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Complete List of Authors:

Chen, Ru; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College,
Ma, Shanrui; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Guan, Chentao; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Song, Guohui; Cixian Cancer Institute in Handan, Cixian cancer registry
Ma, Qing; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Xie, Shuanghua; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Wang, Meng; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Shao, Dantong; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Li, Xinqing; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Wei, Wen-Qiang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College,

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

Ru Chen[1], Shanrui Ma[1], Chentao Guan[1], Guihui Song[2], Qing Ma[1], Shuanghua Xie[1], Meng Wang[1], Dantong Shao[1], Xinqing Li[1], Wenqiang Wei[1*]

1 National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
2 Cixian Cancer Hospital/Cixian Institute for Cancer Prevention and Control, Handan, Hebei, China

*Corresponding author: Wenqiang Wei, MD, PhD, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 South Panjiayuan Lane, Chaoyang District, Beijing 100021, China; E-mail: weiwq@cicams.ac.cn

Abstract

Introduction: Esophageal cancer is one of the most common cancers worldwide and about 50% of all new cases occurred in China. Population-based screening has been conducted in high risk areas in China since 1970s, however, the difference in screening methods and protocols, inconsistencies in questionnaires for risk factors investigation, lack of standards for sample collection and incomplete follow-up information have limited the integration of the results from previous studies and the sharing of existing resources.

Methods and analysis: NCEC-HRP is a prospective cohort study of esophageal cancer screening based on high risk population in China. Eight areas located at eastern, central and western China representing three economical-geographical regions are selected as

screening centers. All local residents aged 40–69 years in the selected areas are invited to take endoscopic examination and risk factors investigation unless they meet the exclusion criteria. A total of 100,000 participants will be enrolled by Dec 2020 and all subjects are to be followed for a long time. This study is designed to be open-ended and has broad research aims. Summary statistics for baseline information will be reported after the recruitment is completed. We will develop a serious of standards and guidelines for esophageal cancer screening during the study. An open and shared research platform linked with epidemiological databases and biobank will be built up for further research.

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

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

Strengths and limitations of this study

1. NCEC-HRP is a prospective large sample cohort of esophageal cancer screening, which is expected to enroll more than 100,000 subjects from 8 regions in China.

2. It is an open-ended study with broad research aims, comprehensive exposure data collection and long-term follow-up.

3. A serious of standards on esophageal cancer screening and relevant issues will be developed based on the high quality evidence provide by the study.

4. An open and shared research platform linked with epidemiological databases and biobank will be provided to researchers to conduct studies on esophageal cancer and many other diseases.

5 The study lacks of risk factors information from non-responders and the findings are

limited to high risk areas.

Introduction

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

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

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

To this end, we have started the NCEC-HRP cohort, a prospective cohort study of esophageal cancer and precancerous lesions based on high risk population in China. As an important part of NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP cohort focus on populations in rural high-incidence ESCC areas. Given the excellent experience of existing large cohorts such as the All of US Research Program,[13] UK Biobank[14] and China Kadoorie Biobank,[15] NCEC-HRP is designed as a platform without

a specific hypothesis, aiming to provide a foundation for future research.

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

Methods and analysis

Study design and site selection

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

Enrollment of participants

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

31th, 2020.

Endoscopic examination and therapy

All endoscopic examinations and therapies are conducted by well-trained doctors at local hospitals. The screening procedure follows the recommendation of expert consensus on early esophageal cancer screening and endoscopic diagnosis and treatment in China.[16] Briefly, screened participants are provided a standard upper gastrointestinal endoscopy with iodine staining. The entire esophagus and stomach are visually examined and biopsies are taken from all focal lesions. Two pathologists independently read the biopsy slides without knowledge of the visual endoscopic findings. Discordances in the diagnosis are solved by discussion.

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

Sample collection

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

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

Data management

All information collected is entered using a pad-based direct data entry app 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 to the data management platform at National Cancer Center. The platform is designed to be an open and shared platform for professional research on esophageal cancer and other health related issues. It will not only include data from questionnaires, but also include diagnostic images from endoscopy and pathology, and linked with biobank at each center.

