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Effect of an Endoscopy Screening on Upper Gastrointestinal Cancer Mortality: A Community-Based Multicenter Cluster Randomized Clinical Trial

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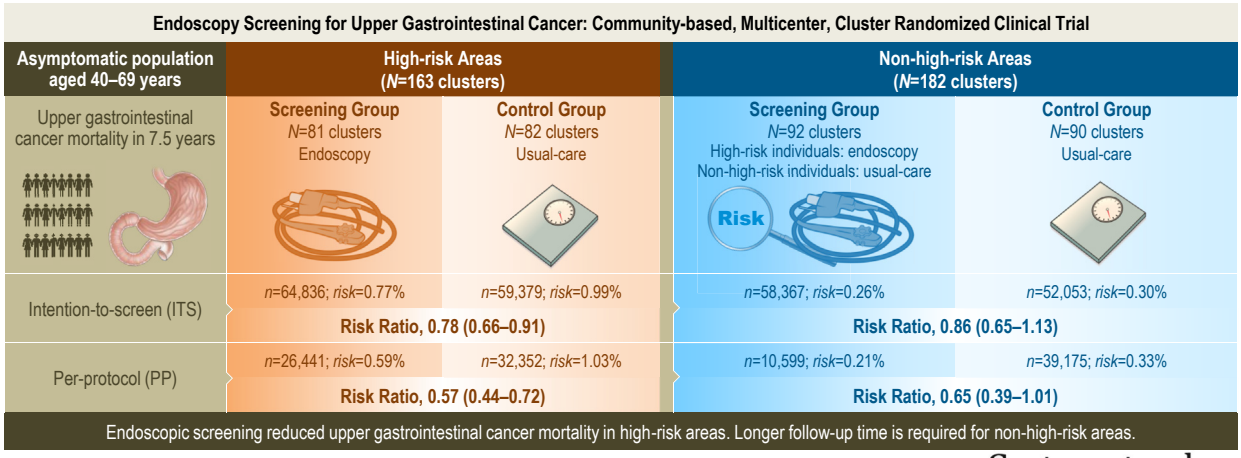

BACKGROUND & AIMS: Population-based observational studies suggest that endoscopic screening may reduce upper gastrointestinal cancer mortality. We aimed to quantify the effect of endoscopy screening. **METHODS:** This is a community-based, multicenter, cluster randomized clinical trial conducted in both high-risk and non–high-risk areas of China. Randomization and recruitment occurred between 2015 and 2017, with follow-up conducted until 2022. The intervention was an invitation to receive endoscopic screening, as opposed to receiving usual care (unscreened). In non–high-risk areas, only participants assessed as high-risk by risk scores in the screening group were invited for endoscopic screening. The primary outcome was the cumulative risk of death from upper gastrointestinal cancer, adjusted for baseline characteristics and cluster effects. **RESULTS:** A total of 234,635 participants were included in the intention-to-screen analysis, with a median age of 52 years. In high-risk areas, 64,836 individuals from 81 clusters were randomized to the screening group, and 59,379 individuals from 82 clusters were randomized to the control group. In non–high-risk areas, 58,367 individuals from 92 clusters were randomized to the screening group, 52,053 individuals from 90 clusters were randomized to the control

group. Among high-risk areas, 480 (adjusted cumulative risk, 0.77%) died due to upper gastrointestinal cancers within 7.5 years in the screening group vs 545 (0.99%) deaths in the control group (risk ratio, 0.78; 95% confidence interval, 0.66–0.91). Among non–high-risk areas, adjusted risk was 0.26% (146 deaths) in the screening group and 0.30% (149 deaths) in the control group (risk ratio, 0.86; 95% confidence interval, 0.65–1.13). **CONCLUSIONS:** An invitation to endoscopic screening reduced upper gastrointestinal cancer mortality in high-risk areas. In non–high-risk areas, an invitation to endoscopic screening based on risk scores did not significantly decrease upper gastrointestinal cancer deaths, but longer follow-up time was required. (Chinese Clinical Trial Registry Identifier: ChiCTR-EOR-16008577.)

Keywords: Endoscopy; Gastrointestinal Neoplasms; Cancer Screening; Public Health; Clinical Trial.

Upper gastrointestinal cancer, including esophageal and gastric cancer, is the fourth most prevalent cancer and the second leading cause of cancer-related deaths globally.[1] It is particularly widespread in Eastern Asia.[2] Approximately 60% of cases of esophageal and gastric cancer are diagnosed at advanced stages, resulting in a 5-year survival rate of only 33%.[3,4] Population screening is an attractive measure to improve survival and reduce mortality of upper gastrointestinal cancer in Eastern Asia and other high-prevalence regions.

The most commonly used screening test for esophageal cancer and gastric cancer is upper endoscopy with biopsy.[5,6] Upper endoscopy enables comprehensive examination of the esophagus and stomach in a single procedure. Because most upper gastrointestinal cancers arise from severe or high-grade dysplasia, which can be detected and removed during endoscopy, endoscopic screening has the potential to decrease the risk of upper gastrointestinal cancer and associated mortality. Three cohort studies conducted in high-risk areas of China demonstrated a 32%–34% lower mortality rate from esophageal cancer among individuals invited for endoscopic screening compared with those who were not invited.[7–9] A meta-analysis comprising 6 cohort studies and 4 nested case-control studies from Asian countries indicated a 40% reduction in gastric cancer mortality with endoscopic screening, while incidence remained unaffected.[10] Furthermore, 2 cohort studies conducted in high-risk areas of China found that individuals undergoing endoscopic screening experienced a 53%–57% reduction in the risk of death from upper gastrointestinal cancer.[7,11]

Because all the evidence regarding the effectiveness of endoscopic screening for upper gastrointestinal cancer is derived from nonrandomized controlled studies in high-risk areas, the true benefits of screening in terms of reducing mortality remain uncertain due to potential selection bias and confounding factors.[10,12,13] Hence, we conducted a large-scale population-based cluster randomized controlled trial in 2015 to determine the effects of endoscopic screening for upper gastrointestinal cancer, in high-risk and non–high-risk areas separately.[12,14] Our trial in non–high-risk areas was not a mere replication of the one conducted in high-risk areas. A risk-stratified screening strategy is a pragmatic trial design that closely resembles population-based screening programs in non–high-risk areas.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Endoscopy has the potential to reduce the mortality rate of upper gastrointestinal cancers. Population-based observational studies have suggested a 60% reduction in esophageal cancer mortality and a 40% reduction in gastric cancer mortality among individuals who underwent endoscopic screening compared with those who did not.

NEW FINDINGS

In this community-based, multicenter, cluster randomized clinical trial, one-time endoscopy screening reduced upper gastrointestinal cancer mortality by 22% in high-risk areas and 14% in non–high-risk areas among participants who were invited to screening, and by 43% and 35% among those who underwent endoscopic screening.

LIMITATIONS

Recruitment occurring after randomization may introduce selection bias. The control group may be at a slight risk of screening contamination. A longer follow-up may be needed.

CLINICAL RESEARCH RELEVANCE

Endoscopic screening reduces upper gastrointestinal cancer mortality in high-risk areas. With ongoing longer-term follow-up, endoscopy shows promise as a population-based screening test in regions with a high burden of upper gastrointestinal cancers.

BASIC RESEARCH RELEVANCE

The significance of endoscopic screening for upper gastrointestinal cancer in non–high-risk areas may be lower compared with high-risk areas. To enhance screening efficiency in non–high-risk areas, it is advisable to incorporate more efficient biomarkers instead of relying solely on questionnaire-based risk factors.

In our trial, baseline endoscopy screening detected 528 positive cases, including 59 cases of esophageal cancer, 167 cases of stomach cancer, 195 cases of severe dysplasia of the esophagus or esophageal cancer in situ, and 117 cases of high-grade dysplasia of the stomach.[14] The initial results indicated a 1.4% detection rate (ie, 1.8% in high-risk areas and 0.4% in non–high-risk areas), with 82.6% of detected cases at an early stage, an 80.5% treatment rate among positive cases, and a 0.03% screening complications rate (including 8 cases with bleeding, 2 with esophageal

Abbreviations used in this paper: **CI, confidence interval; ITS, intention-to-screen; PP, per-protocol; NNI, number needed to invite to screening; NNS, number needed to screen.**

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perforation, 1 with gastric perforation, 1 with gastrospasm, and 0 screen-related deaths).[14] Among the 20% of participants who were randomly selected for testing for *Helicobacter pylori* (*H pylori*) using the ^{13}C-urea breath test,[12] the prevalence rate was 45.9%.[15]

Endoscopy is expected to have preventive effects by detecting and enabling the removal of precancerous lesions and early-stage cancer.[5,6] Therefore, it has the potential to reduce the mortality rate associated with upper gastrointestinal cancer. Here, we present an interim report on the primary outcomes of this trial, a large, multicenter, cluster randomized trial that investigated the effects of community-based endoscopy screening on the risks of death from upper gastrointestinal cancer at 7.5 years.

