Community-Based Upper Gastrointestinal Cancer Screening in a Randomized Controlled Trial: Baseline Results in a Non-high-incidence Area

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ABSTRACT

A cluster-randomized controlled trial (RCT) was conducted to evaluate to the effectiveness of reducing mortality of upper gastrointestinal cancer (UGC) and feasibility of screening through a questionnaire combined with endoscopy in non-high-incidence urban areas in China. The trial design, recruitment performance, and preliminary results from baseline endoscopy are reported. Seventy-five communities in two urban cities with a non-high-incidence of UGC were randomized to a screening endoscopy arm ($n = 38$) or a control arm ($n = 37$). In the screening arm, individuals at high risk of UGC underwent endoscopic screening. The primary outcome was the UGC mortality, and secondary outcomes included the UGC detection rate, incidence rate, survival rate, and clinical stage at the time of diagnosis. A total of 10,416 and 9,565 individuals were recruited into the screening and control arms, respectively. The participation rate was 74.3%. In the screening arm, 5,242 individuals (50.3%) were estimated to be high-risk. Among them, 2,388 (45.6%) underwent endoscopic screening. Age and household income were associated with undergoing endoscopy. Three early esophageal cancer (0.13%), one gastric cancer (0.04%), 29 precancerous esophageal lesions (1.21%), and 53 precancerous gastric lesions (2.22%) were detected. Age, sex, a family history of cancer, intake of meat–egg–milk frequently, superficial gastritis, and clinical symptoms of gastric cancer were associated with the presence of precancerous lesions. The detection rate was low using endoscopic screening in non-high-incidence area given the relatively low compliance rate. These findings provide a reference for designing effective community-based UGC screening strategies in non-high-incidence urban areas.

Background

Upper gastrointestinal cancer (UGC) containing esophageal cancer and gastric cancer is one of the most common cancers worldwide, with about 50% new cases and deaths occurring in China (1, 2). Moreover in China, UGC ranks second both in terms of cancer incidence and cancer-related mortality. The prognosis of UGC is closely related to the time of diagnosis and treatment. The 5-year survival rate of patients diagnosed at an early stage of UGC is much higher than in those diagnosed at an advanced stage (3). In China, the 5-year survival rate of UGC is relatively low at below 36% (4). Therefore, detecting UGC at an early stage is key in improving the survival of these patients, and effective screening is the only way to improve detection.

In China, UGC carries a considerable psychologic and economic burden. The incidence is highest in people living in relatively poor rural areas with limited resources (referred to as high-incidence areas). In these areas, UGC ranks first in terms of both cancer incidence and cancer-related mortality. UGC is also common in urban areas (referred to as non-high-incidence areas), where it ranks second in terms of both cancer incidence and cancer-related mortality. The detection rate of early UGC in China is far lower than in other developed countries, which could result in a large discrepancy regarding the survival rate. A previous study reported that early stomach cancer is detected at a rate of more than 70% in Japan and more than 50% in South Korea but less than 10% in China (5). Therefore, this serious situation impelled China to start a series of major public health programs for UGC screening in 2005 in high-incidence areas expanded to non-high-incidence urban areas in 2012 (6). After 10 years, the detection rate of early gastric cancer increased to 19% in 2015 indicating that the government-led national cancer screening program has achieved initial positive results (7).

Currently, endoscopy combined with biopsy and histology is the procedure with the highest sensitivity and specifically for detecting UGC and is widely used for screening in many countries (8). Japan, South Korea, and China are countries

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with the highest incidence of UGC in the world. In Japan and South Korea national screening programs for UGC have had positive results (9–11). Endoscopic screening has been tested in high-incidence areas in China (12, 13). Some observational studies have indicated that endoscopy could reduce the UGC mortality rate (14). In addition, a recent prospective study with a 10-year follow-up suggested that endoscopic screening could significantly reduce the cumulative incidence and mortality of esophageal cancer in residents in high-incidence rural areas (15). However, these were cross-sectional screening programs, and their ability to provide strong evidence is limited due to bias and confounding factors. Therefore, designing a scientific prospective randomized controlled trial (RCT) is crucial to evaluate whether endoscopy combined with pathologic biopsy can effectively reduce the mortality rate of UGC. In 2015, a national and large-sample size RCT of endoscopic screening for UGC was carried out in three high-incidence and four non-high-incidence areas (16). In Hunan province in 2015, the incidences of esophageal cancer and gastric cancer are both far lower than at national level (EC: $3.52/10^5$ in Hunan vs. $11.28/10^5$ in China, GC: $8.37/10^5$ in Hunan vs. $18.57/10^5$ in China; ref. 17). However, in Hunan Province, UGC still ranks in the top four cancer in terms of incidence and mortality, and is the major cancer that requires preventive screening.

Therefore, Hunan province, as one of four non-high-incidence areas in the national RCT as mentioned above, conducted an RCT with a study population of 20,000 to evaluate the effectiveness for the reduction of UGC mortality and feasibility of implementation through a two-step screening method—a questionnaire combined with endoscopy in non-high-incidence urban areas. Here, the trial design, performance recruitment, and preliminary results from baseline endoscopic screening are reported.

Materials and Methods

Our study started on May 1, 2015, and the recruitment and baseline screening were finished by December 31, 2017, then 10-year follow up would be continuous. Our study was approved by the ethics committee of Cancer Hospital Chinese Academy of Medical Sciences (2015SQ00223), and the trial was registered in the protocol registration system of the Chinese Clinical Trial Registry (ChiCTR-EOR-16008577) and it was performed in accordance with the Declaration of Helsinki.

