-trained doctors at
25 local hospitals. The screening procedure follows the recommendation of expert
26 consensus on early esophageal cancer screening and endoscopic diagnosis and
27 treatment in China.¹⁸ Briefly, screened participants are provided a standard upper
28 gastrointestinal endoscopy with iodine staining. The entire esophagus and stomach are
29 visually examined and biopsies are taken from all focal lesions. Two pathologists
30 independently read the biopsy slides without knowledge of the visual endoscopic
31 findings. Discordances in the diagnosis are solved by discussion.

32
33 If early lesions are histologically diagnosed, participants will be recalled to the clinic,
34 and intervention methods appropriate to the lesions' severity would be used. For
35 esophageal severe dysplasia/carcinoma in situ or intramucosal carcinomas, endoscopic
36 mucosal resection and/or endoscopic submucosal dissection treatments will be used as
37 local therapies. For esophageal cancers, therapies include esophagectomy, radical

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4 operation, radiotherapy, and other conventional treatments.

5 6 **Sample collection**

7 Before endoscopy, blood will be collected into an EDTA containing vacutainer from
8 each participant in the fasting state. A small portion is used for routine test for infectious
9 diseases including HBV, HCV, HIV and syphilis, while the remaining (no less than 5ml)
10 will be dispensed into four pipes after centrifugation, including two pipes of blood cell
11 and two pipes of plasma. All samples will be stored at -80°C freezer for long-term
12 preservation at each local site. Biopsy specimens are fixed in 10% buffered formalin
13 and embedded in paraffin for storage. Pathological specimens and sections are
14 preserved for patients with pathological examination. For each participate, saliva
15 samples are also collected from the oral cavity by drooling and preserved in PreservCyt
16 solution (Hologic, Bedford, MA, United States) at -70°C for use.

17 18 **Follow up and re-examination**

19 We combine the active and passive follow-ups to accurately collect outcome
20 information. For participants diagnosed with esophageal cancer or precancerous
21 lesions during the screening, annual interviews will be used to collect the outcome
22 information through telephone, home visit or other contact methods. Meanwhile, a
23 passive follow-up procedure will be carried out for all participants once a year. We
24 will also collect additional data from local clinical settings, cancer registry system,
25 death surveillance system, as well as medical insurance and claim databases to update
26 the follow-up information. All participants will be followed for at least a decade.

27 Figure 2 shows the enrollment, screening and follow-up procedure.

28 Re-examinations are required according to the diagnosis. For patients diagnosed with
29 esophageal mild dysplasia, a re-examination is required in three years, and for those
30 with esophagus moderate dysplasia, an annual re-examination is required. For patients
31 with severe dysplasia or in situ cancer, those who refuse treatment should be followed
32 at least once a year.

33 34 **Data Collection**

35 Although the cohort is based on esophageal cancer screening population, we plan to use
36 a uniform questionnaire based on the modified China Kadoorie Biobank (CKB)
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questionnaire to collect various exposure information,¹⁷ because that CKB is one of the largest cohorts in the world for common chronic diseases, involving more than 0.5 million people in 10 regions of China.¹⁹ Information collected through face-to-face interview will cover a broad range of variables (Table 1), including demographic factors, indicators of socioeconomic status, smoking, alcohol and green tea consumption, diet, indoor air pollution, physical activity, reproductive history (women), sleep status, medical and family history. Some specific questionnaire were also developed according to the characteristics of esophageal cancer, such as the history of digestive diseases, family history of cancer, drinking water, dietary habits (hot food, softness of food, eating speed), and oral hygiene. Blood pressure, heart rate, height, weight will also be measured.

In consideration of the mental health of screening subjects, we will conduct a pilot survey to investigate the impact of screening detected cancer on participants' psychosocial status. A series of standardized instruments will be used to assess the patients' psychosocial status from multiple aspects, including GAD-7 (General Anxiety Disorder-7) for anxiety,²⁰ PHQ-9 (Patient Health Questionnaire-9) for depression,²¹ CD-RISC (The Connor-Davidson Resilience Scale) for resilience,²² LES (Life Event Scale) for life event stress,²³ PSSS (Perceived Social Support Scale) for social support,²⁴ and SWLS (Satisfaction With Life Scale) for life satisfaction.²⁵

Data management

All information collected is entered using a pad-based direct data entry app that was developed specifically for the project. The survey system has various built-in functions to avoid missing items and minimize logic errors during the interview. All data will be uploaded and stored into the data management platform at National Cancer Center. We aimed to design an open platform for professional research on esophageal cancer and other health related issues. The shared information contain data from questionnaires, diagnostic images from endoscopy and pathology, and biobank information.