Methods

Study Design

This is a community-based, multicenter, cluster randomized clinical trial (Figure 1 and trial protocol in Supplement 1).[12,14] A total of 7 screening centers were selected from high-risk areas (Cixian, Linzhou, and Wuwei) and non–high-risk areas (Changsha, Harbin, Luoshan, and Sheyang) of upper gastrointestinal cancer in China. High-risk areas were defined as counties with an age-standardized rate exceeding 3 times the national average[16,17] Specifically, these high-risk areas had an approximate incidence of upper gastrointestinal cancers >100 per 100,000 (Supplementary Tables 1 and 2). The selected areas had an established cancer registry and vital system at least 5 years before this study. Central ethics approval was obtained from the institutional review board of the Cancer Hospital, Chinese Academy of Medical Sciences (no. 2015SQ00223). All authors had full access to the study data and reviewed and approved the final manuscript.

Clusters and Participants

Randomization occurred at the cluster level (ie, village or community), with eligible clusters having a minimum of 300 household registered residents. Clusters that had implemented endoscopic screening program in the past 3 years and clusters where the cluster guardians were unwilling to participate were excluded. Clusters enrolled participants aged 40–69 years old, who were local residents with household registration, had no personal history of cancer, had not undergone endoscopy in the past 3 years, could understand the study procedures, and voluntarily participated. All enrolled participants provided written informed consent.

Randomization

Randomization occurred at the cluster level. Randomization of clusters rather than individuals could prevent unscheduled screening (ie, screening contamination).[18] A list of the villages or communities (ie, clusters) in 7 screening centers was provided by local project administrator. Clusters in high-risk areas (N = 163) and non–high-risk areas (N = 182) were randomized 1:1 via interactive response technology to the screening group or the control group. A random allocation program was generated by statisticians in the Cancer Hospital, Chinese Academy of Medical Sciences and pre-embedded in a web-based electronic database. The allocation result and a full list of household registered residents aged 40–69 years old were distributed to each cluster. Participants and staff were not masked to randomization.

Intervention

The intervention was an invitation for upper endoscopic screening, and the control group received usual care. Within the screening group, participants from high-risk areas were automatically identified as high-risk individuals; in non–high-risk areas, high-risk individuals were identified by an electronic equipment–aided risk assessment (see Supplement 1 for trial protocol). All high-risk individuals in the screening group were invited to receive upper endoscopic screening. Non–high-risk individuals in the screening group and all participants in the control group did not get invited to receive upper endoscopy.

Recruitment was conducted through an active outreach approach. Each cluster has a cluster guardian who actively contacted every resident between the ages of 40 and 69 through household registration forms and invited them to participate in the trial. Participants came to the screening center on an appointed day and local health workers introduced the study procedures. The screening group and the control group were arranged on separate dates to prevent contamination. All participants were interviewed in person using a standardized questionnaire.

High-risk individuals in the screening group received upper endoscopy to visually examine the entire esophagus and stomach, especially the cardia where gastric adenocarcinoma is often identified. Endoscopic screening procedures were performed by trained local physicians. Lugols' iodine staining in the esophagus and indigo carmine dye in the stomach were performed when necessary. Suspicious lesions were targeted for biopsy for further pathologic diagnosis.[14] The World Health Organization classification of esophageal and gastric tumors was used for histopathologic disagnosis.[19] Participants with abnormal endoscopic findings (lesions of low grade or above) received follow-up examinations, whereas those without abnormal findings did not undergo surveillance (Supplementary Figure 1).[20] At the baseline screening, 3677 patients with precursor were eligible for endoscopy surveillance. During the follow-up period, 1762 (47.9%) of these patients underwent endoscopy surveillance, and 17 upper gastrointestinal cancer cases were detected through surveillance endoscopy. High-grade intraepithelial neoplasia or intramucosal carcinomas were treated with endoscopic mucosal resection and/or endoscopic submucosal dissection. Submucosal cancers and invasive cancers were treated with surgery, radiotherapy, and chemotherapy as appropriate. Among the 312 participants diagnosed with high-grade dysplasia, 80.5% of them received endoscopic submucosal dissection/endoscopic mucosal resection as the clinical recommendation.[14]

Follow-up

All residents aged 40–69 in the randomized clusters were followed up using both passive and active procedures, regardless of whether they participated in the questionnaire interview or underwent endoscopy screening. Passive follow-up was a linkage of data from cancer registries, vital system, medical insurance database, and clinical settings to identify

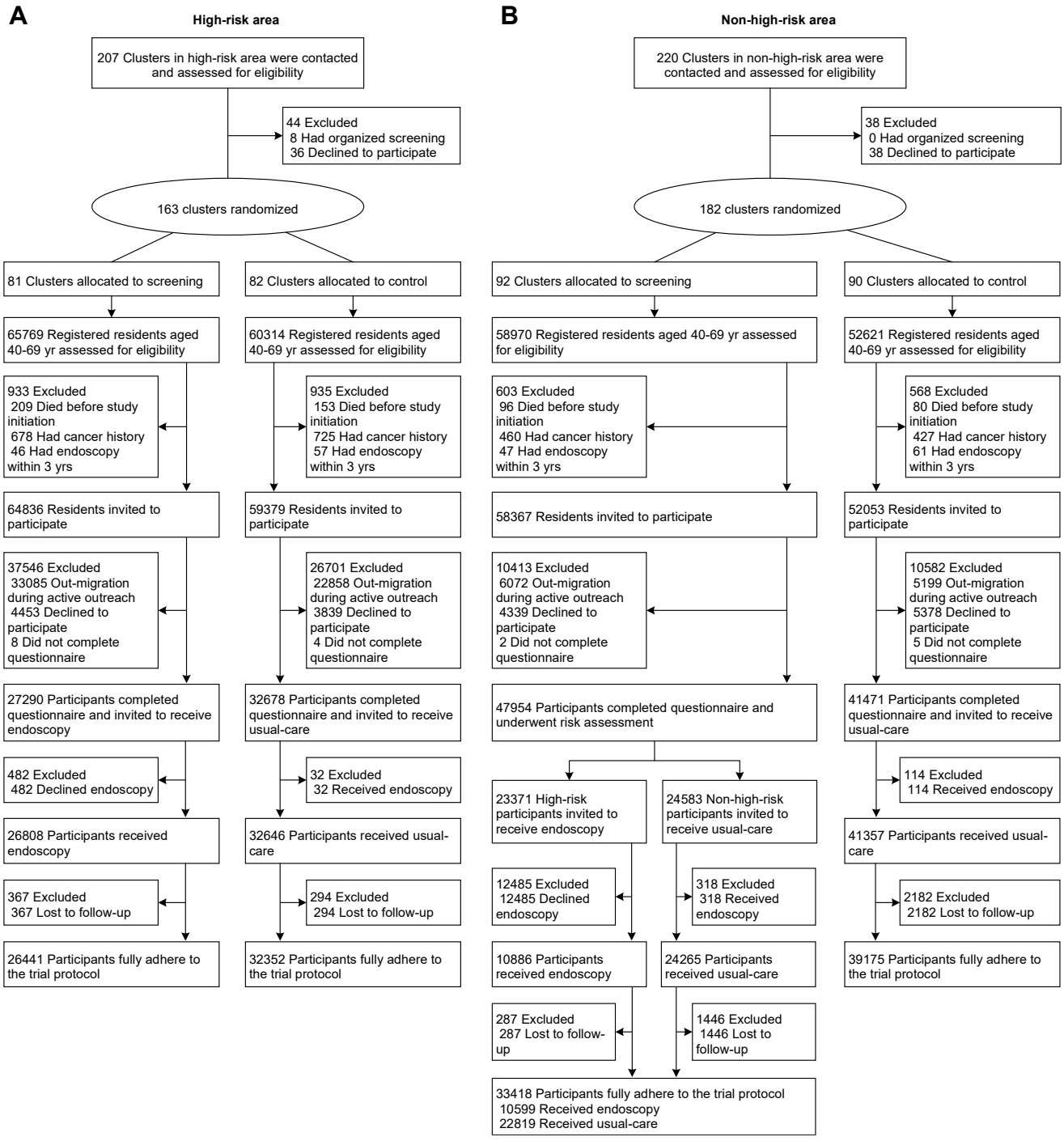

Figure 1. Trial profile in high-risk areas (*A*) and non–high-risk areas (*B*). Randomization occurred at the cluster level (ie, village or community). Participants were enrolled with active recruitment according to the clusters. Unreachable individuals during active outreach were nonpermanent residents, specifically those who had registered with local household registration departments in accordance with the Regulations on Household Registration of the People's Republic of China but migrated annually (not permanent migration) to urban or other regions during the recruitment period. In non–high-risk areas, all participants underwent risk assessment before endoscopy screening. Individuals assessed as high-risk were invited to receive endoscopy screening, whereas those assessed as non–high-risk were not invited. The ITS analysis included the entire eligible population (N = 234,635) according to their allocated groups, regardless of their participation in the questionnaire survey or undergoing an endoscopic examination. Subsidiary analyses were restricted to participants who completed the questionnaire survey (n = 149,393). PP analysis included only participants who fully complied with the screening protocol (n = 131,386).

new cancer cases and deaths. Active follow-up was conducted by local public health workers in each cluster through telephone calls or home visits to assess the participants' latest status. In cases where cancer or precancerous lesions were identified, further investigations were carried out to obtain detailed diagnosis and treatment information. International Classification of Diseases 10th revision codes were used throughout to record all deaths. All participants were followed up for outcomes that occurred through December 31, 2022.