Study areas

Study areas were selected on the basis of a good foundation of cancer screening, cancer registration, and death monitoring. According to previous work, this large-sample study is beyond one city's capacity, so we apply for performing the study in two cities. Changsha, the capital city of Hunan province, was selected as an implementation city for the major national public health project—Early Screening Program in Urban China—from 2012. Moreover, five districts in Changsha (Furong, Kaifu, Tianxin, Yuhua, and Yuelu districts) and Yueyanglou district in Yueyang city are both national-level cancer registration areas. Death monitoring has been carried out in two cities since the 1980s. Finally, we selected five districts in Changsha city (53 communities) and Yueyanglou district (22 communities) as research sites with total age-eligible population of 1.20 million (details in **Table 1**).

Subject enrollment

This was a cluster RCT with a total of 20,000 subjects on basis of the whole national study's calculation. The communities served as the unit of random cluster sampling that was randomly and, respectively, divided into the screening and control arms at a ratio of 1:1 in two cities. The intervention measure in the screening arm was endoscopy for subjects initially screened by risk factor questionnaire to be at high risk of UGC, while the control arm did not receive endoscopy. Each community has an age-eligible individual roster of our study. From the roster, a general practitioner contacted every individual by telephone or a home visit to invite them to participate. Individuals were also given the opportunity sign-up of their own initiative. Through screening for eligibility, general practitioners developed a roster of eligible individuals among those who had been contacted. These individuals were then invited to participate. Those who agreed signed informed consent. Sample size calculation and random cluster sampling are described in the national project protocol (16).

The inclusion criteria were: (i) subjects are local residents aged 40–69 years old; (ii) with no previous history of cancer; (iii) with no endoscopic examination in the last 3 years; and (iv)

Table 1. Subjects distribution of screening and control group in Changsha and Yueyang city.

Cities	District	Age-eligible population	Contacted people	Communities (number of subjects)		Total
				Screening group	Control group	
Changsha	Furong	166,320	3,120	6 (1,038)	6 (890)	12 (1,928)
	Kaifu	171,017	2,344	5 (1,104)	5 (957)	10 (2,061)
	Tianxin	157,265	2,192	6 (1,006)	6 (957)	12 (1,963)
	Yuhua	234,575	2,600	5 (1,020)	5 (899)	10 (1,919)
	Yuelu	247,029	2,815	5 (1,158)	4 (923)	9 (2,081)
	Total of Changsha	**976,206**	**13,071**	**27 (5,326)**	**26 (4,626)**	**53 (9,952)**
Yueyang	**Yueyanglou**	**221,239**	**14,045**	**11 (5,090)**	**11 (4,939)**	**22 (10,029)**
In total		**1,197,445**	**27,116**	**38 (10,416)**	**37 (9,565)**	**75 (19,981)**

Table 2. Comparison of screening and control arm on demographic characteristic variables for UGC.

	Screening arm				Control arm	
Factors	**High risk *n* (%)**	**Non-high risk *n* (%)**	***P*[a]**	**Total**	***n* (%)**	***P*[b]**
Sex						
Male	2,338 (44.6)	2,265 (43.8)	0.397	4,603 (44.2)	4,160 (43.5)	0.319
Female	2,904 (55.4)	2,909 (56.2)		5,813 (55.8)	5,405 (56.5)	
Age (Years)						
40–49	1,578 (30.1)	1,643 (31.8)	0.009	3,221 (30.9)	3,199 (33.4)	<0.001
50–59	1,774 (33.8)	1,607 (31.1)		3,380 (32.5)	3,193 (33.4)	
60–69	1,890 (36.1)	1,924 (37.2)		3,814 (36.6)	3,173 (33.2)	
Ethnicity						
Han	5,228 (99.7)	5,158 (99.7)	0.688	10,386 (99.7)	9,544 (99.8)	0.338
Others	14 (0.3)	16 (0.3)		30 (0.3)	21 (0.2)	
Body mass index (Kg/m^2)						
<18.5	121 (2.3)	85 (1.6)	0.017	206 (2.0)	221 (2.3)	0.004
18.5–24.9	3,880 (74.0)	3,920 (75.8)		7,800 (74.9)	6,971 (72.9)	
≥25.0	1,241 (23.7)	1,169 (22.6)		2,410 (23.1)	2,373 (24.8)	
Education						
Primary school and below	1,126 (21.5)	1,016 (19.6)	0.002	2,142 (20.6)	1,875 (19.6)	0.032
Middle school	3,221 (61.4)	3,153 (60.9)		6,374 (61.2)	6,026 (63.0)	
College and above	895 (17.1)	1,005 (19.4)		1,900 (18.2)	1,664 (17.4)	
Marriage						
Married	5,126 (97.8)	5,057 (97.7)	0.867	10,183 (97.8)	9,362 (97.9)	0.580
Unmarried	116 (2.2)	117 (2.3)		233 (2.2)	203 (2.1)	
Household income (CNY)						
≤40,000	1,392 (26.6)	1,040 (20.1)	<0.001	2,432 (23.3)	2,368 (24.8)	<0.001
40,000–80,000	2,234 (42.6)	2,114 (40.9)		4,348 (41.7)	4,175 (43.6)	
>80,000	1,616 (30.8)	2,020 (39.0)		3,636 (34.9)	3,022 (31.6)	
Family size						
>2	4,317 (82.4)	4,144 (80.1)	0.003	8,461 (81.2)	8,029 (83.9)	0.000
≤2	925 (17.6)	1,030 (19.9)		1,955 (18.8)	1536 (16.1)	

[a]*P* value is for the comparison between high-risk and non-high-risk group in screening arm.
[b]*P* value is for the comparison between screening and control arm.

generally in good condition mentally and physically and can sign the informed consent form. Subjects were excluded if they had other serious diseases; including severe heart and lung dysfunction, acute respiratory infection, extreme weakness caused by systemic conditions, etc.; they were unable to take care of themselves; or were unwilling to undergo screening for our study.

