Original Article

A cluster randomized controlled trial to evaluate the efficacy of esophageal and gastric cancer screening in mortality reduction in a non-high-incidence area: methodology and initial results

Xiao-Yang Wang, Shu-Zheng Liu, Hui-Fang Xu, Yin Liu, Hong Wang, Rui-Hua Kang, Qiong Chen, Lu-Yao Zhang, Lan-Wei Guo, Li-Yang Zheng, Chun-Ya Liu, Yi-Xian Wang, Yi-Ping Jing, You-Lin Qiao, Bin-Bin Han, Shao-Kai Zhang

Department of Cancer Epidemiology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Engineering Research Center of Cancer Prevention and Control, Henan International Joint Laboratory of Cancer Prevention, Zhengzhou, China

Contributions: (I) Conception and design: XY Wang, SK Zhang, BB Han; (II) Administrative support: SK Zhang, BB Han; (III) Provision of study materials: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: XY Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Bin-Bin Han; Shao-Kai Zhang. Department of Cancer Epidemiology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Engineering Research Center of Cancer Prevention and Control, Henan International Joint Laboratory of Cancer Prevention, Zhengzhou, China; Email: zlyyhanbinbin2859@zzu.edu.cn; shaokaizhang@126.com.

Background: A cluster randomized controlled trial of endoscopy-based screening for esophageal cancer (EC) and gastric cancer (GC) was conducted to evaluate the efficacy and feasibility of this strategy in a non-high-incidence rural area of China. The trial design and baseline findings are presented here.

Methods: A total of 33 eligible villages in Luoshan County in Henan Province were assigned randomly to the intervention or control group in a 1:1 ratio by a computer-generated randomization list. Local residents aged 40 to 69 years were enrolled from the villages. Participants in the intervention group were risk-stratified with a questionnaire, and high-risk individuals were subsequently screened by endoscopy. The primary outcomes were EC and GC mortality. The secondary outcomes comprised the detection rate, stage distribution, and the treatment rate. In this study, baseline characteristics were assessed by a questionnaire. Multivariate logistic regression analysis was performed to explore factors associated with endoscopy compliance.

Results: Trial recruitment was completed in 2017, and ultimately, there were 12,475 and 11,442 participants allocated to the intervention (17 clusters) and the control group (16 clusters), respectively. We included 23,653 participants in the analysis, with 12,402 in the intervention group and 11,251 in the control group. A total of 6,286 (50.7%) participants in the intervention group were estimated as high-risk individuals, and 2,719 (43.3%) underwent endoscopy. Multivariate logistic regression analysis demonstrated that some factors including age, gender, education, personality and mental health, and upper gastrointestinal diseases or symptoms might affect endoscopy compliance. The detection rates for positive cases of EC and GC were 0.22% and 0.55%, respectively. The rates for esophageal and gastric precancerous lesions were 0.70% and 2.35%, respectively. The early detection rates for EC and GC were 50.0% and 33.3%, respectively. Additionally, the overall treatment rate for positive cases was 90.0%.

Conclusions: The diagnostic yield of endoscopy-based screening for EC and GC was relatively low in a non-high-incidence rural area. The study may offer clues for the improvement of endoscopy compliance and the optimization of screening strategies for upper gastrointestinal cancer in non-high-incidence areas.

Trial Registration: Chinese Clinical Trial Registry ChiCTR-EOR-16008577.

Keywords: Upper gastrointestinal cancer; esophageal cancer (EC); gastric cancer (GC); endoscopy compliance; detection rate

Submitted Aug 03, 2022. Accepted for publication Sep 09, 2022.
doi: 10.21037/atm-22-4052
View this article at: https://dx.doi.org/10.21037/atm-22-4052

Introduction

Esophageal cancer (EC) and gastric cancer (GC) are common malignancies worldwide, responsible for 1.7 million estimated new cases and 1.3 million new deaths in 2020 (1). In China, EC and GC accounted for approximately 50% of global cases and deaths in 2020, imposing a heavy burden on public health (1). Because of the lack of typical early symptoms, many individuals are initially diagnosed with EC or GC in advanced stages, which may compromise treatment effectiveness and ultimately lead to a dismal prognosis (2). The overall 5-year survival rates of Chinese EC and GC patients are only 30.3% and 35.1%, respectively (3). However, the rates of early-stage EC and GC can be improved substantially to about 86% and 90%, respectively (4-6). Thus, there is a need to promote early detection and treatment of these malignancies to improve prognosis and reduce mortality.

Endoscopy-based screening programs for EC and GC have been implemented in several endemic countries such as Japan and South Korea, showing clinical benefits and mortality reduction (7-9). China has organized a series of endoscopic screening programs for upper gastrointestinal cancer in high-risk populations, with endoscopic examination of the esophagus and stomach at one time. Due to the high incidence and mortality rates of EC and GC in rural areas, the Cancer Screening Program in Rural Areas was launched in high-incidence rural areas in 2005. Such national programs subsequently expanded to Huai River Basin in 2007 (the Cancer Screening Program in Huai River Areas) and non-high-incidence urban areas in 2012 (the Cancer Screening Program in Urban Areas) (10). Currently, the Cancer Screening Program in Rural Areas has been reported to cover more than 200 counties and screen over 1.86 million high-risk individuals, making great advances in the early detection and treatment of upper gastrointestinal cancer.