Outcomes

The primary outcome was the cumulative risk of death from upper gastrointestinal cancer, adjusted for baseline characteristics and cluster effects. Additionally, we also reported the unadjusted cumulative risk of death. Prespecified secondary outcomes assessed were the cumulative risks of death from all cancers, and esophageal cancer and gastric cancer separately. Upper gastrointestinal cancer was defined by International Classification of Diseases 10th revision codes C15 and C16, whereas esophageal cancer was indicated by code C15, and gastric cancer was indicated by code C16. Cardia cancers (C16.0) were included in gastric cancers.

Sample Size

In high-risk areas, the trial was designed with a power of 90% at a 2-sided significance level of .05 to detect a 35% reduction in cumulative mortality from upper gastrointestinal cancer within 5 years, compared with the control group.[12] The mortality rate for upper gastrointestinal cancers in the population aged 40–69 years was 170 per 100,000. Each cluster had an average of 300 participants, and the yearly dropout rate was <3%. Considering the intracluster correlation, we assumed a coefficient variation of 0.3, indicating that the true mortality rates in the control clusters would vary between 70 and 270 per 100,000.[21] Consequently, the design effect would be 1.20 (corresponding to an intracluster correlation of 0.0007), requiring the randomization of at least 73 clusters in each group.[21] Similarly, in non–high-risk areas, it was necessary to randomize a minimum of 78 clusters in each group to detect a 30% reduction in mortality within 10 years. The mortality rate was 60 per 100,000, and the cluster size consisted of 450 participants.[12] The sample size requirements were satisfied, as each group involved 81 clusters with an average of 336 participants in the high-risk areas, and 90 clusters with an average of 460 participants in the non–high-risk areas.

Statistical Analyses

We defined 3 analysis sets because participant recruitment occurred after cluster randomization. Primary analyses were conducted after the intention-to-screen (ITS) principle. The ITS analysis was conducted without excluding participants with protocol violations. Specifically, the entire eligible population (N = 234,635) was included in the ITS analysis, regardless of their participating in the questionnaire survey or undergoing an endoscopic examination. During active recruitment, the eligible population may be unreachable due to annual labor migration (not permanent migration, and not necessarily resulting in loss to follow-up) to urban or other regions,[22] declined to participate, or did not complete the questionnaire survey. Therefore, we restricted the subsidiary analysis to participants who completed the questionnaire survey (n = 149,393). After the recruitment, participants may have violated the trial protocol, resulting in the disruption of randomization or the censoring of outcomes. This included those who were invited for endoscopic screening but refused to undergo the examination, those who were invited for usual care but underwent endoscopic examinations, and those who were lost to follow-up. Per-protocol (PP) analysis was conducted by further excluding participants who violated the trial protocol and only including those who fully complied with the trial protocol (n = 131,386).[23] In non–high-risk areas, an additional PP analysis was conducted by restricting the screening group to participants who underwent endoscopic screening (n = 10,599).

Follow-up time was measured from the date of enrollment to the date of permanent emigration (not annual labor migration, which does not necessarily result in loss to follow-up), the date of death, or to the end of follow-up, whichever came first. All time-to-event data were censored by end of follow-up or death. Characteristics of participants were summarized using descriptive statistics for continuous factors and frequency and percentage for categorical factors. We used the Kaplan-Meier estimator to graphically depict the cumulative curves of death in both the screening and control groups. We chose not to use Cox proportional-hazards models for our analyses due to the nonproportional hazards observed in the risk of death during the follow-up period.[24] We chose to use a modified Poisson regression method (specifically, Poisson regression with a robust error variance for binary data) as an alternative to log binomial regression to estimate the cumulative risks of death.[25,26] In light of the cluster-randomized study design, we applied a mixed-effects Poisson model, treating clusters as a random effect independent of residual error.[27] Baseline characteristics (ie, sex, age group, ethnicity, marriage status, education level, annual family income, body mass index, smoking, and alcohol drinking) were also adjusted in mixed Poisson models.[28] To compare the cumulative risks of death between the screening and control groups, we calculated risk ratios and risk differences using the cumulative risks of death at the follow-up time of 7.5 years. The number needed to screen (NNS) and the number needed to invite to screening (NNI) to prevent one death were calculated as the reciprocal of the risk differences, excluding or including surveillance endoscopies. Bootstrapping that accounted for random effects from clustered design was used to calculate 95% confidence intervals (CIs).[26] All mixed Poisson models demonstrated good fitting performance, as indicated by the deviance test and generalized Pearson chi-square test. The likelihood ratio test suggested that models with random effects provide a better fit than those without.

We conducted main analyses considering competing events (ie, deaths from causes other than upper gastrointestinal cancer) as censoring events. Additionally, we performed additional sensitivity analyses where competing events were not treated as censoring events, as these individuals have known future outcomes and, therefore, never experience the event of upper gastrointestinal cancer deaths.[29] We also reported that the NNI and the NNS include surveillance endoscopies. Subgroup analyses were performed according to the levels of demographics and risk factors. All reported *P* values are 2-sided and are not corrected for multiple testing. $P < .05$ or a 95% CI of the ratios

< or >1 were considered statistically significant. There was no imputation for missing data, because missing data for the primary outcome were negligible. All statistical analyses were performed using R software (v4.4.0, R project).

Results

Participant Characteristics

We randomly assigned 163 clusters in the high-risk area and 182 clusters in the non–high-risk area to the screening group and the control group (Figure 1). In the randomized clusters, a total of 237,674 individuals were assessed for eligibility and 234,635 eligible individuals were identified, with 124,215 in the high-risk areas (64,836 to the screening group and 59,379 to the control group) and 110,420 in the non–high-risk areas (58,367 to the screening group and 52,053 to the control group). The entire eligible population had a median age of 52 years (interquartile range, 46–60 years); 122,968 (52.4%) were women (Table 1).

Between May 1, 2015, and April 19, 2017, all 234,635 identified eligible individuals were invited to participate, and 149,393 (63.7%) participants completed the questionnaire survey. Specifically, 59,968 participants in the high-risk areas completed the questionnaire survey (27,290 to the screening group and 32,678 to the control group); 89,425 participants in non–high-risk areas completed the questionnaire survey (47,954 to the screening group and 41,471 to the control group) (Figure 1). In the high-risk areas, 26,808 (41.3% in 64,836 eligible individuals) participants completed endoscopy screening. In the non–high-risk areas, 23,371 (48.7%) participants in the screening group were assessed as high-risk and invited to receive endoscopy, and 24,583 (51.3%) were assessed as non–high-risk and invited to receive usual care; 10,886 (46.6% in 23,371 participants assessed as high-risk) participants completed the endoscopy screening.

Participants who completed the questionnaire survey had a median age of 53 years (interquartile range, 47–60 years); 81,552 (54.6%) were women; 148,941 (99.7%) were Han ethnicity; 141,749 (94.9%) were married; 68,134 (45.6%) had primary school education or less; 97,040 (65.0%) had an annual family income <60,000 yuan; 74,489 (49.9%) had body mass index >24; 28,593 (19.1%) had current smoking; and 18,220 (12.2%) had alcohol drinking (Table 1).

ITS Analyses

In high-risk areas, the unadjusted 7.5-year cumulative risk of death form upper gastrointestinal cancers was 0.76% (480 deaths) among the screening group and 0.96% (545 deaths) among the control group (unadjusted risk ratio, 0.79; 95% CI, 0.71–0.90); the adjusted cumulative risk was 0.77% among the screening group and 0.99% among the control group (adjusted risk ratio, 0.78; 95% CI, 0.66–0.91) (Figure 2 and Table 2). In non–high-risk areas, the unadjusted 7.5-year cumulative risk of death from upper gastrointestinal cancers was 0.26% (146 deaths) among the screening group and 0.29% (149 deaths) among the control group (unadjusted risk ratio, 0.87; 95% CI, 0.70–1.09); the adjusted cumulative risk was 0.26% among the screening group and 0.30% among the control group (adjusted risk ratio, 0.86; 95% CI, 0.65–1.13). The adjusted NNI without and with surveillance endoscopy to prevent one death from upper gastrointestinal cancer within 7.5 years were 451 and 470, respectively, in high-risk areas, and 2306 and 2357, respectively, in non–high-risk areas.

During the 7.5-year follow-up period, the adjusted risk ratios for deaths from esophageal cancer, gastric cancer, and all cancers between the screening and control groups were 0.73 (95% CI, 0.56–0.97), 0.81 (0.68–0.96), and 0.93 (0.83–1.04), respectively, in high-risk areas, and 0.75 (95% CI, 0.49–1.12), 0.90 (0.67–1.21), and 0.92 (0.81–1.05), respectively, in non–high-risk areas (Table 2 and Supplementary Figures 2–4).

Subsidiary Analyses

In high-risk areas, the unadjusted 7.5 years cumulative risk of death form upper gastrointestinal cancers was 0.57% (145 deaths) among the screening group and 1.03% (311 deaths) among the control group (unadjusted risk ratio, 0.55; 95% CI, 0.45–0.67); the adjusted cumulative risk was 0.59% among the screening group and 1.03% among the control group (adjusted risk ratio, 0.57; 95% CI, 0.46–0.72) (Figure 3, Table 2). In non–high-risk areas, the unadjusted 7.5-year cumulative risk of death from upper gastrointestinal cancers was 0.25% (116 deaths) among the screening group and 0.30% (119 deaths) among the control group (unadjusted risk ratio, 0.84; 95% CI, 0.66–1.10; adjusted risk ratio, 0.83; 95% CI, 0.64–1.06); the adjusted cumulative risk was 0.26% among the screening group and 0.31% among the control group (adjusted risk ratio, 0.83; 95% CI, 0.64–1.06). The adjusted NNI without and with surveillance endoscopy to prevent one death from upper gastrointestinal cancer within 7.5 years were 228 and 251, respectively, in high-risk areas and 1935 and 1987, respectively, in non–high-risk areas.