We treated all data as protected health information and stored it securely as an encrypted and password protected database at the management center. The raw data is backed up in both the pad-based survey system and the specific platform servers. The

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4 collection, shipping and receipt of data carriers were tracked by the management center.

5 **Outcome assessment**

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7 The primary objectives are to investigate the population distribution of esophageal
8 cancer and precancerous lesions in high risk areas and to evaluate the effects of risk
9 factors in a range of different circumstances. By storing blood, tissue and saliva samples,
10 the study will facilitate reliable assessment on genetic factors and related mechanism
11 research. With re-examination and long-term follow-up, dynamic changes in
12 precancerous lesions can be observed and rare outcomes such as incident and death
13 cases will also be accumulated, allowing us to further explore the transformation and
14 progression of precancerous lesions. This will offer evidence for managing positive
15 cases and optimizing screening programs.
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25 **Quality control**

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27 All investigators in the study are trained and assessed for consistency by investigating
28 the same object with an experienced investigator. Ten percent of the participants will
29 be randomly selected from the same village with repeat questionnaire and measures on
30 selected items for quality control. During survey, the management center will regular
31 monitor the recruitment rate, the distribution of certain key variables and the sample
32 collection through the system. The key quality assurance and quality control procedures
33 in the study is summarized in supplementary table 1.
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41 **Sample size calculation**

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43 According to previous studies, the proportion of precancerous lesions in target
44 screening population in high risk areas is about 20-25%. Within the prospective cohort
45 that expected to enroll 100,000 participants, there will be more than 20,000 cases with
46 precancerous lesions. Assuming the detection rate of precancerous lesions is 20%, to
47 achieve a precision of 2% with an α of 0.05, it would need a sample size of 3252 to
48 achieve a power of 80% Therefore, we will has adequate power for all type of
49 precancerous lesions. In the exploring of risk factors for precancerous lesions, for a
50 factor of 10% exposure level, we could also detect a quite small effect (odds ratio of
51 1.1)with 80% power at the 5% level of significance.
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Data analysis plan

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4 First, we will present summary statistics for baseline variables including demographic,
5 socioeconomic and behavioral characteristics, general health related information and
6 family history. Senconde, the detection rate and the distribution of esophageal cancer
7 and precancerous lesions among different population characteristics (e.g. age group,
8 gender, site, screening year et al) will be reported. Third, parametric and nonparametric
9 tests such as t test, χ^2 test, Fisher's exact test and Wilcoxon rank sum test will be applied
10 for univariate analyses to identify risk factors associated with interested outcomes.
11 Fourth, multivariable regression analyses, including linear, logistic, Cox proportional
12 hazard and Poisson models will be selected as appropriate to assess the association
13 between risk factors and outcomes with adjustment for potential confounders. The tests
14 will be two sided and $p < 0.05$ will be considered statistically significant. Data analysis
15 will be undertaken using Stata V14.0 (STATA, College Station, Texas, USA).

26 **Ethics and dissemination**

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29 The study is approved by the independent ethics committee of National Cancer
30 Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union
31 Medical College (Approval Number 16-171/1250). The transmission, storage and
32 analysis of health-related personal data and the storage of biological samples within
33 this project will strictly follow the legal requirements for data protection under the
34 supervision of the ethics committee. Data protection and confidentiality will be
35 guaranteed.

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37 The findings of the study will be disseminated through scientific peer-reviewed journals
38 as well as the public via the NECE study website (<http://www.ncec-china.cn>). The
39 NECE study group is committed to making the cohort data available to the scientific
40 researchers worldwide to produce advance knowledge about the causes, prevention and
41 treatment of esophageal cancer and other diseases. Researchers with related interests
42 are invited to contact us for further discussion. More information on data sharing and
43 application will be published online in the future.

54 **Patient and Public Involvement**

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57 The protocol of this study was discussed and developed by a multidisciplinary team of
58 experts including epidemiologists, clinicians, statisticians, and computer engineers as
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4 well as field investigators, but no patients or public were involved in the design phase.