Previous studies have demonstrated the effectiveness of endoscopic screening for EC and GC in high-incidence areas, which can result in an increase in early detection and a reduction in mortality (11-13). A 10-year follow-up study showed that the cumulative mortality and incidence of esophageal squamous cell carcinoma were significantly lower in the endoscopic screening group compared with the control group without screening (14). Such findings indicate the importance of endoscopic screening for prevention and control of EC and GC in high-incidence areas. However, considering its invasiveness and high cost, endoscopic screening for EC and GC may be not appropriate for the broad application in low- to intermediate-incidence areas (15). Accordingly, in such areas, risk-stratification assessment is recommended to identify subgroups with different risk levels for EC and GC, and high-risk individuals can be subsequently invited to undergo endoscopy (16,17). The endoscopy-based strategy seems to be reasonable for early detection, but evidence on the effectiveness of this approach in non-high-incidence is still insufficient. Therefore, a multi-center cluster randomized controlled trial (RCT) of EC and GC screening was carried out in 3 high-incidence areas and 4 non-high-incidence areas in China in 2015 (18). As part of the national study, a community-based RCT was launched in Luoshan County, one of the 4 non-high-incidence areas, to evaluate the efficacy of endoscopic screening for EC and GC in mortality reduction, and the feasibility of the risk assessment in combination with endoscopic examination in non-high-incidence rural areas. Herein, we reported the baseline characteristics of study participants, endoscopy compliance and its associated factors, and the detection rates as well as the treatment rates of EC and GC in the first-round screening. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4052/rc).

Methods

Study design

We prospectively conducted a community-based cluster RCT. A total of 33 eligible villages in Luoshan County in Henan Province served as the allocation units (clusters) in this trial. We excluded clusters if they underwent endoscopic screening in the last 3 years, or were unwilling to participate. The 33 clusters were assigned randomly to the intervention or control group in a 1:1 ratio. Enrollment began in May 2015 and was completed by July 2017, and then follow-up would last at least 10 years. The study was approved

by the independent ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 2015SQ00223). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and there were no substantial changes to the methods after trial commencement. As part of the multi-center study, more details of this trial can be found in previous literature (18,19).

Randomization and masking

Randomization was performed on the basis of cluster. Villages rather than individuals were regarded as units of randomization, and were allocated to the intervention (N=17) or control (N=16) group by a computer-generated randomization list. Local health workers enrolled participants and completed the allocation in accordance with the group assignment. Researchers, local health workers, and study participants could not be blinded to randomization procedures.

Participant eligibility

Local residents in the eligible villages were considered for inclusion according to the following criteria: aged 40–69 years old, with no history of cancer, being in good physical and mental condition, and having undergone no endoscopic examinations in the past 3 years. Residents who were not willing to undergo endoscopic screening, or had severe diseases that might interfere with participation, were excluded from the trial. Sample size calculation has been described in detail previously (18). After describing the study, local health workers obtained written informed consent from participants.

Interventions

The interventions pertain to the individual level. All the participants in this trial were invited to complete a standardized questionnaire during face-to-face interviews, and underwent physical examination including measurement of height, weight, and blood pressure. The questionnaire covered demography, personality and mental health, behavioral habits, dietary habits, family history of cancer, disease history, and clinical symptoms of EC and GC. Only participants in the intervention group were evaluated to determine whether they were at high risk of upper gastrointestinal cancer by the questionnaire assessment. The assessment criteria has been reported elsewhere (19,20). In brief, participants would be defined as "high-risk individuals" if they met any 2 of items (I)–(III) or any 1 of (IV)–(VI): (I) smoking more than 20 cigarettes per day for at least 10 years; (II) drinking 28 g ethanol or more per day for at least 10 years; (III) eating moldy, salted, or fried food at least once per week; (IV) family history of upper gastrointestinal cancer; (V) upper gastrointestinal symptoms including dysphagia, chest/back pain during swallowing, nausea/vomiting/belching, heartburn/acid regurgitation/abdominal distention, inappetence, epigastric pain, melena, and unexplained weight loss; (VI) personal history of upper gastrointestinal diseases such as reflux esophagitis and gastritis.

High-risk individuals in the intervention group were invited to undergo endoscopic examination in the designated hospitals. Some routine tests were carried out to detect human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis. Standard upper endoscopic examination was then performed by experienced physicians according to the technical proposal for the upper gastrointestinal cancer screening project. The esophagus and stomach were examined visually, and chromoendoscopy with Lugol's iodine staining or indigo carmine dye would be performed to diagnose suspicious lesions in the esophagus or stomach if necessary. Only positive or suspicious lesions were targeted for biopsy, and pathological diagnosis was then determined independently by 2 experienced pathologists. Positive cases were defined as follows: esophageal severe dysplasia, esophageal carcinoma *in situ*, EC, gastric high-grade dysplasia, and GC. Among these, esophageal severe dysplasia, esophageal carcinoma *in situ*, gastric high-grade dysplasia, and stage I EC/GC were considered as early-stage cases.

Follow-up

Outcomes were assessed by both passive and active follow-up annually. Passive follow-up was conducted for all the participants, and data were collected through databases of cancer registries, medical records, death surveillance, and medical insurance. Positive cases identified at baseline and passive follow-up would be interviewed via telephone or home visit by trained health workers. Participants with precancerous lesions would receive an endoscopic reexamination. Specifically, participants with esophageal mild dysplasia were required to undergo a reexamination every 3 years, and those with esophageal moderate dysplasia,

cardia or gastric low-grade dysplasia, severe intestinal metaplasia, or severe atrophic gastritis were required to undergo a reexamination every year.