Screening procedures

All screening interventions were provided free of charge. But some subjects detected positive lesions need to receive further treatment, this part fee should be paid by themselves, which was stated in the informed consent.

Risk factor questionnaire

All enrolled subjects participated in the unified questionnaire. The questionnaire includes eight parts: demography, behavioral habits, food frequency survey, personality and mental health, disease history, family history of cancer, clinical symptoms of esophageal cancer and gastric cancer, and physical examination (details in **Table 2** and Supplementary Table S1).

In this study, the questionnaire survey was conducted electronically and a preliminary screening result presented for the screening arm rather than the control arm. On the basis of the epidemiologic data of UGC in the past 50 years and the discussion of multidisciplinary expert arm, a qualitative high-risk assessment standard was established (18–22). Subjects were assessed to be high risk for UGC if any two items of the following 1–4 or any one item from 5–8 were positive: 1, regular smoking (20 cigarettes/day for more than 10 years); 2, regular drinking (white wine 50 g/day for more than 10 years); 3, often eating moldy and pickled food; 4, eating hot and hard food; 5, a family history of UGC; 6, clinical symptoms of esophageal cancer (eating with retrosternal or subxiphoid pain and progressive dysphagia); 7, clinical symptoms of gastric cancer (loss of appetite, abdominal distension, heartburn and regurgitation, malignant vomiting, belching, hematemesis, black stool, progressive wasting, etc.); and 8, and a history of reflux esophagitis or gastropathy.

Helicobacter pylori detection

To explore the relation between *Helicobacter pylori* infection and UGPL, and to find the balance between screen and control arm in non-high-risk area, we randomly select 20% of the enrolled population (4,000 cases) from both arms to undergo the ^{13}C-urea breath test to detect *Helicobacter pylori* infection. About 54 subjects are randomly selected from every

community's roster and are notified to receive the test in the community hospitals by general practitioners. Every community hospital used the same type of *Helicobacter pylori* detection instrument and the instruments were regularly calibrated by a single technician.

Endoscopic screening

High-risk individuals underwent endoscopic screening at the designated hospital. Routine examinations, such as hepatitis B virus, hepatitis C virus, human immunodeficiency virus, syphilis, coagulation function, and electrocardiogram only for people over 60 years old, were performed before endoscopy. Endoscopy was performed according to the "Technical program of UGC screening and early diagnosis and treatment project (2014 trial version)" (11). Requirements for taking pathologic biopsy are as follows: (i) if any positive or suspicious lesion is found in the mucosa of esophagus, cardia and stomach under endoscopic observation, biopsy should be taken in the corresponding area. The number of biopsies depends on the size of lesion. Iodine staining of the esophagus and indigo carmine dye staining of the stomach were used as necessary to aid in the diagnosis of suspicious lesions. Then, the biopsy specimen was/were processed and sent for pathologic examination. (ii) If no suspicious morphologic changes are found, biopsy is not required. So, for some special subjects, endoscopy doctors could collect multiple lesion sites specimens from esophagus to gastric area.

We freely provided to subjects for normal endoscopy performed under without anesthesia. But for some subjects who wanted to accept endoscopy under anesthesia, they just needed to pay some extra anesthetic fees by themselves. As endoscopy is an invasive examination, we made an emergency plan to deal with some adverse events during the endoscopic process, such as stomachache, bleeding, perforation, or stenosis.

Follow-up and reexamination

We wanted to acquire the subjects' outcome through active and passive follow-up. The outcomes contain primary outcome (mortality caused by UGC) and secondary outcomes (detection rate, incidence rate, survival rate, and clinical stage distribution of UGC). For positive subjects, general practitioners take active follow-up by telephone or in-home visits, whereas, general practitioners take passive follow-up by matching databases of cancer registration and death monitoring system for negative subjects.

Positive subjects

Upon endoscopic screening, subjects pathologically diagnosed with severe esophageal dysplasia, carcinoma *in situ*, esophageal cancer, severe gastric dysplasia (high-grade intraepithelial neoplasia), gastric cancer, and other cancers were defined as positive subjects. They were advised to undergo further treatment and were actively followed up at least once a year. Meanwhile, a follow-up form for cancer collected general, diagnosis, and follow-up information. In the second follow-up, only the follow-up information required updating.

All patients with UGC were pathologically diagnosed, and clinical staging was based on the American Joint Committee on Cancer seventh edition staging system.

Reexamination for precancerous lesions subjects

Patients with detected precancerous lesions were notified of reexaminations using the same technique as the baseline screening. After reexamination, patients with disease progression to carcinoma *in situ*, severe dysplasia, or cancer were transferred to positive subjects; patients with disease alleviation were excluded from reexamination and general practitioners will follow-up them as negative subjects. Reexamination requirements were as follows: patients with mild esophageal dysplasia required reexamination once every three years; those with moderate esophageal dyspepsia, cardiac, or gastric low-grade intraepithelial neoplasia, severe atrophic gastritis, or severe intestinal metaplasia required reexamination annually.