5 **Discussion**

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7 Strengths of the study include the prospectively collected exposure data, an
8 exceptionally large sample size and the opportunity to follow all participants through
9 various resources. Based on the high quality evidence provide by the study, we would
10 also develop a serious of standards and guidelines on esophageal cancer screening, early
11 diagnosis and treatment, risk factors investigation, sample collection and follow-up.
12 Those achievements might be implemented to other high risk areas, especially in
13 developing countries in Central and East Asia and Eastern Africa. In addition, the
14 biobank with blood, tissue and saliva will lay the foundation for further exploration on
15 the genetic risk factors and relevant mechanism of esophageal cancer and other diseases.
16 Finally, as an open-ended prospective study, the exposure measurements are not only
17 designed for esophageal cancer, but also for many other chronic diseases. Through
18 linking epidemiological databases tothe biobank, NCEC-HRP will also provide an open
19 and shared research platform for researchers worldwide to conduct studies on
20 esophageal cancer and many other diseases.
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34 A major limitation in this study is the lack of risk factors information from non-
35 attenders. However, a questionnaire and sampling method for non-attenders is already
36 under design. We also try to obtain the baseline and outcome information of non-
37 participants by referring to various date sources to improve the accuracy of the research
38 results from multiple aspects. Second, our cohort are limited to high-incidence areas,
39 which might affect its extrapolation in low-incidence areas.
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46 The preexisting cohorts and ongoing trials bring new insights into esophageal cancer,
47 however, the lack of standardization and sharing limit the popularization and
48 application of results. A large cohort is urgently needed which should own uniform
49 standards on esophageal cancer screening, early diagnosis and treatment, risk factors
50 investigation, sample collection and follow-up. Our cohort is aimed to establish
51 databases and biobank in order to offer sufficient samples and complete data for
52 subsequent multi-omics researches. With large sample size and long-term follow-up,
53 we could achieve a more comprehensive understanding of the epidemiology of
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4 esophageal cancer and precancerous lesions, including the incidence and mortality, risk
5 factors, progress and survival et al. NCEC-HRP is part of the NCEC study and, together
6 with other four cohorts including standardized diagnosis and treatment of clinical
7 cohort, minimally invasive treatment of early stage and precancerous lesion cohort,
8 genetic lineage cohort and prospective cohort based on urban community, will construct
9 a comprehensive research platform for esophageal cancer and precancerous lesions.
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21 **Contributors** Ru Chen, Shanrui Ma, Chentao Guan and Wenqiang Wei: study
22 conception and design; Shanrui Ma: questionnaire for psychosocial status; Shuanghua
23 Xie: questionnaire for baseline risk factors investigation; Guohui Song: biobank
24 establishment; Guohui Song, Shuanghua Xie and Dantong Shao: sample collection
25 method; Chentao Guan, Qing Ma and Meng Wang: screening procedure; Ru Chen: data
26 management and analysis; Xinqing Li: quality control; Ru Chen and Wenqiang Wei:
27 manuscript draft. All authors have contributed to research platform design and
28 management and approved the final manuscript.
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44 **Competing interests statement** None declared.
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46 **Patient consent** Obtained.
47

48 **Ethics approval** The NCEC study has been approved by the Ethics Committee of
49 Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking
50 Union Medical College (Approval Number 16-171/1250).
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54 **Word Count** 2788
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58 **References**
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Figure legends

Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

Figure 2 Enrollment, screening and follow-up procedure

Table legends

Table 1 Summary of questionnaire data collected in the NCEC-HRP

Category	Example variables
Demographic information	gender, race, birthday, address, contact number
Socioeconomic information	marriage, education, occupation, number of house member, house income, insurance type
Behavioral factors	alcohol, smoking, green tea, drinking water, consumption of

		certain food (fresh vegetables, meat/poultry, fish/sea food,
		egg, soybean, dairy products, beverages, pickled food, moldy
		food, spicy food), dietary habits (hot food, softness of food,
		eating speed), nutritional supplement, physical activity
General	health	self-rated health status (self-reported health status, oral
related information		hygiene, history of trauma, history of cancer and related
		therapy, history of digestive disease, <i>Helicobacter pylori</i>
		infection status, history of chronic disease), current
		medication(non-steroidal anti-inflammatory drugs, steroidal
		anti-inflammatory drugs, acid inhibitor, antibiotics),
		exposure to indoor air pollution from cooking/heating fuel,
		exposure to passive smoking, sleep situation
Family history		parental age/or age of death, number of siblings, number of
		children, family history of cancer, family history of chronic
		disease
Reproductive history		age of first menstrual period, menopause status, history of
(for women)		contraceptive pills use, history of hysterectomy and of
		ovary/breast surgery

Supplementary table 1 Summary of quality assurance and quality control procedures in NCEC-HRP study

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Figure 1 Location of selected sites and covering provinces for esophageal cancer screening in China