Outcomes

Outcomes were measured at the individual level. The primary outcomes were EC and GC mortality. The secondary outcomes comprised the detection rate (the proportion of positive cases among participants undergoing endoscopy), the early detection rate (the proportion of cases in stage 0/I among all the positive cases), and the treatment rate (the proportion of positive cases receiving clinical treatment). There were no changes to outcomes after the trial commenced.

Statistical analysis

Baseline characteristics of participants were reported for the intervention and control groups. Student's *t* test was employed to compare 2 groups with respect to continuous variables, and the Chi-square test or Fisher's exact test was performed for categorical variables. To explore factors potentially involved in endoscopy compliance (the proportion of participants undergoing endoscopy among high-risk individuals), univariate logistic regression analyses were performed, and variables with P<0.1 were selected for subsequent multivariate analysis. A multivariate regression model was then developed to estimate odds ratios (ORs) as well as 95% confidence intervals (CIs). Statistical analyses were conducted using R v3.6.1, and a two-sided P value of <0.05 was considered statistically significant.

Results

Enrollment and participant characteristics

Between May 2015 and July 2017, a total of 23,917 individuals from 33 villages attended the baseline survey, with 12,475 allocated to the intervention group (17 villages) and 11,442 allocated to the control group (16 villages). Of these, 264 were excluded owing to personal cancer history (N=146), received endoscopy examinations in the past 3 years (N=93), age nonconformity (N=12), or erroneous data (N=13). Finally, 23,653 individuals were eligible for inclusion in the analysis, with 12,402 in the intervention group and 11,251 in the control group (*Figure 1*).

Baseline characteristics including age, gender, marital status, smoking, and strong adaptability were well balanced between the trial groups (P>0.05). The average (± SD) age of participants was 52.1 (±7.8). About 51.3% of participants were men, and the majority of participants (94.2%) were married. A total of 80.2% of participants never smoked. In addition, most participants (92.9%) reported that they had strong adaptability. Other variables on sociodemographic characteristics and risk factors are reported in *Table 1*.

Endoscopy compliance and its associated factors

In the intervention group, 12,402 participants finished the questionnaire. Of these, 6,286 (50.7%) were estimated as high-risk individuals and were invited to receive endoscopic examination. There were ultimately 2,719 participants undergoing endoscopy. The compliance rate of endoscopy was 43.3%.

To explore factors associated with endoscopy compliance, we performed univariate logistic regression analyses based on variables presented in *Table 1*. Significant variables (P<0.1) were then incorporated into a multivariate logistic regression model. As shown in *Table 2*, the results demonstrated that participants aged 50–59 and 60–69 years were more likely to undergo endoscopy than those aged 40–49 years (OR =1.38, 95% CI: 1.22–1.56, P<0.001; OR =1.82, 95% CI: 1.58–2.10, P<0.001). Compared with males, females showed higher endoscopy compliance (OR =1.38, 95% CI: 1.24–1.54, P<0.001). Participants who completed primary school, middle school, or college and above had a higher probability of attending endoscopy than those with no schooling (OR =1.41, 95% CI: 1.15–1.74, P=0.001; OR =1.68, 95% CI: 1.34–2.11, P<0.001; OR =2.70, 95% CI: 1.27–5.88, P=0.011). Regarding personality and mental health, participants that did not have a type A personality or strong adaptability, or those with depression were less likely to accept endoscopic examination (OR =0.78, 95% CI: 0.69–0.87, P<0.001; OR =0.78, 95% CI: 0.64–0.95, P=0.016; OR =0.54, 95% CI: 0.35–0.80, P=0.003). Furthermore, participants with a personal history of gastric and duodenal ulcers or superficial gastritis were more prone to undergo endoscopy (OR =1.38, 95% CI: 1.18–1.62, P<0.001; OR =1.16, 95% CI: 1.03–1.30, P=0.014). Positive associations were observed between upper gastrointestinal symptoms and endoscopy compliance. Participants with heartburn, acid regurgitation, and abdominal distention tended to attend endoscopic screening (OR =1.38, 95% CI: 1.22–1.56, P<0.001). Likewise, participants with nausea,