Negative subjects

Subjects who pathologically diagnosed with neither positive subjects nor precancerous lesions were defined as negative subjects. They were followed up passively by general practitioners who received strict training. All 20,000 participants were followed up passively once a year; thus, information regarding cancer incidence and death were obtained. Notably, general practitioners will actively follow up subjects who were diagnosed as UGC during the passive follow-up.

Quality control

Administrative management

In China, many scientific projects implementing smoothly depend on administrative power from government. Before the start of our study, the government issued a document to the relevant administrative management agencies regarding the implementation site. Moreover, a three-level technical management center—Hunan Provincial Office of Cancer Prevention and Control, the distinct disease control and prevention center (CDC), and the community health service center—ensured high-quality implementation of the study.

Data entry quality control

The risk factor questionnaire and screening data were entered electronically into the information system. Data accuracy was ensured mainly using three levels of quality control: (i) a quality controller to check the accuracy of the data after the first input; (ii) an electronic system with a logical self-inspection function to identify missing or incorrect contents; and (iii) a project management center to periodically perform quality control again after submitting the data; certain problems were returned to the person(s) originally responsible for data input to make modifications or verify the data.

Follow-up quality control

The project team developed five measures to improve the follow-up rate: (i) we perform regular technical training for general practitioners, mainly about the method of active

follow-up; (ii) 20% new UGC cases found in the process of active and passive follow-up by general practitioners are randomly selected for a recheck by CDCs to ensure data accuracy; (iii) attempts were made to maintain the loss-of-visit rate below 10% for the whole subjects; communities with a loss-of-visit rate over 5% required careful investigation and an analysis of the reason behind the loss of visit; and (iv) due to the proximity of the community location, people in the control arm may have been influenced by subjects in the screening arm; therefore, some control subjects may have actively requested endoscopic screening. In the process of endoscopy appointment for these control people, the worker of CDCs will check and exclude them if confirmed.

Statistical analysis

Continuous and categorical variables were analyzed using Student *t* test and the χ^2 test (or Fisher exact test), respectively. Variables with $P < 0.35$ in univariate analysis were entered into the logistic regression analysis using a backward step-down process performed using the likelihood ratio test to find independent risk factors for UGC precancerous lesions and *Helicobacter pylori* infection. All data management and statistical analyses were performed using Microsoft Excel 2010 and SPSS version 19.0 software (IBM Corp.). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline recruitment and potential risk factor distribution

Fifty-three communities in Changsha and 22 in Yueyang city were selected as our study sites. The communities were randomized into a screening arm (38 communities) and a control arm (37 communities) at a ratio of approximately 1:1 (detailed subject distribution shown in **Table 1**). A total of 27,116 individuals were contacted. Of these individuals, 20,156 consented to participate (10,531 subjects in the screening arm and 9,625 in the control arm), and the participation rate was 74.3%. After data cleaning, we excluded 115 and 60 participants from the screening and control arms, respectively, due to a prior history of cancer, age nonconformity, or repetitive identity numbers. The remaining 10,416 individuals in the screening arm and 9,565 in the control arm were enrolled in the study. The detailed flow of the study is shown in **Fig. 1**.

The screening and control arm consisted of 4,603 (44.2%) and 4,160 (43.5%) men, respectively, and they were nonsignificantly different. The average age of the screening arm was older than that of the control arm (55.12 vs. 54.45 years, $P < 0.001$). Other demographic characteristic variables and potential risk factors for UGC were also compared between the screening and control arms (**Table 2**; Supplementary Table S1). In the screening arm, 5,242 individuals (50.3%) were estimated to be high-risk. Similarly, we compared high-risk and non-high-risk group in screening arm on same factors, and found that most factors had significant difference. The risk did not differ significantly according to sex, ethnicity, marital status, consumption of bean products, or interpersonal relationships (**Table 2**; Supplementary Table S1).

Compliance of endoscopic screening

All high-risk subjects were invited to undergo endoscopic screening. Among them, 2,388 individuals participated in the endoscopic screening for UGC with a compliance rate of 45.6%.

We used univariate analysis to determine the endoscopy compliance rate according to baseline characteristics (**Table 3**). Then, with variables of $P < 0.35$ in univariate analysis entering into the multivariate analysis, we found age group and household income group were independently associated with the compliance rate. For example, compared with those aged 40 to 49 years, those aged 50 to 59 years and 60 to 69 years were significantly more likely to undergo screening endoscopy [OR = 1.49, 95% confidence interval (CI) = 1.30–1.70, $P < 0.001$; and OR = 1.27, 95% CI = 1.11–1.45, $P < 0.001$, respectively]. Participants with a household income between 40,000 and 80,000 CNY were more willing to accept endoscopy compared with participants with household income $\leq$40,000 CNY (OR = 1.41, 95% CI = 1.22–1.62, $P < 0.001$; Supplementary Table S2).

Endoscopic screening results for the screening arm

All positive or suspicious lesions were taken pathologic biopsy under endoscopy. Finally, 1,488 cases were detected pathologically (62.3%). Esophageal pathology results reported three cases of EC (0.13%), including two of severe hyperplasia and one of squamous carcinoma (Ib/T2N0M0 stage). Twenty-nine cases were diagnosed as esophageal precancerous lesions (1.21%), including two cases of moderate dysplasia and 27 of mild dysplasia. Moreover, we identified 152 cases of abnormality pathology, including 141 of mild esophagitis, eight of squamous acanthosis, two of basal cell hyperplasia, and one of moderate esophagitis.