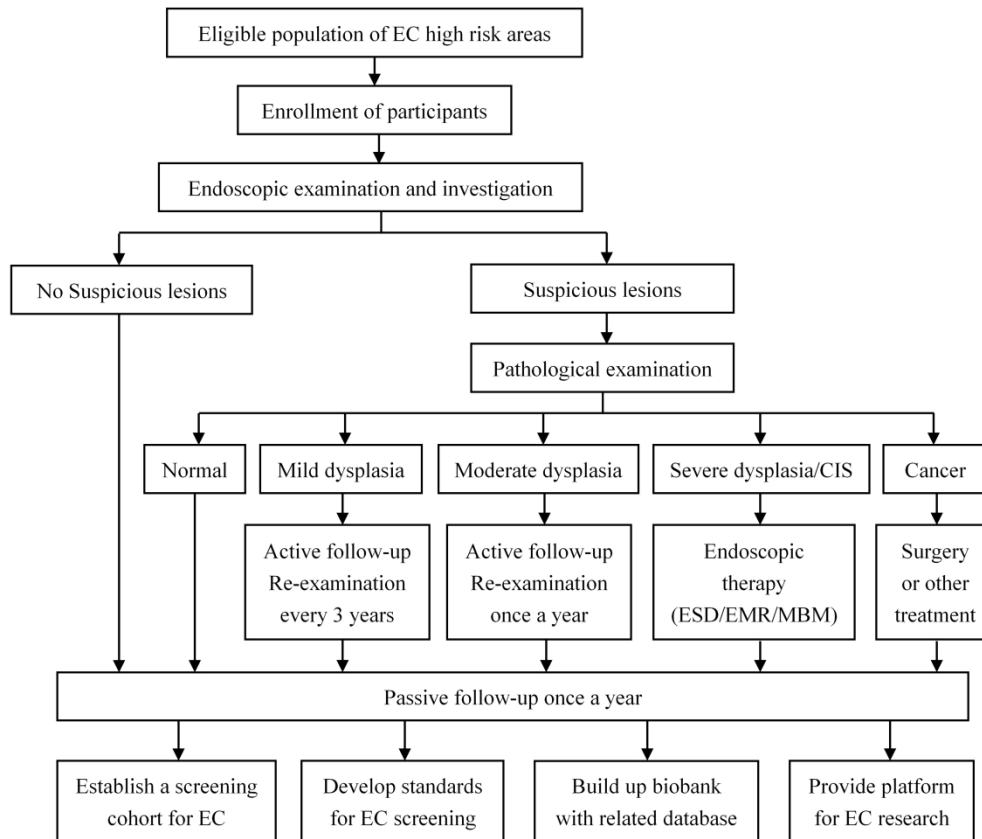


Figure 2 Enrollment, screening and follow-up procedure. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

Supplementary table 1 Summary of quality assurance and quality control procedures in NCEC-HRP study

Aspects	Quality assurance and quality control procedures
Research design	<p data-bbox="331 213 622 250">Protocol development</p> <ul data-bbox="353 268 2152 416" style="list-style-type: none"> <li data-bbox="353 268 2152 363">• The objectives, research design, participants' recruitment, sample size, as well as other basic points of the research protocol were developed by the NCEC Project Committee and its Advisory Committees. <li data-bbox="353 379 1715 416">• Small adjustments to the initial protocol were performed during the operationalization of the research. <p data-bbox="331 432 864 469">Development of the Operations Manual</p> <ul data-bbox="353 485 2152 580" style="list-style-type: none"> <li data-bbox="353 485 2152 580">• The Operations Manual with a clear and detailed description of all the activities were produced by the Project Committee and working group in the planning stage.
	Training, Certification and pre-survey
Data collection and analysis	

monitoring team

Data analysis

- All data would be cleaned and encrypted before analysis
- An analytical protocol would be developed prior to data analysis and all results would be reported

Sample collection

Sample collection and transportation

- A standard procedure for sample collection, storage and transportation were developed by the Project Committee and working group
 - Samples were collected from each center and dispensed according to the protocol
 - Reagents and tubes were purchased uniformly to ensure consistency
- Sample transportation and storage
- Tissue, saliva sample and half of the blood samples, including two pipes of blood cell and two pipes would be transported on dry ice to the central biobank in Linxian
 - All samples would be stored at -80°C freezer for long-term preservation at each local site and central biobank
 - All samples were tracked by the management center

Periodic site visits

- Periodic site visits to each center to check whether the screening were carried out according to the protocol
- Periodic centralized communication to one center to exchange experience and answer questions

Supervision and assessment

Assessment

- There were a series of indicators to assess the investigators, including the quality of the questionnaire, the duration of the survey, and the completeness of the questionnaire, etc. For the investigators who fail in the assessment, a re-training and re-certification was required before they participated in the survey.
- An annual report with detail work description in the previous year was required for each center at the end of the year
- Performance was evaluated based on the annual report and assessment of periodic site visits