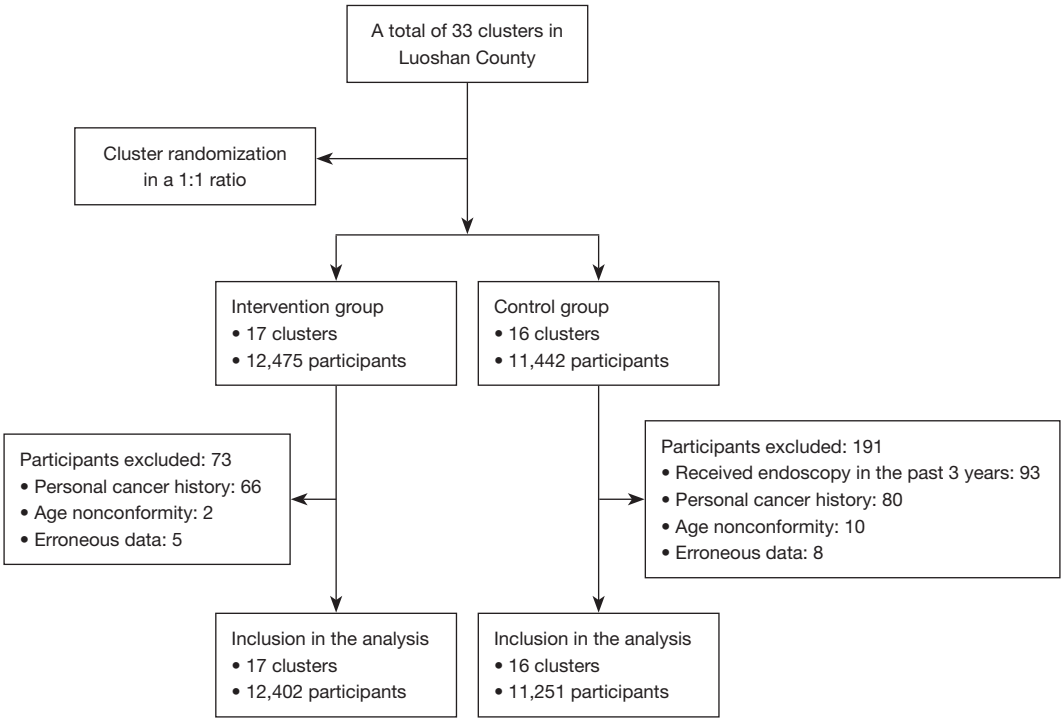

Figure 1 Participant flow diagram of the trial.

vomiting, and belching showed greater odds of endoscopy compliance (OR =1.43, 95% CI: 1.28–1.60, P<0.001), and those with dysphagia or epigastric pain exhibited similar results (OR =1.57, 95% CI: 1.12–2.20, P=0.008; OR =1.38, 95% CI: 1.24–1.53, P<0.001).

Esophageal and gastric cancer detection

Among participants receiving endoscopy examination, a total of 1,784 (65.6%) participants underwent pathological biopsy due to positive or suspicious lesions. There were 20 positive cases detected, with a detection rate of 0.74%. The pathological distribution of all the lesions is shown in *Table 3*. Out of the 36 cases with esophageal lesions, 6 were reported as positive cases (0.22%), including 3 cases of EC and 3 cases of severe dysplasia. Moreover, 19 cases with esophageal precancerous lesions were detected (0.70%), with 7 moderate dysplasia cases and 12 mild dysplasia cases. Other abnormal esophageal pathology results included 1 case of moderate esophagitis and 10 cases of basal cell hyperplasia. With regard to the 1,623 cases with stomach lesions, 15 were identified as positive cases (0.55%), including 12 cases of GC and 3 cases of high-grade dysplasia. The 64 cases with stomach precancerous lesions (2.35%) consisted of 28 low-grade dysplasia cases and 36 severe atrophic gastritis cases. Other abnormal stomach pathology results included 128 cases of moderate atrophic gastritis, 88 cases of mild atrophic gastritis, and 1,328 cases of non-atrophic gastritis.

Clinical stage and treatment of positive cases

Clinical stage and treatment information of positive cases are shown in *Table 4*. Out of the 20 positive cases, 8 (40.0%) were in the early stage. The early detection rates for EC and GC were 50.0% and 33.3%, respectively. Additionally, the overall treatment rate for positive cases was 90.0%. For EC, all the 6 (100.0%) positive cases received clinical treatment. For GC, 13 cases received treatment, with a treatment rate of 86.7%.

Discussion

The efficacy and feasibility of endoscopy-based screening for EC and GC in non-high-incidence rural areas of China are not clear. Here, we conducted a cluster RCT with at least 10 years of follow-up and reported the baseline findings. After the questionnaire assessment was completed,