During the 7.5-year follow-up period, the adjusted risk ratios for deaths from esophageal cancer, gastric cancer, and all cancers between the screening and control groups were 0.51 (95% CI, 0.36–0.76), 0.63 (0.48–0.81), and 0.74 (0.63–0.88), respectively, in high-risk areas, and 0.91 (95% CI, 0.59–1.39), 0.79 (0.58–1.08), and 0.95 (0.84–1.07), respectively, in non–high-risk areas (Table 2, Supplementary Figures 5–7).

PP Analyses

During the baseline endoscopic screening, we observed some contamination among participants who were not invited to receive endoscopic screening (Figure 1). Specifically, 32 (0.1%) participants from high-risk areas and 114 (0.3%) participants from non–high-risk areas underwent endoscopy examination outside our trial, although they were included in the control group. In non–high-risk areas, among individuals assessed as non–high-risk in the screening group, 318 (1.3%) participants underwent endoscopy examinations outside our trial. During the follow-up period, a

Table 1. Participant Characteristics

Characteristics	No./total (%)					
	All areas		High-risk area		Non–high-risk area	
	Screening	Control	Screening	Control	Screening	Control
ITS analysis[a]						
No.	123,203	111,432	64,836	59,379	58,367	52,053
Sex						
Men	58,256 (47.3%)	53,411 (47.9%)	31,695 (48.9%)	29,361 (49.4%)	26,561 (45.5%)	24,050 (46.2%)
Women	64,947 (52.7%)	58,021 (52.1%)	33,141 (51.1%)	30,018 (50.6%)	31,806 (54.5%)	28,003 (53.8%)
Age (*y*)						
Median (IQR)	52 (46–60)	52 (46–60)	51 (46–60)	51 (46–60)	53 (47–61)	53 (47–60)
40–49	47,273 (38.4%)	44,477 (39.9%)	27,167 (41.9%)	25,449 (42.9%)	20,106 (34.4%)	19,028 (36.6%)
50–59	42,217 (34.3%)	37,587 (33.7%)	21,346 (32.9%)	18,949 (31.9%)	20,871 (35.8%)	18,638 (35.8%)
60–69	33,713 (27.4%)	29,368 (26.4%)	16,323 (25.2%)	14,981 (25.2%)	17,390 (29.8%)	14,387 (27.6%)
Subsidiary analysis[b]						
No.	75,244	74,149	27,290	32,678	47,954	41,471
Sex						
Men	33,470 (44.5%)	34,371 (46.4%)	11,923 (43.7%)	15,435 (47.2%)	21,547 (44.9%)	18,936 (45.7%)
Women	41,774 (55.5%)	39,778 (53.6%)	15,367 (56.3%)	17,243 (52.8%)	26,407 (55.1%)	22,535 (54.3%)
Age (*y*)						
Median (IQR)	53 (47–60)	52 (47–60)	52 (47–60)	52 (47–60)	54 (47–61)	53 (47–60)
40–49	25,807 (34.3%)	27,317 (36.8%)	10,092 (37.0%)	12,384 (37.9%)	15,715 (32.8%)	14,933 (36.0%)
50–59	27,800 (36.9%)	26,039 (35.1%)	10,291 (37.7%)	11,217 (34.3%)	17,509 (36.5%)	14,822 (35.7%)
60–69	21,637 (28.8%)	20,793 (28.0%)	6907 (25.3%)	9077 (27.8%)	14,730 (30.7%)	11,716 (28.3%)
Ethnicity						
Han	74,959 (99.6%)	73,982 (99.8%)	27,251 (99.9%)	32,662 (100.0%)	47,708 (99.5%)	41,320 (99.6%)
Minority	285 (0.4%)	167 (0.2%)	39 (0.1%)	16 (0.0%)	246 (0.5%)	151 (0.4%)
Marriage status						
Never married	691 (0.9%)	594 (0.8%)	168 (0.6%)	166 (0.5%)	523 (1.1%)	428 (1.0%)
Married	71,079 (94.5%)	70,670 (95.3%)	25,662 (94.0%)	31,185 (95.4%)	45,417 (94.7%)	39,485 (95.2%)
Divorced	667 (0.9%)	497 (0.7%)	120 (0.4%)	116 (0.4%)	547 (1.1%)	381 (0.9%)
Widowed	2807 (3.7%)	2388 (3.2%)	1340 (4.9%)	1211 (3.7%)	1467 (3.1%)	1177 (2.8%)
Education						
No schooling	7738 (10.3%)	7053 (9.5%)	4577 (16.8%)	4554 (13.9%)	3161 (6.6%)	2499 (6.0%)
Primary school	25,279 (33.6%)	28,064 (37.8%)	9364 (34.3%)	13,854 (42.4%)	15,915 (33.2%)	14,210 (34.3%)
Middle school	34,935 (46.4%)	33,605 (45.3%)	13,021 (47.7%)	14,022 (42.9%)	21,914 (45.7%)	19,583 (47.2%)
College and above	7292 (9.7%)	5427 (7.3%)	328 (1.2%)	248 (0.8%)	6964 (14.5%)	5179 (12.5%)
Annual family income (Chinese yuan/y)						
<30,000	17,534 (23.3%)	15,304 (20.6%)	8157 (29.9%)	7510 (23.0%)	9377 (19.6%)	7794 (18.8%)
30,000–59,999	31,608 (42.0%)	32,594 (44.0%)	15,077 (55.2%)	15,653 (47.9%)	16,531 (34.5%)	16,941 (40.9%)
60,000–99,999	17,447 (23.2%)	19,112 (25.8%)	3758 (13.8%)	8470 (25.9%)	13,689 (28.5%)	10,642 (25.7%)
>100,000	8655 (11.5%)	7139 (9.6%)	298 (1.1%)	1045 (3.2%)	8357 (17.4%)	6094 (14.7%)
BMI						
<18.5	1447 (1.9%)	1416 (1.9%)	489 (1.8%)	634 (1.9%)	958 (2.0%)	782 (1.9%)
18.5–23.9	36,179 (48.1%)	35,862 (48.4%)	11,458 (42.0%)	14,387 (44.0%)	24,721 (51.6%)	21,475 (51.8%)
24.0–27.9	28,632 (38.1%)	29,761 (40.1%)	11,162 (40.9%)	13,913 (42.6%)	17,470 (36.4%)	15,848 (38.2%)
>28.0	8986 (11.9%)	7110 (9.6%)	4181 (15.3%)	3744 (11.5%)	4805 (10.0%)	3366 (8.1%)
Smoking						
Never	59,396 (78.9%)	57,869 (78.0%)	20,245 (74.2%)	24,320 (74.4%)	39,151 (81.6%)	33,549 (80.9%)
Current	13,942 (18.5%)	14,651 (19.8%)	6340 (23.2%)	7647 (23.4%)	7602 (15.9%)	7004 (16.9%)
Former	1906 (2.5%)	1629 (2.2%)	705 (2.6%)	711 (2.2%)	1201 (2.5%)	918 (2.2%)
Alcohol drinking						
No	65,627 (87.2%)	65,546 (88.4%)	24,064 (88.2%)	29,644 (90.7%)	41,563 (86.7%)	35,902 (86.6%)
Yes	9617 (12.8%)	8603 (11.6%)	3226 (11.8%)	3034 (9.3%)	6391 (13.3%)	5569 (13.4%)

BMI, body mass index; IQR, interquartile range.
[a]ITS analysis included the entire eligible population (N = 234,635) according to their allocated groups, regardless of their participation in the questionnaire survey or undergoing an endoscopic examination.
[b]Subsidiary analyses were restricted to participants who completed the questionnaire survey (n = 149,393).