Outcome assessment

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

Sample size calculation

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

Data analysis plan

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

Ethics and dissemination

The study is approved by the independent ethics committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval Number 16-171/1250). The transmission, storage and analysis of health-related personal data and the storage of biological samples within this project will

strictly follow the legal requirements for data protection and will be performed under the supervision of the ethics committee. Data protection and confidentiality will be guaranteed. The findings of the study will be disseminated through scientific peer-reviewed journals and be provided to the public via the NECE study website (http://www.ncec-china.cn). The NCEC study group is committed to making the cohort data available to the scientific researchers worldwide to advance knowledge about the causes, prevention and treatment of esophageal cancer and other diseases. Researchers wishing to undertake additional analyses based on the resources are invited to contact us for further discussion. More information on date sharing and application will be published online in the future.

Discussion

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

A major limitation in this study is the lack of risk factors information from non-attenders since the investigation is for screening subjects. The questionnaire and sampling method for non-attenders is still under design. Besides, the study sites are limited to high-incidence

areas, so whether the results are applicable to individuals in low-incidence areas remains to be verified.

Unlike the ongoing randomized controlled trials aiming at evaluating the efficacy of esophageal cancer screening,[24 25] our study focuses on the establishment of databases and biobank to provide sufficient samples and complete data for subsequent multi-omics researches. NCEC-HRP is part of the NCEC study and, together with other four cohorts including standardized diagnosis and treatment of clinical cohort, minimally invasive treatment of early stage and precancerous lesion cohort, genetic lineage cohort and prospective cohort based on urban community, will provide a comprehensive research platform for esophageal cancer and precancerous lesions.

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

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Competing interests statement None declared.

Patient consent Obtained.

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

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

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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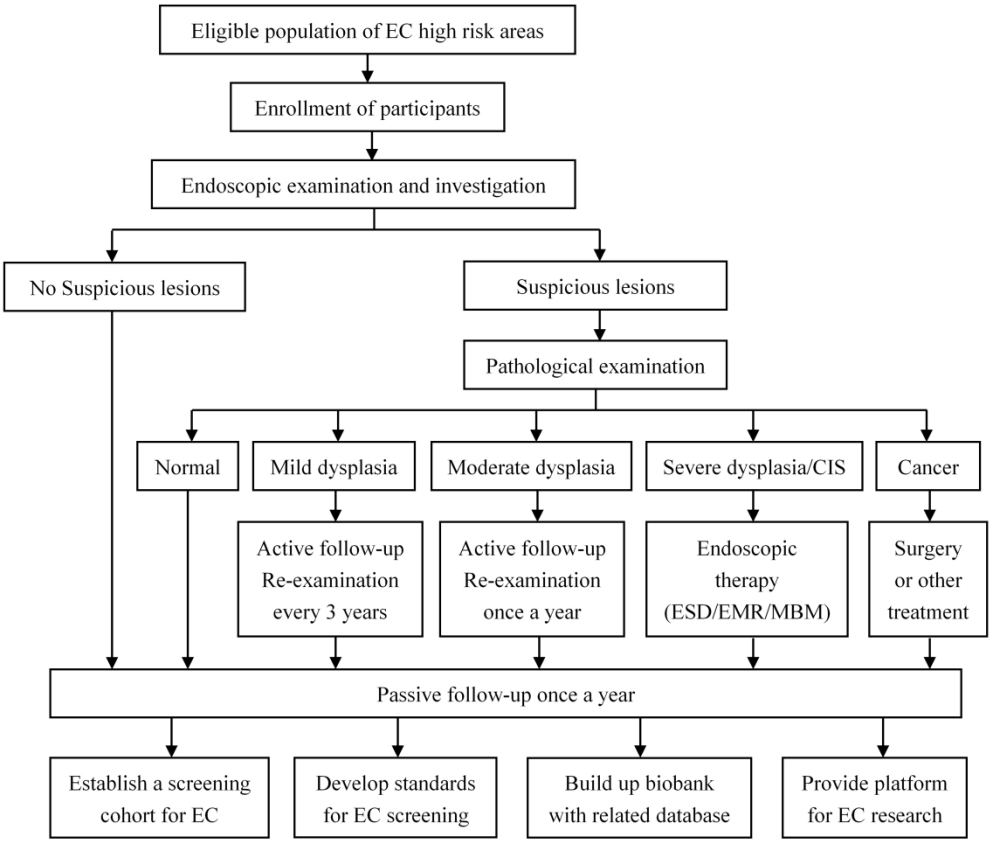