Table 1 Baseline characteristics of study participants

Variables	Total	Intervention group	Control group	P
Age (years), mean (SD)	52.1 (7.8)	52.2 (7.8)	52.0 (7.8)	0.058
40–49	10,357 (43.8)	5,327 (43.0)	5,030 (44.7)	0.023
50–59	8,052 (34.0)	4,297 (34.6)	3,755 (33.4)	
60–69	5,244 (22.2)	2,778 (22.4)	2,466 (21.9)	
Gender, n (%)				
Male	12,130 (51.3)	6,345 (51.2)	5,785 (51.4)	0.693
Female	11,523 (48.7)	6,057 (48.8)	5,466 (48.6)	
Ethnicity, n (%)				
Han	23,630 (99.9)	12,395 (99.9)	11,235 (99.9)	0.035
Others	23 (0.1)	7 (0.1)	16 (0.1)	
Education, n (%)				
No schooling	1,481 (6.3)	810 (6.5)	671 (6.0)	<0.001
Primary school	14,097 (59.6)	7,559 (60.9)	6,538 (58.1)	
Middle school	7,966 (33.7)	3,982 (32.1)	3,984 (35.4)	
College and above	109 (0.5)	51 (0.4)	58 (0.5)	
Marital status, n (%)				
Not married/divorced/widowed	1,377 (5.8)	739 (6.0)	638 (5.7)	0.345
Married	22,276 (94.2)	11,663 (94.0)	10,613 (94.3)	
Family size[a], n (%)				
≤2	2,098 (8.9)	1,049 (8.5)	1,049 (9.3)	0.019
>2	21,552 (91.1)	11,353 (91.5)	10,199 (90.7)	
Smoking[a], n (%)				
No	18,968 (80.2)	9,983 (80.5)	8,985 (79.9)	0.226
Yes	4,684 (19.8)	2,419 (19.5)	2,265 (20.1)	
Drinking, n (%)				
No	19,825 (83.8)	10,600 (85.5)	9,225 (82.0)	<0.001
Yes	3,828 (16.2)	1,802 (14.5)	2,026 (18.0)	
Type A personality[a], n (%)				
Yes	16,510 (69.8)	8,133 (65.6)	8,377 (74.5)	<0.001
No	7,142 (30.2)	4,269 (34.4)	2,873 (25.5)	
Strong adaptability[a], n (%)				
Yes	21,960 (92.9)	11,550 (93.1)	10,410 (92.5)	0.079
No	1,691 (7.1)	852 (6.9)	839 (7.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total	Intervention group	Control group	P
Trauma[a], n (%)				
No	22,739 (96.1)	11,990 (96.7)	10,749 (95.6)	<0.001
Yes	911 (3.9)	411 (3.3)	500 (4.4)	
Depression, n (%)				
No	23,252 (98.3)	12,224 (98.6)	11,028 (98.0)	0.001
Yes	401 (1.7)	178 (1.4)	223 (2.0)	
Gastric and duodenal ulcers, n (%)				
No	22,254 (94.1)	11,571 (93.3)	10,683 (95.0)	<0.001
Yes	1,399 (5.9)	831 (6.7)	568 (5.0)	
Reflux esophagitis, n (%)				
No	22,638 (95.7)	11,765 (94.9)	10,873 (96.6)	<0.001
Yes	1,015 (4.3)	637 (5.1)	378 (3.4)	
Superficial gastritis, n (%)				
No	20,108 (85.0)	10,326 (83.3)	9,782 (86.9)	<0.001
Yes	3,545 (15.0)	2,076 (16.7)	1,469 (13.1)	
Atrophic gastritis, n (%)				
No	23,450 (99.1)	12,278 (99.0)	11,172 (99.3)	0.013
Yes	203 (0.9)	124 (1.0)	79 (0.7)	
Family history of cancer, n (%)				
No	22,759 (96.2)	11,967 (96.5)	10,792 (95.9)	0.021
Yes	894 (3.8)	435 (3.5)	459 (4.1)	
Dysphagia, n (%)				
No	23,441 (99.1)	12,246 (98.7)	11,195 (99.5)	<0.001
Yes	212 (0.9)	156 (1.3)	56 (0.5)	
Heartburn, acid regurgitation, and abdominal distention, n (%)				
No	18,004 (76.1)	7,960 (64.2)	10,044 (89.3)	<0.001
Yes	5,649 (23.9)	4,442 (35.8)	1,207 (10.7)	
Nausea, vomiting, and belching, n (%)				
No	20,073 (84.9)	9,457 (76.3)	10,616 (94.4)	<0.001
Yes	3,580 (15.1)	2,945 (23.7)	635 (5.6)	
Epigastric pain, n (%)				
No	20,279 (85.7)	9,587 (77.3)	10,692 (95.0)	<0.001
Yes	3,374 (14.3)	2,815 (22.7)	559 (5.0)	

[a], there were missing values. SD, standard deviation.

Table 2 Factors associated with endoscopy compliance assessed by multivariate logistic regression analysis

Variables	Endoscopy (N=2,719)	No endoscopy (N=3,567)	Adjusted OR (95% CI)	P
Age, n (%)				
40–49	798 (29.3)	1,349 (37.8)	Ref.	
50–59	1,034 (38.0)	1,304 (36.6)	1.38 (1.22–1.56)	<0.001
60–69	887 (32.6)	914 (25.6)	1.82 (1.58–2.10)	<0.001
Gender, n (%)				
Male	1,175 (43.2)	1,855 (52.0)	Ref.	
Female	1,544 (56.8)	1,712 (48.0)	1.38 (1.24–1.54)	<0.001
Education, n (%)				
No schooling	193 (7.1)	286 (8.0)	Ref.	
Primary school	1,680 (61.8)	2,162 (60.6)	1.41 (1.15–1.74)	0.001
Middle school	828 (30.5)	1,106 (31.0)	1.68 (1.34–2.11)	<0.001
College and above	18 (0.7)	13 (0.4)	2.70 (1.27–5.88)	0.011
Type A personality, n (%)				
Yes	1,916 (70.5)	2,262 (63.4)	Ref.	
No	803 (29.5)	1,305 (36.6)	0.78 (0.69–0.87)	<0.001
Strong adaptability, n (%)				
Yes	2,546 (93.6)	3,244 (90.9)	Ref.	
No	173 (6.4)	323 (9.1)	0.78 (0.64–0.95)	0.016
Depression, n (%)				
No	2,682 (98.6)	3,482 (97.6)	Ref.	
Yes	37 (1.4)	85 (2.4)	0.54 (0.35–0.80)	0.003
Gastric and duodenal ulcers, n (%)				
No	2,304 (84.7)	3,220 (90.3)	Ref.	
Yes	415 (15.3)	347 (9.7)	1.38 (1.18–1.62)	<0.001
Superficial gastritis, n (%)				
No	1,736 (63.8)	2,582 (72.4)	Ref.	
Yes	983 (36.2)	985 (27.6)	1.16 (1.03–1.30)	0.014
Dysphagia, n (%)				
No	2,626 (96.6)	3,504 (98.2)	Ref.	
Yes	93 (3.4)	63 (1.8)	1.57 (1.12–2.20)	0.008
Heartburn, acid regurgitation, and abdominal distention, n (%)				
No	649 (23.9)	1,195 (33.5)	Ref.	
Yes	2,070 (76.1)	2,372 (66.5)	1.38 (1.22–1.56)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Endoscopy (N=2,719)	No endoscopy (N=3,567)	Adjusted OR (95% CI)	P
Nausea, vomiting, and belching, n (%)				
No	1,289 (47.4)	2,170 (60.8)	Ref.	
Yes	1,430 (52.6)	1,397 (39.2)	1.43 (1.28–1.60)	<0.001
Epigastric pain, n (%)				
No	1,363 (50.1)	2,108 (59.1)	Ref.	
Yes	1,356 (49.9)	1,459 (40.9)	1.38 (1.24–1.53)	<0.001