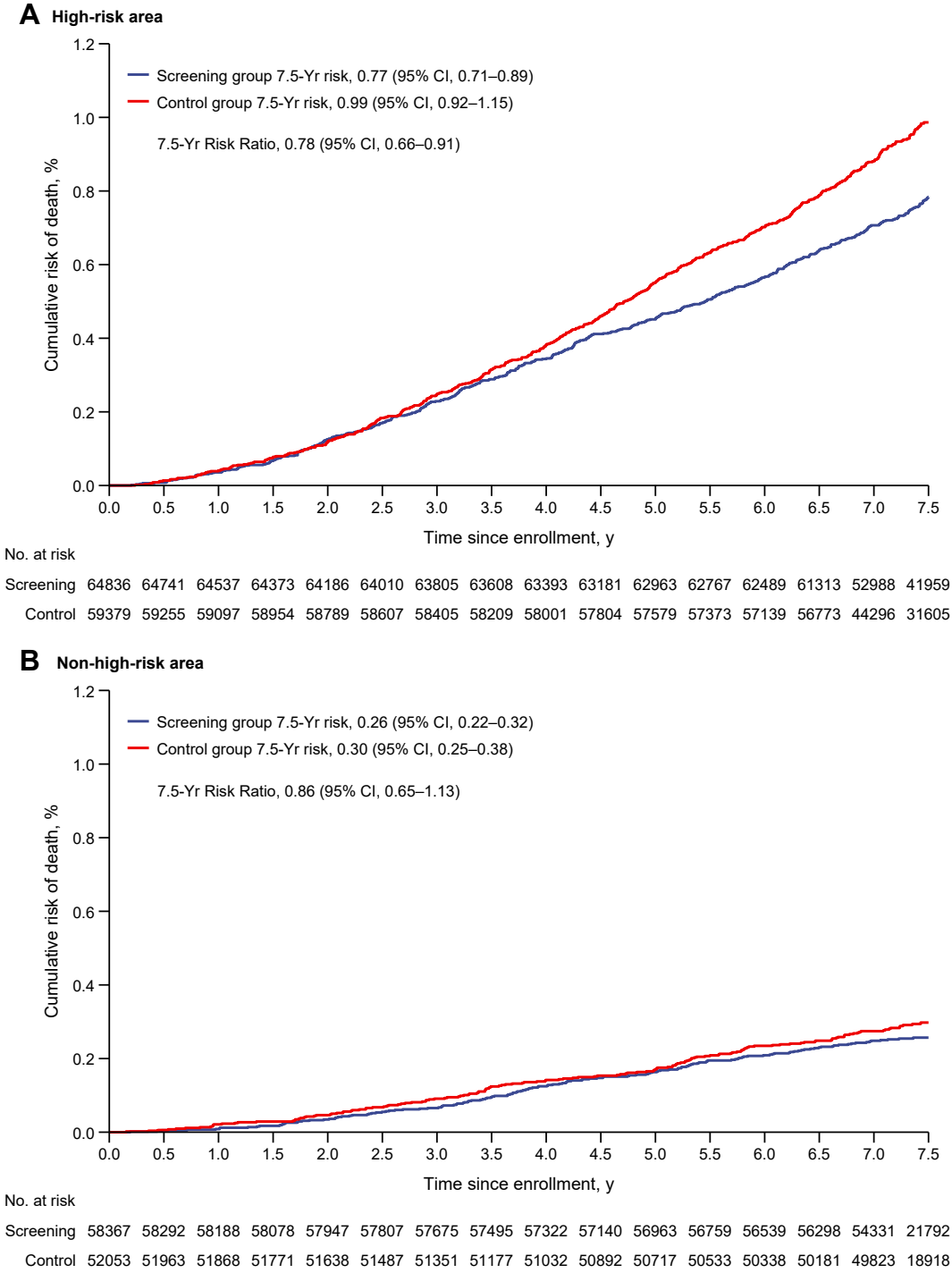

Figure 2. Cumulative risk of death from upper gastrointestinal cancer in ITS analyses in high-risk areas (*A*) and non–high-risk areas (*B*). ITS analysis included the entire eligible population (N = 234,635) according to their allocated groups, regardless of their participation in the questionnaire survey or undergoing an endoscopic examination. Risks and risk ratios were adjusted by fixed effects from sex and age group, and random effects from clusters. 95% CI were estimated using the bootstrap method.

total of 661 (1.1%) participants from high-risk areas and 3915 (4.4%) participants from non–high-risk areas were lost to follow-up as of December 31, 2022.

In the PP analyses, which aimed to estimate the effect of screening if all the participants who were randomly assigned to screening had actually undergone the procedure, while excluding those who experienced screening contaminations and were lost to follow-up, the adjusted 7.5-year cumulative risk of death from upper gastrointestinal cancers between the control group and the screening group decreased from 1.03% to 0.59% in high-risk areas and from 0.31% to 0.24% in non–high-risk

Table 2. Primary and Secondary Outcomes of ITS Analyses and Subsidiary Analyses

End point	Screening group		Control group		Risk difference, % (95% CI)	Risk ratio (95% CI)	NNI to prevent 1 death (95% CI)	
	Deaths	7.5-y risk, % (95% CI)	Deaths	7.5-y risk, % (95% CI)			Baseline only	With surveillance
ITS analysis[a]								
Unadjusted								
High-risk area								
Upper gastrointestinal cancer	480	0.76 (0.69–0.82)	545	0.96 (0.88–1.03)	-0.20 (-0.29 to -0.09)	0.79 (0.71–0.90)	508 (340–1102)	529 (355–1149)
Esophageal cancer	209	0.33 (0.28–0.38)	247	0.43 (0.38–0.49)	-0.10 (-0.17 to -0.03)	0.76 (0.63–0.92)	973 (573–3002)	1015 (597–3131)
Gastric cancer	271	0.43 (0.38–0.48)	298	0.52 (0.47–0.58)	-0.09 (-0.17 to -0.02)	0.82 (0.69–0.97)	1061 (586–6058)	1107 (611–6319)
All cancer	1095	1.73 (1.63–1.84)	1036	1.82 (1.71–1.93)	-0.09 (-0.23 to 0.06)	0.95 (0.88–1.04)	1165 (431–N/A)	1215 (450–N/A)
Non–high-risk area								
Upper gastrointestinal cancer	146	0.26 (0.22–0.30)	149	0.29 (0.25–0.34)	-0.04 (-0.10 to 0.02)	0.87 (0.70–1.09)	2667 (1021–N/A)	2726 (1044–N/A)
Esophageal cancer	46	0.08 (0.06–0.11)	53	0.10 (0.08–0.14)	-0.02 (-0.06 to 0.02)	0.77 (0.51–1.20)	4202 (1608–N/A)	4296 (1644–N/A)
Gastric cancer	100	0.18 (0.14–0.21)	96	0.19 (0.15–0.23)	-0.01 (-0.06 to 0.03)	0.93 (0.71–1.19)	7301 (1635–N/A)	7462 (1671–N/A)
All cancer	857	1.51 (1.41–1.61)	808	1.60 (1.50–1.71)	-0.09 (-0.24 to 0.06)	0.94 (0.86–1.04)	1133 (412–N/A)	1158 (422–N/A)
Adjusted[b]								
High-risk area								
Upper gastrointestinal cancer	480	0.77 (0.71–0.89)	545	0.99 (0.92–1.15)	-0.22 (-0.38 to -0.09)	0.78 (0.66–0.91)	451 (265–1172)	470 (277–1223)
Esophageal cancer	209	0.33 (0.31–0.48)	247	0.45 (0.42–0.65)	-0.12 (-0.27 to -0.01)	0.73 (0.56–0.97)	823 (375–8547)	858 (391–8915)
Gastric cancer	271	0.44 (0.39–0.50)	298	0.54 (0.48–0.61)	-0.10 (-0.19 to -0.02)	0.81 (0.68–0.96)	984 (536–4958)	1026 (559–5172)
All cancer	1095	1.74 (1.64–1.94)	1036	1.88 (1.75–2.11)	-0.14 (-0.36 to 0.06)	0.93 (0.83–1.04)	731 (277–N/A)	763 (289–N/A)
Non–high-risk area								
Upper gastrointestinal cancer	146	0.26 (0.22–0.32)	149	0.30 (0.25–0.38)	-0.04 (-0.13 to 0.04)	0.86 (0.65–1.13)	2306 (794–N/A)	2357 (812–N/A)
Esophageal cancer	46	0.08 (0.06–0.11)	53	0.11 (0.08–0.14)	-0.03 (-0.07 to 0.01)	0.75 (0.49–1.12)	3678 (1463–N/A)	3759 (1495–N/A)
Gastric cancer	100	0.18 (0.15–0.23)	96	0.20 (0.16–0.25)	-0.02 (-0.08 to 0.04)	0.90 (0.67–1.21)	4842 (1325–N/A)	4949 (1354–N/A)
All cancer	857	1.51 (1.39–1.66)	808	1.64 (1.50–1.79)	-0.13 (-0.32 to 0.07)	0.92 (0.81–1.05)	773 (308–N/A)	790 (315–N/A)
Subsidiary analysis[c]								
Unadjusted								
High-risk area								
Upper gastrointestinal cancer	145	0.57 (0.48–0.66)	311	1.03 (0.92–1.14)	-0.46 (-0.61 to -0.31)	0.55 (0.45–0.67)	217 (164–319)	239 (181–351)
Esophageal cancer	55	0.21 (0.16–0.27)	143	0.47 (0.40–0.55)	-0.26 (-0.35 to -0.16)	0.45 (0.33–0.61)	389 (286–608)	428 (316–670)
Gastric cancer	90	0.35 (0.28–0.43)	168	0.55 (0.47–0.64)	-0.20 (-0.32 to -0.09)	0.63 (0.48–0.82)	492 (316–1073)	542 (349–1,183)
All cancer	335	1.31 (1.18–1.46)	551	1.82 (1.68–1.97)	-0.51 (-0.72 to -0.31)	0.72 (0.63–0.82)	196 (140–327)	216 (154–360)
Non–high-risk area								
Upper gastrointestinal cancer	116	0.25 (0.21–0.30)	119	0.30 (0.25–0.35)	-0.05 (-0.11 to 0.02)	0.84 (0.66–1.10)	2114 (905–N/A)	2171 (929–N/A)
Esophageal cancer	41	0.09 (0.06–0.12)	39	0.10 (0.07–0.13)	-0.01 (-0.05 to 0.03)	0.91 (0.61–1.42)	11,061 (2140–N/A)	11,359 (2198–N/A)
Gastric cancer	75	0.16 (0.13–0.20)	80	0.20 (0.16–0.24)	-0.04 (-0.09 to 0.02)	0.81 (0.59–1.12)	2614 (1063–N/A)	2685 (1091–N/A)
All cancer	711	1.54 (1.42–1.66)	622	1.56 (1.43–1.68)	-0.02 (-0.18 to 0.15)	0.99 (0.89–1.10)	4867 (541–N/A)	4998 (556–N/A)
Adjusted[d]								
High-risk area								
Upper gastrointestinal cancer	145	0.59 (0.51–0.73)	311	1.03 (0.93–1.22)	-0.44 (-0.64 to -0.27)	0.57 (0.46–0.72)	228 (156–375)	251 (171–413)
Esophageal cancer	55	0.23 (0.20–0.38)	143	0.46 (0.43–0.68)	-0.23 (-0.40 to -0.11)	0.51 (0.36–0.76)	440 (250–899)	485 (276–990)
Gastric cancer	90	0.36 (0.28–0.44)	168	0.56 (0.48–0.65)	-0.21 (-0.32 to -0.09)	0.63 (0.48–0.81)	482 (311–1064)	531 (343–1172)
All cancer	335	1.35 (1.22–1.58)	551	1.82 (1.66–2.10)	-0.47 (-0.74 to -0.21)	0.74 (0.63–0.88)	214 (136–472)	236 (149–520)