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1 National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

2 Cixian Cancer Hospital/Cixian Institute for Cancer Prevention and Control, Handan, Hebei, China

*Corresponding author: Wenqiang Wei, MD, PhD, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 South Panjiayuan Lane, Chaoyang District, Beijing 100021, China; E-mail: weiwq@cicams.ac.cn

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Esophageal cancer remains a significant source of morbidity and mortality worldwide. According to GLOBOCAN report, there are an estimated 572,034 new cases and 508,585 cancer deaths in 2018, with three quarters of the cases occurring in developing countries and approximately a half of all new cases occurring in China.[1 2] Esophageal cancer has been the fifth most common cancer and the fourth most common cause of death in China.[3] The incidence rate and mortality of esophageal cancer were 18.85/100,000 and 14.11/100,000 respectively in China in 2014.[3] The two main types of esophageal cancer are squamous cell carcinoma (ESCC) and adenocarcinoma. ESCC accounts for over 90% of all cases of esophageal cancer in China and causes the majority burden of it.[4 5]

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

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

To this end, we have started the NCEC-HRP cohort, a prospective cohort study of

esophageal cancer and precancerous lesions based on high risk population in China. As an important part of NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP cohort focus on populations in rural high-incidence ESCC areas. Given the excellent experience of existing large cohorts such as the All of US Research Program,[15] UK Biobank[16] and China Kadoorie Biobank,[17] NCEC-HRP is designed as a platform without a specific hypothesis, aiming to provide a foundation for future research.

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

Methods and analysis

Study design and site selection

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

A total of eight sites are selected as the study centers (Figure1), including Feicheng of Shandong province, Yangzhong of Jiangsu province, Cixian of Hebei province, Linxian

and Huaxian of Henan province, Yangcheng of Shanxi province, Yanting of Sichuan province and Chaoshan of Guangdong province. The incidence rates among selected areas ranged between 35.52/100,000 to 81.23/100,000.

Enrollment of participants

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

Endoscopic examination and therapy

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

If early lesions are histologically diagnosed, participants will be recalled to the clinic, and intervention methods appropriate to the lesions' severity would be used. For esophageal severe dysplasia/carcinoma in situ or intramucosal carcinomas, endoscopic mucosal resection and/or endoscopic submucosal dissection treatments will be used as

local therapies. For esophageal cancers, therapies include esophagectomy, radical operation, radiotherapy, and other conventional treatments.

Sample collection

Before endoscopy, blood will be collected into an EDTA containing vacutainer from each participant in the fasting state, and a small sample of this is used for routine test for infectious diseases including HBV, HCV, HIV and syphilis. The remaining blood (no less than 5ml) will be dispensed into four pipes after centrifugation, including two pipes of blood cell and two pipes of plasma. All samples will be stored at -80℃ freezer for long-term preservation at each local site. Biopsy specimens are fixed in 10% buffered formalin and embedded in paraffin for storage. Pathological specimens and sections are preserved for patients with pathological examination. For each participate, saliva samples are also collected from the oral cavity by drooling and preserved in PreservCyt solution (Hologic, Bedford, MA, United States) at -70℃ 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.[17] 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. We have also developed some specific questionnaire based on 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 and so on. 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. A serious 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 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 to the data management platform at National Cancer Center. The platform is designed to be an open and shared platform for professional research on esophageal cancer and other health related issues. It will not only include data from questionnaires, but also include diagnostic images from endoscopy and pathology, and linked with biobank at each center.