Gastric pathology results reported one case (0.04%) of invasive adenocarcinoma (Ia/T1N0M0 stage). Fifty-three cases were diagnosed as gastric precancerous lesions (2.22%), including 16 cases of severe intestinal metaplasia, 6 of uncertain dysplasia, and 31 of mild dysplasia. Similarly, we found 1, 276 cases with other problems, including 1,123 cases of superficial gastritis, 83 of moderate intestinal metaplasia, 59 of mild intestinal metaplasia, 5 of atrophic gastritis, and 6 of other lesions.

Risk factors for esophageal and gastric precancerous lesions

Potential risk factors for esophageal and gastric precancerous lesions in the screening arm were first evaluated using univariate analysis; variables with $P < 0.35$ were entered into the logistic regression analysis. In the final multivariate model, older age (OR = 1.07; 95% CI = 1.02–1.13, $P = 0.006$), male gender (OR = 2.42; 95% CI = 1.11–5.27, $P = 0.026$), and family

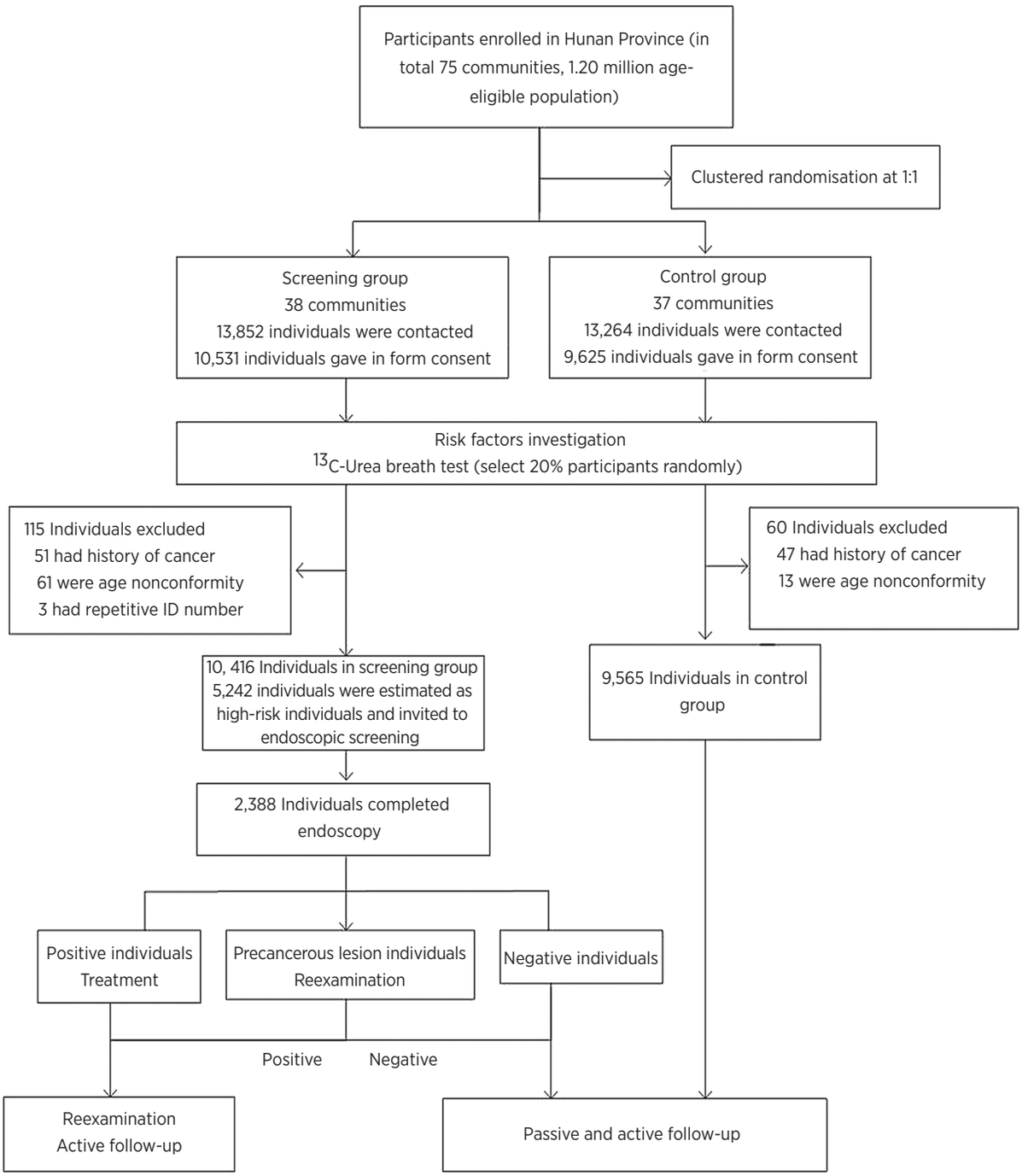

Figure 1.
Flow of participants in the questionnaire combined with endoscopy screening for upper gastrointestinal cancer.

history of cancer (OR = 2.62; 95% CI = 1.23–5.57, $P = 0.012$) were associated with a higher risk of esophageal precancerous lesions, while intake of meat–egg–milk frequently was a protective factor (OR = 0.36; 95% CI = 0.17–0.77, $P = 0.009$).