OR, odds ratio; CI, confidence interval.

Table 3 Pathological distribution of lesions detected by endoscopy with biopsy

Pathological diagnosis	Cases	Detection rate (%)
Subjects under endoscopy	2,719	
Esophagus		
Esophageal cancer	3	0.11
Severe dysplasia	3	0.11
Moderate dysplasia	7	0.26
Mild dysplasia	12	0.44
Moderate esophagitis	1	0.04
Basal cell hyperplasia	10	0.37
Stomach		
Gastric cancer	12	0.44
High-grade dysplasia	3	0.11
Low-grade dysplasia	28	1.03
Severe atrophic gastritis	36	1.32
Moderate atrophic gastritis	128	4.71
Mild atrophic gastritis	88	3.24
Non-atrophic gastritis	1,328	48.84
Positive cases in total	20	0.74

Table 4 Stage distribution and treatment rate for positive cases

Variables	All (N=20)	Esophagus (N=6)	Stomach (N=15)
Stage, n (%)			
0	4 (20.0)	2 (33.3)	2 (13.3)
I	4 (20.0)	1 (16.7)	3 (20.0)
II	6 (30.0)	1 (16.7)	6 (40.0)
III/IV	6 (30.0)	2 (33.3)	4 (26.7)
Early stage[a], n (%)			
No	12 (60.0)	3 (50.0)	10 (66.7)
Yes	8 (40.0)	3 (50.0)	5 (33.3)
Treatment, n (%)			
No	2 (10.0)	0 (0.0)	2 (13.3)
Yes	18 (90.0)	6 (100.0)	13 (86.7)

[a], positive cases at stage 0/I.

high-risk individuals in the intervention group were invited to undergo endoscopic examination, with a compliance rate of 43.3%. Multivariate logistic regression analysis showed that several factors including age, gender, education, personality and mental health, and upper gastrointestinal diseases or symptoms might affect endoscopy compliance. The detection rate for positive cases of EC or GC was 0.74%, and of the positive cases, 40.0% were in the early stage. Furthermore, the overall treatment rate for positive cases was 90.0%. Our findings may offer important clues for optimal screening strategies for EC and GC in non-high-incidence areas of China.

For upper gastrointestinal cancer screening programs implemented in high-incidence areas of China, all the local participants are regarded as high-risk individuals and are invited to undergo endoscopy. However, owing to the invasiveness and high cost of this technique, participants in non-high-incidence areas are first risk-stratified with a standardized questionnaire, and only those evaluated as high-risk individuals are advised to attend endoscopic examination. As a result, we found that about half (50.7%) of the participants completing the risk assessment were

estimated as high-risk individuals, while the detection rate for positive cases of EC or GC was low (0.74%). These results suggest that the risk assessment tool used in non-incidence areas may not accurately distinguish risk levels, and further risk stratification methods need to be developed to identify high-risk individuals. Numerous studies have indicated that multiple biomarkers such as tumor-associated antigens, autoantibodies, miRNAs, and methylated DNA markers exhibit good performance for the early detection and diagnosis of EC and GC (21-26). Thus, the combination of epidemiological risk factors (obtained by the questionnaire) and promising biomarkers, which may be used to develop risk prediction models, may help to optimize the risk stratification and improve screening efficacy.

In this study, the endoscopy compliance rate of high-risk individuals in the intervention group was 43.3%, which was relatively lower than that in high-incidence areas of China such as Feicheng, Linzhou, and Cixian (14,27,28). One of the possible reasons was the differences in awareness of upper gastrointestinal cancer screening among these areas (29). For decades, upper gastrointestinal cancer prevention and control programs, along with publicity and education, have been implemented in high-incidence areas (20). Numerous studies such as risk factor research, general population nutrition intervention trials, dysplasia population nutrition intervention trials, and chemoprevention trials have been also performed in these areas (30-38). Such efforts not only resulted in a decrease in incidence (30), but also probably increased the awareness of cancer prevention. Thus, there is a need to enhance social mobilization campaigns and health education on cancer prevention and screening in non-high-incidence areas. Moreover, we found that some factors were significantly associated with endoscopy compliance. As a result, elderly individuals and females were more likely to undergo endoscopic examination. This is probably because such populations prefer to attend education sessions and follow healthcare advice (39). Another prominent factor associated with endoscopy compliance was educational attainment, with relatively well-educated individuals more prone to attend endoscopy. This may be because individuals with higher education have greater awareness and knowledge of cancer prevention (40). We also observed that participants that did not have a type A personality or strong adaptability, or those with depression showed lower endoscopy compliance, which is a reflection that negative personality or mental health issues probably affect health-related behaviors. Furthermore, participants with upper gastrointestinal symptoms (dysphagia, epigastric pain, heartburn, acid regurgitation and abdominal distention, nausea, vomiting, and belching) or a personal history of upper gastrointestinal diseases (gastric and duodenal ulcers, superficial gastritis) tended to participate in endoscopic screening. Part of the reason may be that these individuals have a relatively more urgent need to seek medical help for upper gastrointestinal problems and thus accept endoscopy. Based on these findings, targeted education, especially targeting males, individuals aged 40–49 years, those with lower education levels, or those with negative personality traits, will be important for the improvement of endoscopy compliance.