We treated all data as protected health information and stored it securely in 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 platform servers built for the study. The collection, shipping and receipt of data carriers were tracked by the management center.

Outcome assessment

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

Quality control

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

Sample size calculation

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

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

Data analysis plan

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

Ethics and dissemination

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

The findings of the study will be disseminated through scientific peer-reviewed journals and be provided to the public via the NECE study website (http://www.ncec-china.cn). The NCEC study group is committed to making the cohort data available to the scientific researchers worldwide to advance knowledge about the causes, prevention and treatment of esophageal cancer and other diseases. Researchers wishing to undertake additional analyses based on the resources are invited to contact us for further

discussion. More information on date sharing and application will be published online in the future.

Patient and Public Involvement

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

Discussion

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

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

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

application of results. Therefore, there is an urgent need for a large cohort to be established with uniform standards on esophageal cancer screening, early diagnosis and treatment, risk factors investigation, sample collection and follow-up. This study focuses on the establishment of databases and biobank to provide sufficient samples and complete data for subsequent multi-omics researches. With large sample size and long-term follow-up, we can have a more comprehensive understanding of the epidemiology of esophageal cancer and precancerous lesions, including the incidence and mortality, risk factors, progress and survival et al. NCEC-HRP is part of the NCEC study and, together with other four cohorts including standardized diagnosis and treatment of clinical cohort, minimally invasive treatment of early stage and precancerous lesion cohort, genetic lineage cohort and prospective cohort based on urban community, will provide a comprehensive research platform for esophageal cancer and precancerous lesions.

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Contributors Ru Chen, Shanrui Ma, Chentao Guan and Wenqiang Wei: study conception and design; Shanrui Ma: questionnaire for psychosocial status; Shuanghua Xie: questionnaire for baseline risk factors investigation; Guohui Song: biobank establishment; Guohui Song, Shuanghua Xie and Dantong Shao: sample collection method; Chentao Guan, Qing Ma and Meng Wang: screening procedure; Ru Chen: data management and analysis; Xinqing Li: quality control; Ru Chen and Wenqiang Wei: manuscript draft. All authors have contributed to research platform design and management and approved the final manuscript.

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Competing interests statement None declared.

Patient consent Obtained.

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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