Older age (OR = 1.04; 95% CI = 1.01–1.08, $P = 0.026$) and male gender (OR = 2.34, 95% CI = 1.33–4.17, $P = 0.003$) were found to correlated with a higher risk of gastric precancerous lesions, while superficial gastritis (OR = 0.52; 95% CI = 0.28–0.96, $P = 0.036$) and clinical symptoms of gastric cancer (OR = 0.48; 95% CI = 0.26–0.90, $P = 0.022$) were related with a lower risk of gastric precancerous lesions (**Table 4**).

Table 3. Baseline characteristics of study population and compliance rates in different groups.

Factors	Participants of high risk of UGC (%)	Participants of undertaking endoscopy (%)	Compliance rate (%)	*P*
Sex				
Male	2,338 (44.6)	1,029 (43.1)	44.0	0.044
Female	2,904 (55.4)	1,359 (56.9)	46.8	
Age, y				
40–49	1,578 (30.1)	793 (33.2)	50.3	<0.001
50–59	1,774 (33.8)	827 (34.6)	46.6	
60–69	1,890 (36.1)	768 (32.2)	40.6	
Ethnicity				
Han	5,228 (99.7)	2,379 (99.6)	45.5	0.159
Others	14 (0.3)	9 (0.4)	64.3	
Body mass index (kg/m^2)				
<18.5	121 (2.3)	64 (2.7)	52.9	0.199
18.5–24.9	3,880 (74.0)	1,772 (74.2)	45.7	
≥25.0	1,241 (23.7)	552 (23.1)	44.5	
Education				
Primary school and below	1,126 (21.5)	475 (19.9)	42.2	0.035
Middle school	3,221 (61.4)	1,492 (62.5)	46.3	
College and above	895 (17.1)	421 (17.6)	47.0	
Marriage				
Married	5,126 (97.8)	2,328 (97.5)	45.4	0.177
Unmarried	116 (2.2)	60 (2.5)	51.7	
Household income (CNY)				
≤40,000	1,392 (26.6)	719 (30.1)	51.7	<0.001
40,000–80,000	2,234 (42.6)	970 (40.6)	43.4	
>80,000	1,616 (30.8)	699 (29.3)	43.3	
Family size				
>2	4,317 (82.4)	1,973 (82.6)	45.7	0.642
≤2	925 (17.6)	415 (17.4)	44.9	

Table 4. Multivariate logistic analysis of risk factors for esophageal and gastric precancerous lesions in screening group.

	Esophageal precancerous lesions				Gastric precancerous lesions			
Variables[a]	Case (*n* = 29) *n* (%)	Negative (*n* = 2359) *n* (%)	Adjusted OR (95% CI)	*P*	Case (*n* = 53) *n* (%)	Negative (*n* = 2335) *n* (%)	Adjusted OR (95% CI)	*P*
Age (**x** ±**s**)[b]	59.14 ± 7.45	54.79 ± 8.46	1.07 (1.02–1.13)	0.006	56.92 ± 7.48	54.25± 8.23	1.04 (1.01–1.08)	0.026
Gender								
Male	19 (65.5)	1,010 (42.8)	2.42 (1.11–5.27)	0.026	34 (64.2)	995 (42.6)	2.34 (1.33–4.17)	0.003
Female	10 (34.5)	1,349 (57.2)		Ref	19 (35.8)	1,340 (57.4)		Ref
Intake of meat-egg-milk frequently								
Yes	17 (58.6)	1,955 (82.9)	0.36 (0.17–0.77)	0.009	—	—	—	—
No	12 (41.4)	404 (17.1)		Ref	—	—	—	—
Family history of cancer								
Yes	13 (44.8)	538 (22.8)	2.62 (1.23–5.57)	0.012	—	—	—	—
No	16 (55.2)	1,821 (77.2)		Ref	—	—	—	—
Superficial gastritis								
Yes	—	—	—	—	15 (28.3)	975 (41.8)	0.52 (0.28–0.96)	0.036
No	—	—	—	—	38 (71.7)	1359 (58.2)		Ref
Clinical symptoms of gastric cancer[c]								
Yes	—	—	—	—	39 (73.6)	2023 (86.6)	0.48 (0.26–0.90)	0.022
No	—	—	—	—	14 (26.4)	312 (13.4)		Ref

[a]All variables were evaluated firstly by univariate analysis, then variables with $P < 0.35$ were selected into logistic regression analysis, and only significant variables were reported in the table.
[b]Variables were described by mean (**x**) and SD(**s**).
[c]Clinical symptoms of esophageal cancer refers to eating with retrosternal or subxiphoid pain and progressive dysphagia.

Table 5. The association between UGC precancerous lesions and HP infection.

Site	HP Positive		HP Negative		OR (95% CI)	*P*
	PL	Negative	PL	Negative		
Esophageal	6	461	9	813	1.18 (0.42–3.32)	0.760
Stomach	14	453	16	806	1.56 (0.75–3.22)	0.232
UGC	20	447	25	797	1.42 (0.78–2.60)	0.245

Abbreviations: CI: Confidence Interval; HP: Helicobacter Pylori; OR: Odd Ratio; PL: Precancerous Lesions; UGC: Upper Gastrointestinal Cancer.