The detection rates for positive cases of EC and GC were 0.22% and 0.55%, respectively, which were lower than those in high-incidence areas in previous studies (27,41). The reasons may include differences in the prevalence of upper gastrointestinal cancer between these areas, and a lack of endoscopy training or experience in non-high-incidence areas (42). This also suggests that the risk assessment needs to be improved to identify high-risk individuals more efficiently.

Despite the large community-based RCT design with long-term follow-up and quality implementation processes, our study still has several limitations. First, the trial was only part of a multi-center study, which might affect the generalizability of the research findings. Second, selection bias due to nonparticipation in the recruitment and endoscopy screening processes probably influenced the validity of the results. Further analyses will be performed in our subsequent study to investigate and adjust for potential selection bias.

Overall, our study is a cluster community-based RCT of EC and GC screening in a non-high-incidence area of China, with a total of 23,917 participants included in the trial. The preliminary results described baseline recruitment, endoscopy participation and its associated factors, detection of positive cases, and treatment rates. The findings highlight the need to develop efficient risk assessment in non-high-incidence areas, and indicate the importance of improving endoscopy compliance partly through targeted education. Follow-up of study participants is progressing, which is expected to offer further clues as to the efficacy of endoscopy-based screening for EC and GC and the feasibility of this screening strategy in non-high-incidence areas.

Acknowledgments

We gratefully acknowledge the team at the National Cancer Center and all the staff as well as the participants in this study for their support and contribution to this work.
Funding: This study was funded by the Special Fund for Health Research in the Public Interest (No. 201502001).

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4052/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4052/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4052/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4052/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the independent ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 2015SQ00223). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Santero M, Pérez-Bracchiglione J, Acosta-Dighero R, et al. Efficacy of systemic oncological treatments in patients with advanced esophageal or gastric cancers at high risk of dying in the middle and short term: an overview of systematic reviews. BMC Cancer 2021;21:712.
3. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018;6:e555-67.
4. Wang GQ, Jiao GG, Chang FB, et al. Long-term results of operation for 420 patients with early squamous cell esophageal carcinoma discovered by screening. Ann Thorac Surg 2004;77:1740-4.
5. Katai H, Ishikawa T, Akazawa K, et al. Five-year survival analysis of surgically resected gastric cancer cases in Japan: a retrospective analysis of more than 100,000 patients from the nationwide registry of the Japanese Gastric Cancer Association (2001-2007). Gastric Cancer 2018;21:144-54.
6. Xia R, Zeng H, Liu W, et al. Estimated Cost-effectiveness of Endoscopic Screening for Upper Gastrointestinal Tract Cancer in High-Risk Areas in China. JAMA Netw Open 2021;4:e2121403.
7. Mabe K, Inoue K, Kamada T, et al. Endoscopic screening for gastric cancer in Japan: Current status and future perspectives. Dig Endosc 2022;34:412-9.
8. Hamashima C; Systematic Review Group and Guideline Development Group for Gastric Cancer Screening Guidelines. Update version of the Japanese Guidelines for Gastric Cancer Screening. Jpn J Clin Oncol 2018;48:673-83.
9. Jun JK, Choi KS, Lee HY, et al. Effectiveness of the Korean National Cancer Screening Program in Reducing Gastric Cancer Mortality. Gastroenterology 2017;152:1319-1328.e7.
10. Zhou J, Zheng R, Zhang S, et al. Gastric and esophageal cancer in China 2000 to 2030: Recent trends and short-term predictions of the future burden. Cancer Med 2022;11:1902-12.
11. Codipilly DC, Qin Y, Dawsey SM, et al. Screening for esophageal squamous cell carcinoma: recent advances. Gastrointest Endosc 2018;88:413-26.
12. Chen R, Liu Y, Song G, et al. Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. Gut 2021;70:251-60.