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

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

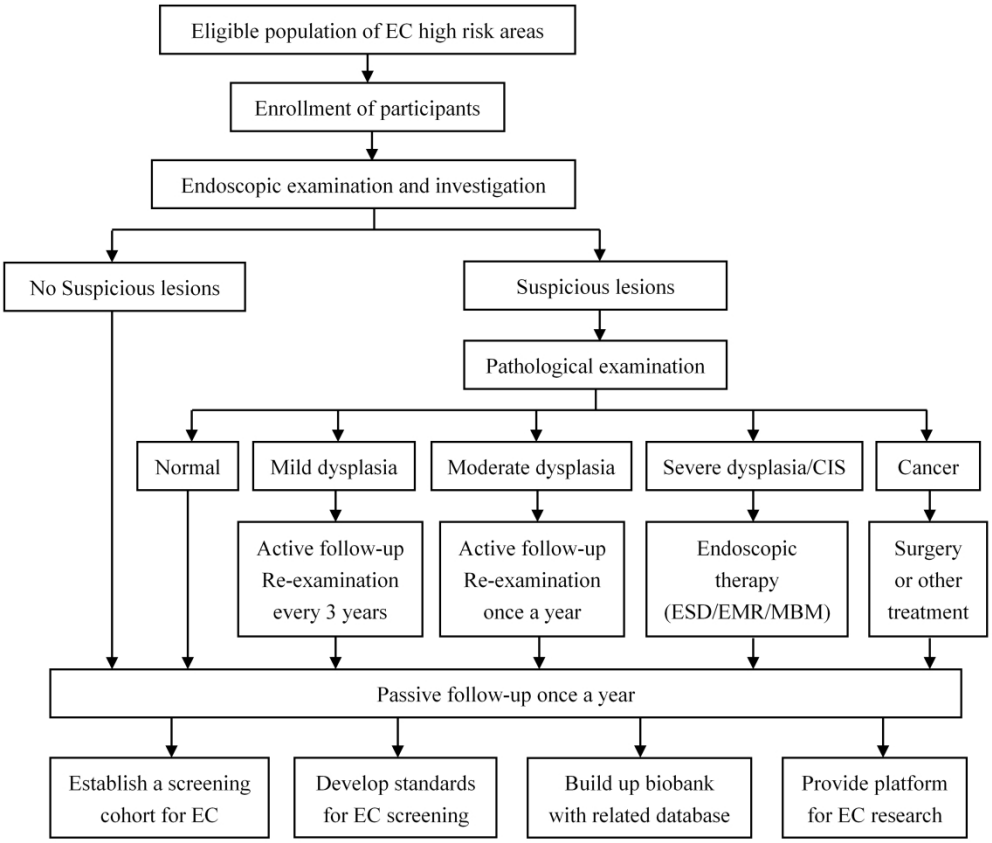

Figure 2 Enrollment, screening and follow-up procedure. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

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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): study protocol

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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): study protocol

Ru Chen[1], Shanrui Ma[1], Chentao Guan[1], Guihui Song[2], Qing Ma[1], Shuanghua Xie[1], Meng Wang[1], Dantong Shao[1], Xinqing Li[1], Wenqiang Wei[1*]

1 National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

2 Cixian Cancer Hospital/Cixian Institute for Cancer Prevention and Control, Handan, Hebei, China

*Corresponding author: Wenqiang Wei, MD, PhD, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 South Panjiayuan Lane, Chaoyang District, Beijing 100021, China; E-mail: weiwq@cicams.ac.cn

Abstract

Introduction: Esophageal cancer is one of the most common cancers worldwide and about 50% of all new cases occurred in China. Population-based screening has been conducted in high risk areas in China since 1970s, however, a few factors have limited the integration of the results from previous studies and the sharing of existing resources, such as the difference in screening methods and protocols, inconsistencies in questionnaires for risk factors investigation, lack of standards for sample collection and incomplete follow-up information.

Methods and analysis: NCEC-HRP is a prospective cohort study of esophageal cancer screening based on high risk population in China supported by the National Key R&D Program. Eight areas located at eastern, central and western China are selected as

screening centers to represent three economical-geographical regions. All local residents aged 40–69 years in the selected areas are invited to take endoscopic examination and risk factors investigation unless they meet the exclusion criteria. The recruitment began on Jun 2017 and a total of 100,000 participants will be enrolled by Dec 2020 and all subjects will be followed for a long time. This study is designed as open-ended and has broad research aims. Summary statistics for baseline information will be reported after the completion of recruitment. We will develop a serious of standards and guidelines for esophageal cancer screening during the study. An open and shared research platform linked with epidemiological databases and biobank will be built up for further research.

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

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

Strengths and limitations of this study

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

limited to high risk areas in China.

Introduction

Esophageal cancer remains a significant source of morbidity and mortality worldwide. According to GLOBOCAN report, there are an estimated 572,034 new cases and 508,585 cancer deaths in 2018, with approximately a half of all new cases occurring in China.[1 2] Esophageal cancer has been the fifth most common cancer and the fourth most common cause of death in China.[3] The incidence rate and mortality of esophageal cancer were 18.85/100,000 and 14.11/100,000 respectively in China in 2014.[3] The two main types of esophageal cancer are squamous cell carcinoma (ESCC) and adenocarcinoma, with. ESCC accounting for over 90% of all cases of esophageal cancer in[4 5]

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

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

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

in China(NCEC-HRP) cohort, a prospective cohort study of esophageal cancer and precancerous lesions based on high risk population in China. As an important part of NCEC (National Cohort of Esophageal Cancer) study, NCEC-HRP cohort focuses on populations in rural areas with high-incidence of ESCC. Learning from existing large cohorts such as the All of US Research Program,[15] UK Biobank[16] and China Kadoorie Biobank,[17] NCEC-HRP is designed as a platform without a specific hypothesis in order to facilitate future research.