Risk factors analysis of *Helicobacter pylori* infection and precancerous lesions

Twenty percent of the subjects ($n = 4{,}000$) were randomly selected from both arms to undergo *Helicobacter pylori* testing. Among the 3,617 subjects (90.5%) who completed the test, the infection rate was 35.1%. The infection rate was not significantly different between the screening (34.4%) and the control (35.7%) arms ($\chi^2 = 0.599$, $P = 0.439$). Potential risk factors for *Helicobacter pylori* infection were evaluated by univariate analysis, but no variable was associated with *Helicobacter pylori* infection (all $P > 0.05$).

Among the endoscopic screening participants, a total of 1,289 (53.88%) took the *Helicobacter pylori* test. We found 15 diagnosed cases of esophageal precancerous lesions and 30 of gastric precancerous lesions. The risks of esophageal precancerous lesions (OR = 1.18; 95% CI = 0.42–3.32, $P = 0.760$) and gastric precancerous lesions (OR = 1.56; 95% CI = 0.75–3.22, $P = 0.232$) were not associated with *Helicobacter pylori*–positive infection (**Table 5**).

Discussion

To our knowledge, screening for UGC has not been assessed in a randomized controlled trial in non-high-risk areas of China. In this interim analysis of the baseline screening, we reported the trial design, recruitment performance and preliminary screening results. Totally, 19,981 individuals were recruited with a participation rate of 74.3%, including 10,416 in the screening arm and 9,565 in the control arm. We designed a questionnaire to initially evaluate participants to identify those at high risk on UGC. In the screening arm, 50.3% of individuals were estimated to be high-risk and were invited to undergo endoscopy, with a compliance rate of 45.6%, and the compliance rate of endoscopy was associated with age and household income. The detection rates of endoscopy for early esophageal cancer, gastric cancer, ECPL, and GCPL were 0.13%, 0.04%, 1.21%, and 2.22%, respectively. Factors including age, sex, a family history of cancer, frequent intake of meat–eggs–milk, superficial gastritis, and clinical symptoms of gastric cancer were associated with the presence of precancerous lesions.

The rate of high-risk UGC individuals was high (50.3%) through questionnaire evaluation, which indicated that we did not effectively concentrate the UGC high-risk individuals. Probably, the high-risk eligibility of designed questionnaire was not strict enough. Moreover, adding another step evaluation using other tests could be required after questionnaire evaluation. Pepe and colleagues proposed a strategic process for biomarker development for cancer screening (23). Another cross-sectional study showed that five stomach-specific circulating biomarkers—pepsinogen I (PGI), PGII, PGI/II ratio, anti-*Helicobacter pylori* antibody, and gastrin-17—were effective for stratifying individuals' risk of developing gastric cancer (24).Therefore, in future research, we could apply these serology tests when targeting the high-risk UGC population and try to improve the questionnaire evaluation, so that a step-by-step strategy of evaluation could be developed.

Among the high-risk individuals, 2,388 participated in the endoscopic screening for UGC; the compliance rate of 45.6% was lower than the compliance rate in high-incidence areas (Linxian in Henan province, Feicheng in Shandong province, and Cixian in Hebei province; ref. 25). The main reason may be that people's awareness of early screening is lower in non-high-incidence areas than in high-incidence areas where screening for UGC has been conducted with substantial publicity by local government since the 1970s. Moreover, endoscopic screening is a traumatic procedure, especially when performed alongside biopsy. Some adverse effects might occur, including bleeding, mucosal laceration, anaphylactic shock, and respiratory depression (26). Even death while under sedation has been reported in Japan (27). Furthermore, some people do not tolerate the discomfort, because normal endoscopy was preferred in our study as it was free for them. Finally, the long screening process may have affected the participation rate. In our study, participants with hospital appointments on weekend mornings first underwent coagulation function tests that take about 1 hour to complete. If the result was normal, they were advised to undergo endoscopy. So there is room for improvement regarding the UGC screening process. Age group and household income level were independently associated with the compliance rate of endoscopy. The compliance rate of subjects with aged from 50 to 59 years old was higher than other two age groups. Probably, subjects in this age group pay more attention to their health, and participants with modern level of household income were more willing to accept endoscopy than lower level of household income. The underlying reasons included the poor awareness and knowledge about UGC screening for lower income subjects. In a word, this low participation rate indicated that the only endoscopy for UGC screening might not be appropriately performed in non-high-incidence area, and combining with some other simple biological test would be more acceptable.

Only 0.13% of esophageal cancer, 0.04% of gastric cancer, 1.21% of ECPL, and 2.22% of GCPL were diagnosed, indicating lower UGC detection rates than in high-incidence areas of China (25, 28, 29). Several Chinese scholars reported that the detection rate of endoscopic screening for esophageal cancer and gastric cancer was 0.15%–0.98% and 0.50%–0.86%, respectively, in high-incidence areas (25). As very few cases of UGC

were found, we analyzed the risk factors for precancerous lesions. Older age, male sex, and family history of cancer have been shown to be risk factors for UGPL, which have been conducted in high-incidence areas (30–32). A high consumption of protein, superficial gastritis, and clinical symptoms of gastric cancer were associated with a lower risk of UGPL. Possible reasons for this finding include better general health and closer monitoring of those with symptoms. Therefore, a risk prediction model for UGPL can be constructed on basis of these factors to identity accurately high-risk populations before clinical screening, thus making screening more efficient in non-high-incidence area for UGC by applying for the model in step-by-step evaluation.