areas. This corresponded to unadjusted and adjusted risk ratio of 0.55 (95% CI, 0.46–0.66) and 0.57 (0.44–0.72) in high-risk areas, and 0.71 (0.52–0.97) and 0.76 (0.55–1.02) in non–high-risk areas (Table 3). By restricting the analysis set of the screening group to only participants who underwent endoscopy screening, the unadjusted and adjusted risk ratio for death from upper gastrointestinal cancers in non–high-risk areas were 0.72 (0.44–1.09) and 0.65 (0.39–1.01). Among those who completed endoscopic screening, the adjusted NNS without and with surveillance endoscopy to prevent one death from upper gastrointestinal cancer within 7.5 years were 228 and 252 in high-risk areas, and 872 and 970 in non–high-risk areas.

Subgroup and Sensitivity Analyses

The screening effect with regard to upper gastrointestinal cancer deaths varied across the subgroups (Figure 4). In both high-risk areas and non–high-risk areas, women and participants in the younger age group experienced greater reductions in mortality compared with men and those in the older age group, irrespective of ITS analyses or subsidiary analyses. Mortality risk ratios of upper gastrointestinal cancer were generally lower in subgroups that never smoked and without alcohol drinking in high-risk areas. Analyses in which competing events were not treated as censoring events showed results that were similar to those in the main analysis (Supplementary Table 3).

Discussion

In this large-scale, community-based, multicenter cluster randomized trial, we observed a significant reduction (22% in ITS analysis and 43% in PP analysis) in the risk of death from upper gastrointestinal cancers by endoscopic screening, as compared with those assigned to the usual care group in high-risk areas. The reduction in non–high-risk areas was smaller (14% in ITS analysis and 24% in PP analysis) compared with high-risk areas, and the observed reductions were not statistically significant because only participants assessed as high-risk in the screening group were invited to receive endoscopic screening.

The purpose of this trial was to quantify the effectiveness of endoscopy in community-based screening for upper gastrointestinal cancers. Therefore, we designed a cluster randomized trial with active recruitment.[18] This pragmatic trial design is similar to population-based screening programs and effectively mitigates contamination. However, this approach has the drawback of differential recruitment between active clusters, and potential selection bias may render the participant characteristics in the screening group and the control group incomparable.[18,30] The selection bias caused by differential recruitment may dilute the true effect of endoscopic screening, as demonstrated in an earlier single-center cluster trial evaluating the risk of esophageal cancer with endoscopic screening, which only included approximately 20% of randomized subjects.[13,31] To address the issue, we identified all eligible populations through household registration before randomizing the clusters. This helped prevent selection bias by using ITS analyses.

Table 2. Continued

End point	Screening group		Control group		Risk difference, % (95% CI)	Risk ratio (95% CI)	NNI to prevent 1 death (95% CI)	
	Deaths	7.5-y risk, % (95% CI)	Deaths	7.5-y risk, % (95% CI)			Baseline only	With surveillance
Non–high-risk area								
Upper gastrointestinal cancer	116	0.26 (0.21–0.31)	119	0.31 (0.26–0.37)	-0.05 (-0.13 to 0.02)	0.83 (0.64–1.06)	1935 (792–N/A)	1987 (813–N/A)
Esophageal cancer	41	0.09 (0.06–0.12)	39	0.10 (0.07–0.13)	-0.01 (-0.05 to 0.03)	0.91 (0.59–1.39)	10,909 (1997–N/A)	11,204 (2051–N/A)
Gastric cancer	75	0.16 (0.13–0.20)	80	0.21 (0.16–0.25)	-0.04 (-0.10 to 0.01)	0.79 (0.58–1.08)	2353 (992–N/A)	2417 (1019–N/A)
All cancer	711	1.53 (1.41–1.68)	622	1.61 (1.47–1.77)	-0.08 (-0.28 to 0.11)	0.95 (0.84–1.07)	1257 (356–N/A)	1291 (366–N/A)

NOTE. 95% CI were estimated using the bootstrap method.
CI, confidence interval; N/A, not available.
[a]ITS analysis included the entire eligible population (N = 234,635) according to their allocated groups, regardless of their participation in the questionnaire survey or undergoing an endoscopic examination.
[b]Risks, risk differences, and risk ratios were adjusted by fixed effects from sex, age group, and random effects from clusters.
[c]Subsidiary analyses were restricted to participants who completed the questionnaire survey (n = 149,393).
[d]Risks, risk differences, and risk ratios were adjusted by fixed effects from sex, age group, ethnicity, marriage status, education level, annual family income, BMI, smoking, and alcohol drinking, and random effects from clusters.

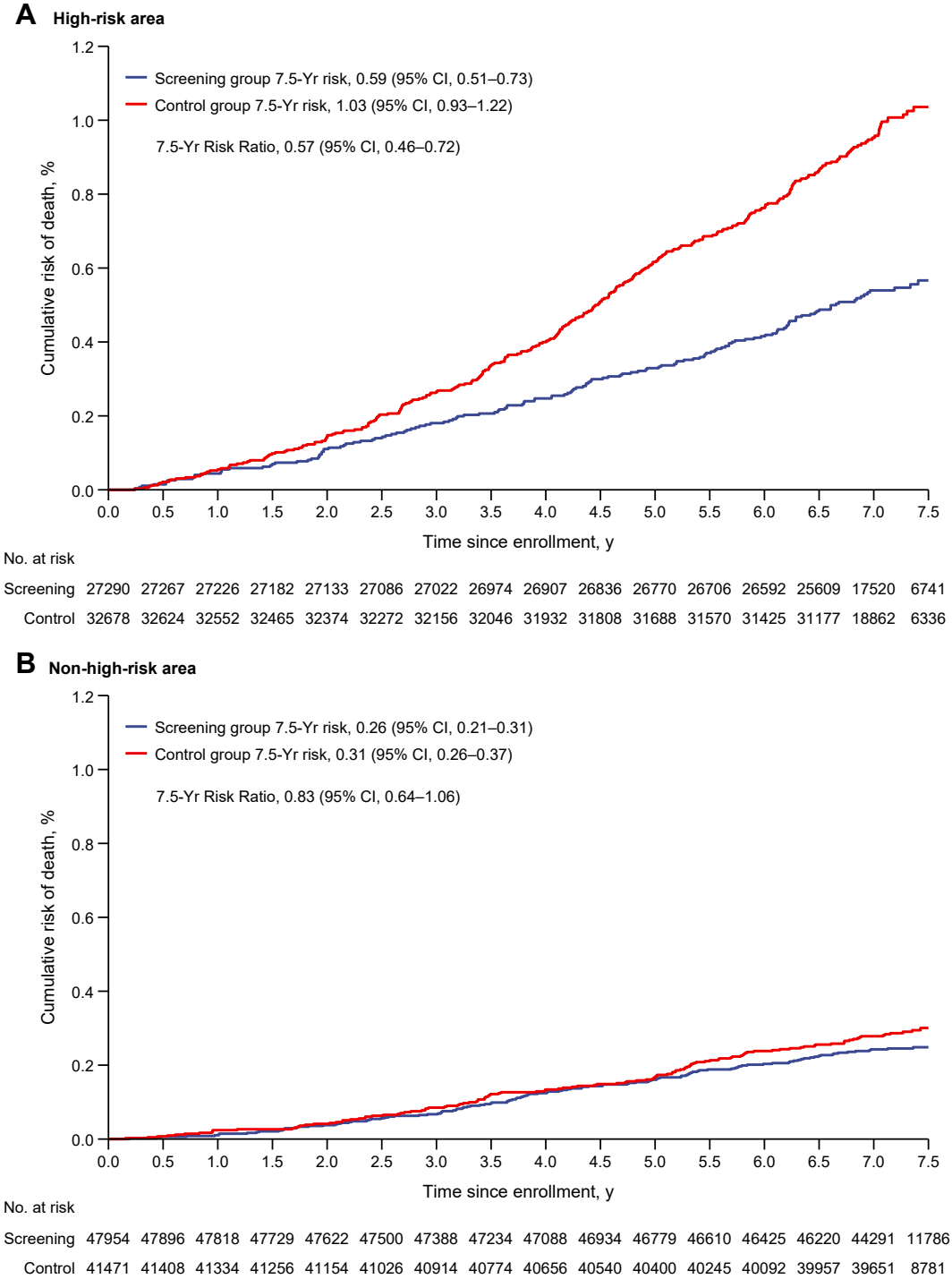

Figure 3. Cumulative risk of death from upper gastrointestinal cancer in subsidiary analyses in high-risk areas (*A*) and non–high-risk areas (*B*). Subsidiary analyses were restricted to participants who completed the questionnaire survey (n = 149,393). Risks and risk ratios were adjusted by fixed effects from sex, age group, ethnicity, marriage status, education level, annual family income, body mass index, smoking, and alcohol drinking, and random effects from clusters. 95% CI were estimated using the bootstrap method.