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

Methods and analysis

Study design and site selection

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

A total of eight sites are selected as the study centers (Figure1), including Feicheng of Shandong province, Yangzhong of Jiangsu province, Cixian of Hebei province, Linxian and Huaxian of Henan province, Yangcheng of Shanxi province, Yanting of Sichuan

province and Chaoshan of Guangdong province. The incidence rates among selected areas ranged from 35.52/100,000 to 81.23/100,000.

Enrollment of participants

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

Endoscopic examination and therapy

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

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

operation, radiotherapy, and other conventional treatments.

Sample collection

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

Follow up and re-examination

We combine the active and passive follow-ups to accurately collect outcome information. For participants diagnosed with esophageal cancer or precancerous lesions during the screening, annual interviews will be used to collect the outcome information through telephone, home visit or other contact methods. Meanwhile, a passive follow-up procedure will be carried out for all participants once a year. We will also collect additional 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 will 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 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 serious 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

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

Outcome assessment

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

Quality control

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

Sample size calculation

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

Data analysis plan

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

Ethics and dissemination

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

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

Patient and Public Involvement

The protocol of this study was discussed and developed by a multidisciplinary team of experts including epidemiologists, clinicians, statisticians, and computer engineers as

well as field investigators, but no patients or public were involved in the design phase.

Discussion

Strengths of the study include the prospectively collected exposure data, an exceptionally large sample size and the opportunity to follow all participants through various resources. Based on the high quality evidence provide by the study, we would also develop a serious of standards and guidelines on esophageal cancer screening, early diagnosis and treatment, risk factors investigation, sample collection and follow-up. Those achievements might be implemented to other high risk areas, especially in developing countries in Central and East Asia and Eastern Africa. In addition, the biobank with blood, tissue and saliva will lay the foundation for further exploration on the genetic risk factors and relevant mechanism of esophageal cancer and other diseases. Finally, as an open-ended prospective study, the exposure measurements are not only designed for esophageal cancer, but also for many other chronic diseases. Through linking epidemiological databases tothe biobank, NCEC-HRP will also provide an open and shared research platform for researchers worldwide to conduct studies on esophageal cancer and many other diseases.

A major limitation in this study is the lack of risk factors information from non-attenders. However, a questionnaire and sampling method for non-attenders is already under design. We also try to obtain the baseline and outcome information of non-participants by referring to various date sources to improve the accuracy of the research results from multiple aspects. Second, our cohort are limited to high-incidence areas, which might affect its extrapolation in low-incidence areas.

The preexisting cohorts and ongoing trials bring new insights into esophageal cancer, however, the lack of standardization and sharing limit the popularization and application of results. A large cohort is urgently needed which should own uniform standards on esophageal cancer screening, early diagnosis and treatment, risk factors investigation, sample collection and follow-up. Our cohort is aimed to establish databases and biobank in order to offer sufficient samples and complete data for subsequent multi-omics researches. With large sample size and long-term follow-up, we could achieve a more comprehensive understanding of the epidemiology of

esophageal cancer and precancerous lesions, including the incidence and mortality, risk factors, progress and survival et al. NCEC-HRP is part of the NCEC study and, together with other four cohorts including standardized diagnosis and treatment of clinical cohort, minimally invasive treatment of early stage and precancerous lesion cohort, genetic lineage cohort and prospective cohort based on urban community, will construct a comprehensive research platform for esophageal cancer and precancerous lesions.

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Competing interests statement None declared.

Patient consent Obtained.