Worldwide, the *Helicobacter pylori* infection rate is extremely high at over 60%; in developing countries, this rate goes up to 80% (33, 34). A study showed that the *Helicobacter pylori* infection rate is also high in China, ranging between 40% and 90% with an average of 59% (34). The rate of infection was not significantly different between the two arms, suggesting similar exposure. The average *Helicobacter pylori* infection rate was lower than the infection rate at national level, in high-incidence areas (35), even lower than other low-incidence area (42% in Guangdong province) from a national investigation with 26,341 individuals participated in among 19 provinces or municipality (30). Potential risk factors for *Helicobacter pylori* infection were evaluated by univariate analysis, but we found no association between any variable and *Helicobacter pylori* infection. This finding indicates that risk factors for *Helicobacter pylori* infection in non-high-incidence areas differ from those in high-incidence areas in China; it is necessary to design further studies to explore urbanized risk factors for *Helicobacter pylori* infection, to provide evidence for primary prevention.

Helicobacter pylori infection is closely associated with upper gastrointestinal diseases. A study suggested that esophageal cancer is related to gastroesophageal reflux disease, but every stage from reflux esophagitis to Barrett esophagus, dysplasia, and esophageal cancer is associated with *Helicobacter pylori* infection (36). We analyzed the correlation between *Helicobacter pylori* infection and precancerous lesions instead of cancer in this study, but there was no significant relation. At present, the association between *Helicobacter pylori* infection and esophageal cancer is controversial. Some scholars believe that *Helicobacter pylori* infection is a protective factor (37, 38), while others believe it is unrelated to esophageal cancer (39, 40). For *Helicobacter pylori* infection and gastric cancer, studies have reported that the change from normal gastric mucosa to atrophic gastritis is caused by *Helicobacter pylori* infection, resulting in the start of precancerous lesions, progression to atrophic gastritis and intestinal metaplasia, and final progression to hyperplasia and gastric cancer. At this point, gastric cancer is no longer considered to be due to *Helicobacter pylori* infection, indicating that the pathogenic effects of *Helicobacter pylori* infection mainly occur during the early stages of disease progression, thus increasing the risk of gastric cancer (41–43). Moreover, some therapeutic studies on *Helicobacter pylori* infection showed that *Helicobacter pylori* treatment could reduce the incidence of gastric cancer (43). According to the progression of gastric cancer, it can be inferred that *Helicobacter pylori* treatment can reduce the occurrence of GCPL, which is an effective measure to prevent the occurrence of gastric cancer. We found that *Helicobacter pylori* infection was also nonstatistically associated with the occurrence of GCPL, which is inconsistent with the findings above. This may be explained by the lower precancerous lesion detection rate in our study; a large-sample trial is needed to verify this in non-high-incidence areas.

Attention needs to be paid to the strengths and limitations of the study when interpreting the results. A major strength is that our study is the first to report the trial design, recruitment performance, and preliminary results of baseline endoscopy screening in a large community-based cluster-RCT of UGC in a non-high-incidence area of China. Second, the data quality was ensured by collecting detailed information on risk factors using a questionnaire administered by trained study staff, and questionnaire and clinical screening data (endoscopy and histology) were collected electronically in a standardized manner. Furthermore, the overall study design and implementation process was supported and monitored by an expert panel from the National Cancer Center to ensure the academic rigor and accuracy of the results. However, there are also some limitations. First, our trial is not a multicenter study as we just performed in two cities; therefore, the generalizability of our results could be limited to some extent. Second, we were not accessible for integrating data of other three non-high-incidence area from the national study. Thus, the sample of our study could not meet the original sample assumption of the national study, so that our results' generalizability on efficiency of screening strategy would be affected in the nation though future long-term follow-up. Third, as this was a cluster-RCT, not all eligible individuals participated, and Yuelu district have singular communities (in total 9 communities), in considering of some administrative reasons, 1:1 allocation rules had to be broken, so selection bias cannot be ruled out. Finally, our study did not evaluate the participation in recruitment due to limitations in the study design.

In summary, this study successfully recruited almost 20,000 individuals in a non-high-incidence area of UGC in China and 2,388 standard endoscopies were performed to detect early upper gastrointestinal lesions. The proportion of individuals with a high-risk of UGC was relatively high using questionnaire pre-screening, but the detection rate was low using endoscopy screening partially due to the relatively low compliance rate. Further efforts to optimize the identification of high-risk individuals and to develop a stepwise screening process using noninvasive biological tests are required. Moreover, we identified several factors associated with compliance in endoscopy screening and risk factors for UGPL. This provides a basis for constructing a risk prediction model for UGC precancerous lesions to accurately identify high-risk individuals before

endoscopy. Further follow-up of the study participants will provide valuable data regarding the effect of screening on esophageal cancer and gastric cancer mortality.

Disclosure of Potential Conflicts of Interest

H.-F. Xiao, S.-P. Yan, Y.-F. Chen, Z. Shi, Y.-H. Zou, S.-L. Zhu, K.-K. Xu, and X.-Z. Liao report receiving grants from Ministry of Health China during the conduct of the study (grant no. 201502001). No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: H.-F. Xiao, X.-Z. Liao
Development of methodology: H.-F. Xiao, X.-Z. Liao
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.-P. Yan, Y.-F. Chen, Z. Shi, Y.-H. Zou, S.-L. Zhu, K.-K. Xu, T. Song
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.-F. Xiao
Writing, review, and/or revision of the manuscript: H.-F. Xiao, X.-Z. Liao
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.-Z. Liao
Study supervision: H.-F. Xiao, X.-Z. Liao

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