13. Chen Q, Yu L, Hao CQ, et al. Effectiveness of endoscopic gastric cancer screening in a rural area of Linzhou, China: results from a case-control study. Cancer Med 2016;5:2615-22.
14. Wei WQ, Chen ZF, He YT, et al. Long-Term Follow-Up of a Community Assignment, One-Time Endoscopic Screening Study of Esophageal Cancer in China. J Clin Oncol 2015;33:1951-7.
15. Marabotto E, Pellegatta G, Sheijani AD, et al. Prevention Strategies for Esophageal Cancer-An Expert Review. Cancers (Basel) 2021;13:2183.
16. Choi IJ. Endoscopic gastric cancer screening and surveillance in high-risk groups. Clin Endosc 2014;47:497-503.
17. Rubenstein JH, Thrift AP. Risk factors and populations at risk: selection of patients for screening for Barrett's oesophagus. Best Pract Res Clin Gastroenterol 2015;29:41-50.
18. Chen W, Zeng H, Chen R, et al. Evaluating efficacy of screening for upper gastrointestinal cancer in China: a study protocol for a randomized controlled trial. Chin J Cancer Res 2017;29:294-302.
19. Zeng H, Sun K, Cao M, et al. Initial results from a multi-center population-based cluster randomized trial of esophageal and gastric cancer screening in China. BMC Gastroenterol 2020;20:398.
20. Xiao HF, Yan SP, Chen YF, et al. Community-Based Upper Gastrointestinal Cancer Screening in a Randomized Controlled Trial: Baseline Results in a Non-high-incidence Area. Cancer Prev Res (Phila) 2020;13:317-28.
21. Xu YW, Peng YH, Chen B, et al. Autoantibodies as potential biomarkers for the early detection of esophageal squamous cell carcinoma. Am J Gastroenterol 2014;109:36-45.
22. Kannan S, Lakku RA, Niranjali D, et al. Expression of peanut agglutinin-binding mucin-type glycoprotein in human esophageal squamous cell carcinoma as a marker. Mol Cancer 2003;2:38.
23. Miyoshi J, Zhu Z, Luo A, et al. A microRNA-based liquid biopsy signature for the early detection of esophageal squamous cell carcinoma: a retrospective, prospective and multicenter study. Mol Cancer 2022;21:44.
24. Qin Y, Wu CW, Taylor WR, et al. Discovery, Validation, and Application of Novel Methylated DNA Markers for Detection of Esophageal Cancer in Plasma. Clin Cancer Res 2019;25:7396-404.
25. Liu K, Zhao T, Wang J, et al. Etiology, cancer stem cells and potential diagnostic biomarkers for esophageal cancer. Cancer Lett 2019;458:21-8.
26. Herrera-Pariente C, Montori S, Llach J, et al. Biomarkers for Gastric Cancer Screening and Early Diagnosis. Biomedicines 2021;9:1448.
27. Wang M, Hao C, Ma Q, et al. DNA image cytometry test for primary screening of esophageal cancer: a population-based multi-center study in high-risk areas in China. Chin J Cancer Res 2016;28:404-12.
28. Zhang N, Li Y, Chang X, et al. Long-term effectiveness of one-time endoscopic screening for esophageal cancer: A community-based study in rural China. Cancer 2020;126:4511-20.
29. Jia S, Li H, Zeng H, et al. Association of cancer prevention awareness with esophageal cancer screening participation rates: Results from a population-based cancer screening program in rural China. Chin J Cancer Res 2019;31:601-8.
30. Wang SM, Abnet CC, Qiao YL. What have we learned from Linxian esophageal cancer etiological studies? Thorac Cancer 2019;10:1036-42.
31. Islami F, Ren JS, Taylor PR, et al. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer 2009;101:1641-7.
32. Kamangar F, Chow WH, Abnet CC, et al. Environmental causes of esophageal cancer. Gastroenterol Clin North Am 2009;38:27-57, vii.
33. Wei WQ, Abnet CC, Lu N, et al. Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. Gut 2005;54:759-63.
34. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 2005;113:456-63.
35. Wang SM, Taylor PR, Fan JH, et al. Effects of Nutrition Intervention on Total and Cancer Mortality: 25-Year Post-trial Follow-up of the 5.25-Year Linxian Nutrition Intervention Trial. J Natl Cancer Inst 2018;110:1229-38.
36. Taylor PR, Qiao YL, Abnet CC, et al. Prospective study of serum vitamin E levels and esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1414-6.
37. Wang JB, Abnet CC, Fan JH, et al. The randomized Linxian Dysplasia Nutrition Intervention Trial after 26 years of follow-up: no effect of multivitamin supplementation on mortality. JAMA Intern Med 2013;173:1259-61.
38. Limburg PJ, Wei W, Ahnen DJ, et al. Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. Gastroenterology 2005;129:863-73.

39. Deeks A, Lombard C, Michelmore J, et al. The effects of gender and age on health related behaviors. BMC Public Health 2009;9:213.
40. Li H, Zeng HM, Zou XN, et al. Awareness of cancer prevention knowledge among rural residents in the middle of China. China Cancer (Chinese Journal) 2018;27:561-7.
41. Zhang LW, Wen DG, Wang SJ, et al. Epidemic strength of cardia cancer and stomach cancer in high risk region of esophageal cancer and implication for endoscopic screening. Cancer Research on Prevention and Treatment (Chinese Journal) 2005;32:792-5.
42. Yoshimizu S, Hirasawa T, Horiuchi Y, et al. Differences in upper gastrointestinal neoplasm detection rates based on inspection time and esophagogastroduodenoscopy training. Endosc Int Open 2018;6:E1190-7.

Cite this article as: Wang XY, Liu SZ, Xu HF, Liu Y, Wang H, Kang RH, Chen Q, Zhang LY, Guo LW, Zheng LY, Liu CY, Wang YX, Jing YP, Qiao YL, Han BB, Zhang SK. A cluster randomized controlled trial to evaluate the efficacy of esophageal and gastric cancer screening in mortality reduction in a non-high-incidence area: methodology and initial results. Ann Transl Med 2022;10(18):994. doi: 10.21037/atm-22-4052