Furthermore, we have adjusted all estimated screening effects for baseline characteristics.

The ITS analysis suggested that at 7.5 years, the risk of death from upper gastrointestinal cancer in high-risk areas and non–high-risk areas decreased by 22% and 14%, respectively. However, it is important to note that our ITS analyses may underestimate the effectiveness of endoscopic screening because many nonparticipants were not excluded due to unwillingness or personal health conditions, but rather because they had migrated annually to other areas during the enrollment period. This type of annual labor migration was particularly common in rural areas of China,

Table 3. Primary and Secondary Outcomes of PP Analyses

End point	Screening group		Control group		Risk difference, % (95% CI)	Risk ratio (95% CI)	NNS to prevent 1 death (95% CI)	
	Deaths	7.5-y risk, % (95% CI)	Deaths	7.5-y risk, % (95% CI)			Baseline only	With surveillance
Unadjusted								
High-risk area								
Upper gastrointestinal cancer	141	0.57 (0.49–0.67)	308	1.03 (0.91–1.14)	-0.46 (-0.60 to -0.31)	0.55 (0.46–0.66)	218 (168–318)	241 (185–351)
Esophageal cancer	53	0.21 (0.16–0.27)	141	0.47 (0.39–0.54)	-0.26 (-0.34 to -0.16)	0.45 (0.32–0.62)	390 (291–625)	430 (322–690)
Gastric cancer	88	0.35 (0.29–0.43)	167	0.56 (0.48–0.64)	-0.20 (-0.32 to -0.09)	0.64 (0.48–0.81)	494 (315–1077)	546 (348–1189)
All cancer	327	1.32 (1.18–1.46)	545	1.82 (1.67–1.96)	-0.50 (-0.70 to -0.30)	0.72 (0.63–0.83)	200 (143–337)	221 (158–372)
Non–high-risk area[a]								
Upper gastrointestinal cancer	72	0.22 (0.17–0.28)	118	0.31 (0.26–0.37)	-0.09 (-0.17 to -0.01)	0.71 (0.52–0.97)	1113 (596–11,822)	1153 (617–12,247)
Esophageal cancer	28	0.09 (0.06–0.12)	39	0.10 (0.07–0.14)	-0.02 (-0.06 to 0.03)	0.84 (0.49–1.36)	6006 (1601–N/A)	6222 (1658–N/A)
Gastric cancer	44	0.14 (0.10–0.18)	79	0.21 (0.16–0.26)	-0.07 (-0.13 to -0.01)	0.65 (0.45–0.95)	1366 (754–11,197)	1415 (781–11,599)
All cancer	486	1.51 (1.37–1.65)	620	1.65 (1.52–1.78)	-0.14 (-0.35 to 0.05)	0.92 (0.80–1.03)	726 (286–N/A)	752 (296–N/A)
Non–high-risk area[b]								
Upper gastrointestinal cancer	23	0.23 (0.14–0.34)	118	0.31 (0.26–0.37)	-0.09 (-0.18 to 0.03)	0.72 (0.44–1.09)	1150 (546–N/A)	1280 (608–N/A)
Esophageal cancer	11	0.11 (0.05–0.18)	39	0.10 (0.07–0.14)	0.00 (-0.06 to 0.08)	1.05 (0.45–1.97)	N/A (1580–N/A)	N/A (1759–N/A)
Gastric cancer	12	0.12 (0.06–0.20)	79	0.21 (0.17–0.25)	-0.09 (-0.17 to -0.01)	0.56 (0.26–0.97)	1091 (594–18,579)	1,214 (661–20,681)
All cancer	139	1.37 (1.16–1.61)	620	1.65 (1.52–1.77)	-0.28 (-0.54 to -0.01)	0.83 (0.69–0.99)	359 (187–7721)	400 (208–8595)
Adjusted[c]								
High-risk area								
Upper gastrointestinal cancer	141	0.59 (0.51–0.73)	308	1.03 (0.93–1.25)	-0.44 (-0.67 to -0.27)	0.57 (0.44–0.72)	228 (149–367)	252 (165–405)
Eesophageal cancer	53	0.23 (0.20–0.37)	141	0.46 (0.42–0.69)	-0.23 (-0.43 to -0.12)	0.50 (0.35–0.74)	436 (234–845)	481 (258–933)
Gastric cancer	88	0.36 (0.28–0.43)	167	0.57 (0.48–0.66)	-0.21 (-0.33 to -0.09)	0.64 (0.48–0.81)	487 (301–1071)	537 (332–1183)
All cancer	327	1.36 (1.24–1.60)	545	1.82 (1.68–2.10)	-0.46 (-0.75 to -0.20)	0.75 (0.63–0.89)	218 (133–494)	241 (146–545)
Non–high-risk area[a]								
Upper gastrointestinal cancer	72	0.24 (0.19–0.29)	118	0.31 (0.26–0.37)	-0.08 (-0.16 to 0.00)	0.76 (0.55–1.02)	1310 (639–N/A)	1357 (662–N/A)
Esophageal cancer	28	0.09 (0.06–0.13)	39	0.10 (0.07–0.14)	-0.01 (-0.06 to 0.04)	0.93 (0.55–1.48)	13,954 (1785–N/A)	14,454 (1849–N/A)
Gastric cancer	44	0.14 (0.10–0.18)	79	0.21 (0.16–0.25)	-0.07 (-0.13 to -0.01)	0.67 (0.45–0.95)	1440 (748–11,433)	1492 (775–11,843)
All cancer	486	1.53 (1.39–1.72)	620	1.67 (1.53–1.86)	-0.15 (-0.38 to 0.09)	0.91 (0.79–1.06)	687 (263–N/A)	712 (272–N/A)
Non–high-risk area[b]								
Upper gastrointestinal cancer	23	0.21 (0.13–0.32)	118	0.33 (0.27–0.41)	-0.11 (-0.23 to 0.00)	0.65 (0.39–1.01)	872 (440–N/A)	970 (490–N/A)
Esophageal cancer	11	0.10 (0.04–0.17)	39	0.11 (0.08–0.14)	-0.01 (-0.07 to 0.06)	0.92 (0.40–1.70)	11,227 (1341–N/A)	12,497 (1492–N/A)
Gastric cancer	12	0.11 (0.05–0.17)	79	0.22 (0.18–0.27)	-0.11 (-0.19 to -0.03)	0.50 (0.23–0.86)	901 (524–3550)	1003 (583–3952)
All cancer	139	1.29 (1.11–1.56)	620	1.70 (1.58–1.92)	-0.41 (-0.69 to -0.13)	0.76 (0.62–0.92)	244 (146–757)	272 (162–843)

NOTE. 95% CI were estimated using the bootstrap method.
CI, confidence interval; N/A, not available.
[a]Participants analyzed in the screening group included 10,604 high-risk individuals who underwent endoscopy screening and 22,852 non–high-risk individuals who received usual care.
[b]Participants analyzed in the screening group only included 10,604 high-risk individuals who underwent endoscopy screening.
[c]Risks, risk differences, and risk ratios were adjusted by fixed effects from sex, age group, ethnicity, marriage status, education level, annual family income, BMI, smoking, and alcohol drinking, and random effects from clusters.