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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 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 related information	self-rated health status (self-reported health status, oral hygiene, history of trauma, history of cancer and related therapy, history of digestive disease, *Helicobacter pylori* 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 (for women)	age of first menstrual period, menopause status, history of 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

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

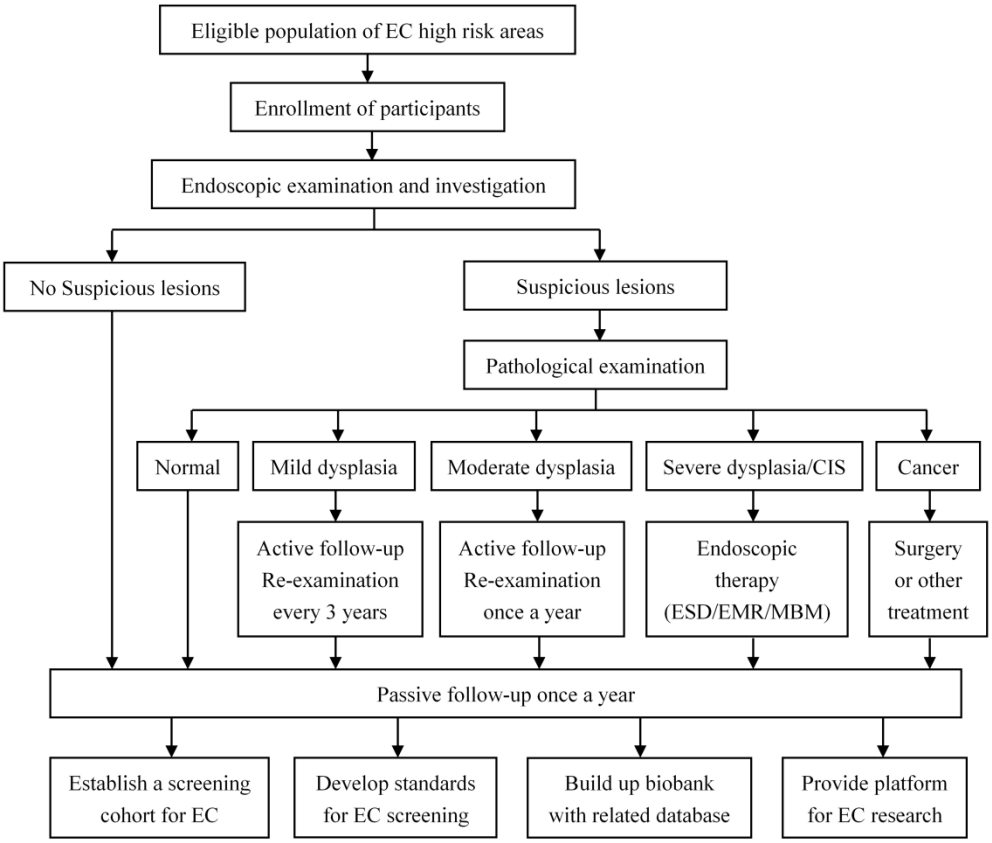

Figure 2 Enrollment, screening and follow-up procedure. EC: esophageal cancer; CIS: carcinoma in situ; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; MBM: Multiband mucosectomy

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

Aspects	Quality assurance and quality control procedures
Research design	Protocol development • 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. • Small adjustments to the initial protocol were performed during the operationalization of the research. Development of the Operations Manual • 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	Training and certifications of interviewers for data collection • Trainings and certifications were planned before the pilot study and performed by experts from the National Cancer Center • Training was first conducted in a centralized way to ensure uniformity. Then the training team went to the each center for further training possible if needed. • Certification of the interviewers was carried out at the end of the training process. The interviewer completed a specific questionnaire according to the simulated on-site survey and compared it with the standard answer. Certification could only be approved when the consistency of the survey is met. Pre-survey • A pilot study was conducted in Feicheng, Shandong before the official study began. • The flowchart to execute the procedures was tested, including the difficulties for understanding of the questionnaire by the participants, arrangements for investigation and endoscopy, and the limitations of pad-based survey. • Problems were discussed and the necessary alterations were made to the protocol and manuals.
Data collection and analysis	Data collection • Survey system were designed with built-in functions to avoid missing items and minimize logic errors during the interview • Repeat questionnaire and measures on selected items were conducted based on a 10% randomly selection of the participants • The data were uploaded to the platform weekly and were checked for skip errors, missing values, outliers and discrepant values by data

	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 and transportation	Sample collection • 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℃ freezer for long-term preservation at each local site and central biobank • All samples were tracked by the management center
Supervision and assessment	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 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