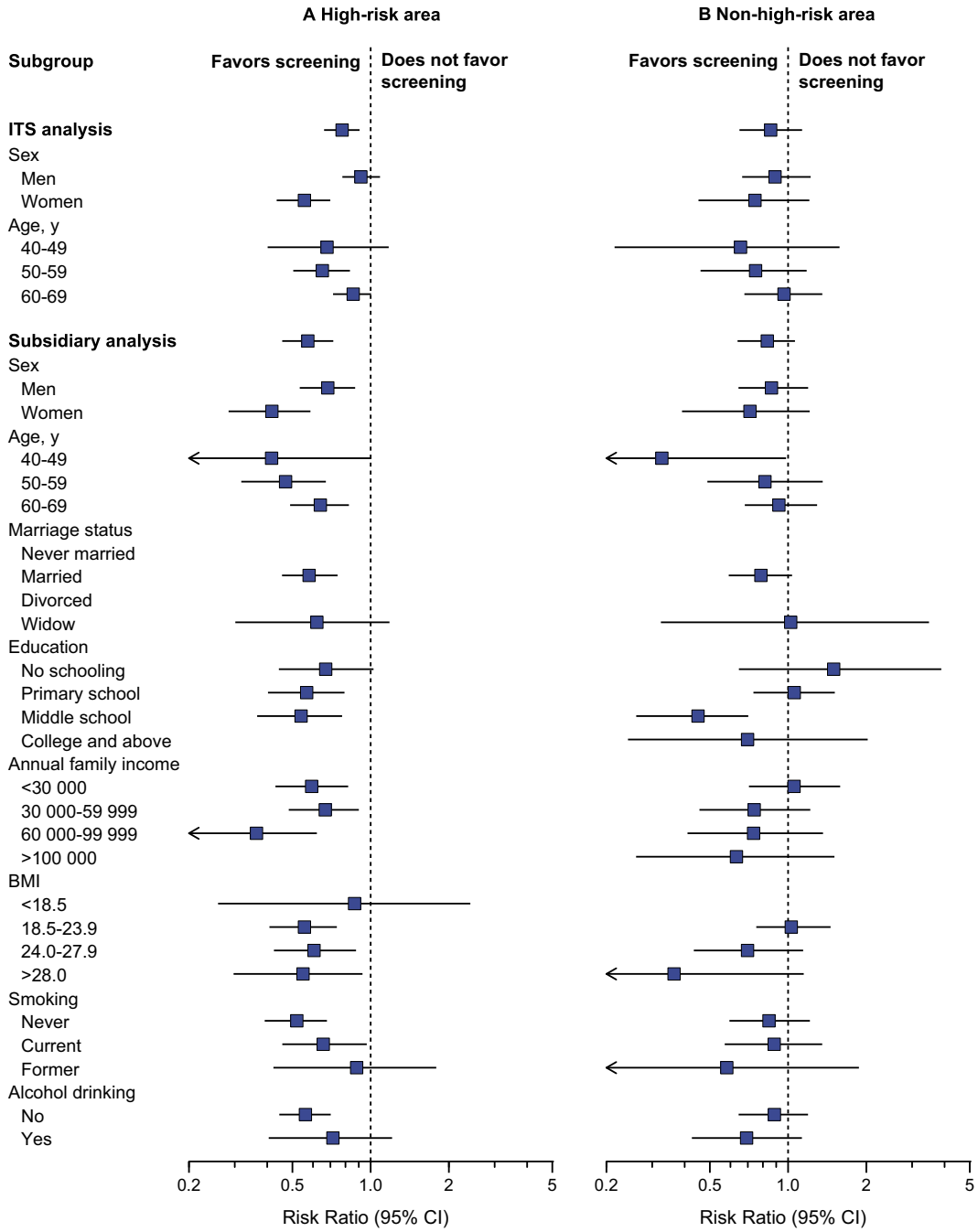

Figure 4. Subgroup analyses of mortality risk ratios for upper gastrointestinal cancer in high-risk areas (*A*) and non–high-risk areas (*B*). Risk ratios were adjusted by fixed effects from sex, age group, ethnicity, marriage status, education level, annual family income, BMI, smoking, and alcohol drinking, and random effects from clusters. 95% CI were estimated using the bootstrap method. BMI, body mass index.

as many rural residents sought job opportunities in urban or more developed regions, which categorized them as nonpermanent residents of the screening area (Figure 1).[22] A multicenter population-based cohort study conducted in high-risk areas of China demonstrated that a one-time endoscopic screening program was associated with a 57% decrease in upper gastrointestinal cancer mortality in the screened group and a 31% decrease in the invited group.[7] The larger magnitude of reduction observed in the cohort study, as compared with our trial, may be attributed to a longer follow-up duration, the inclusion of annually migrated individuals in our trial, and the presence of selection bias and the inclusion of prevalent cancers in the observational study. Our subsidiary estimates of a 43% decrease in upper gastrointestinal cancers in high-risk areas were similar to those reported in nonrandomized studies.[7]

For esophageal cancers, our ITS analysis and subsidiary analyses yielded a significant decrease in mortality rates of

27% and 49%, respectively, in high-risk areas. In a single-center community assignment study conducted in a high-risk area of China, one-time endoscopic screening reduced mortality from esophageal squamous cell carcinoma by 55% during the baseline period.[9] In a high-risk area of China, a 9-year follow-up of a single-center cluster randomized controlled trial demonstrated that chromoendoscopic screening was associated with an approximate 20% reduction in the incidence and mortality of esophageal squamous cell carcinoma; however, all of these reductions were not statistically significant.[31] The relatively small reduction observed in that trial can be attributed to several limitations, including high intracluster correlation within the single-center clusters, substantial selection bias, contamination by endoscopies outside the trial, and inclusion of a higher proportion of prevalent cases in the control group.[31,32] To address these limitations, our trial was conducted in high-risk areas involving 3 centers, enabling a larger sample size and better control over potential biases. As a result, we observed an effect similar to that reported in population-based cohort studies, namely, a 49% reduction in the risk of death from esophageal cancer in subsidiary analyses.[7,8,11]

For gastric cancers, our ITS analysis and subsidiary analyses yielded a significant decrease in mortality rates of 19% and 37%, respectively, in high-risk areas. A meta-analysis that included 6 cohort studies and 4 nested case-control studies from Asia indicated that endoscopic screening was associated with a 40% reduction in gastric cancer mortality.[10] Another meta-analysis revealed a significant average mortality reduction of endoscopy (relative risk 0.52; 95% CI, 0.39–0.79) based on the PP principle; however, the mortality reduction in the ITS effect was substantially diluted due to the low attendance rates (relative risk 0.94; 95% CI; 0.71–1.28).[33] According to a synthetic control study, the rate ratio of mortality in South Korea, compared with the synthetic control countries, was found to be 0.59 by the 15th year after the implementation of nationwide screening.[34] The significant reduction in mortality can be attributed to the fact that 72.55% of the participants in South Korea opted for biennial endoscopic screening for eligible residents in 2011.[34] Our trial confirmed that endoscopic screening significantly reduced gastric cancer mortality in high-risk areas, as observed in both ITS and PP analyses. However, in non–high-risk areas, although the magnitude of reduction might have been similar to that in high-risk areas, it required a longer follow-up period to obtain conclusive evidence.

Because individuals assessed as non–high-risk were not invited to receive endoscopy, noninvited and noncompliant participants were likely to have led to an underestimation of the endoscopy screening benefits. The different baseline characteristics between endoscopy compliers and non-compliers may introduce bias when estimating the PP effectiveness (Supplementary Table 4). Therefore, we conducted PP analyses while making adjustments for potential confounders. However, restricting PP analyses to those who underwent endoscopy would have inflated the screening effect because it exclusively consisted of individuals assessed as high-risk. As such, our estimates of a 35% decrease in upper gastrointestinal cancer-related deaths within 7.5 years may have overestimated the benefits. During the 7.5-year follow-up period, the potential maximum risk reduction in non–high-risk areas (35%) was lower than that in high-risk areas (43%). Considering that the screening benefits in non–high-risk areas appeared to gradually expand, future follow-up of our trial results may provide more precise estimates of the PP effects of endoscopy screening for non–high-risk areas.

The absolute risks of upper gastrointestinal cancer-related death in non–high-risk areas were much lower than those in high-risk areas. Thus, the NNI and NNS to prevent one death of upper gastrointestinal cancer were higher in non–high-risk areas than that in the high-risk areas, although the adjusted relative effects were similar. These findings underscore the importance of absolute risks and effects when planning upper gastrointestinal cancer screening programs.[35] The relatively high NNI and NNS in our trial were due to the use of "death" prevention over "cases" and a follow-up period of only 7.5 years. A decrease in the NNS is likely as the follow-up time extends. The comparative absolute benefits, harms, cost-effectiveness, and burden of endoscopy in both high-risk areas and non–high-risk areas should be considered by health policy decision makers and cancer screening program managers.[36]

Our study has limitations. First, we only excluded participants who had undergone an endoscopy in the past 3 years. However, the preventive effect of endoscopy may extend beyond 5 years.[37] Therefore, there is a possibility of a preventive effect from previous endoscopies. It is important to consider that, due to the low rate of endoscopy use,[38] the potential impact of previous endoscopies on prevention might be relatively small. Second, recruitment occurring after randomization is likely to result in lower participation rates compared with trials where randomization follows informed consent. Although these active recruitment design should produce more realistic estimates in the context of real-life screening programs, it is important to consider the potential impact of selection bias due to open-label recruitment and nonparticipation in our trial. To address this, we used the ITS principle to report our results and adjusted for potential confounders to reduce any selection bias. Third, approximately 20% of participants underwent *H pylori* testing to establish the association between current *H pylori* infection and upper gastrointestinal lesions and cancers.[15] Of these participants, 12,444 tested positive for *H pylori*.[15] Although our trial did not provide eradication therapies, some individuals may have voluntarily sought eradication. Considering that the *H pylori* eradication rate in the Chinese population was only 13.44%,[39] the results and conclusions of our trial would not be significantly influenced by the preventive effect of *H pylori* eradication. Fourth, during the follow-up period, all randomized clusters were excluded from participating in organized upper gastrointestinal cancer screening programs. Nevertheless, opportunistic screenings and diagnostic upper gastrointestinal endoscopies were inevitable. Therefore, there is a risk that the control group may have been contaminated by endoscopies conducted outside the trial,[38] potentially leading to an underestimation of the screening effectiveness. Finally, we

reported the mortality risk at 7.5 years; however, a longer follow-up may be needed to capture the full effect of endoscopy screening, particularly for non–high-risk areas. Because the effects of endoscopic screening may extend for 15 years, this interim analysis should not be considered as a final analysis (see trial protocol).

In summary, this cluster-randomized clinical trial is the first to demonstrate that an endoscopic screening significantly reduces mortality from upper gastrointestinal cancer in individuals aged 40–69 years in high-risk areas. Although endoscopic screening also shows potential in reducing the risk of upper gastrointestinal cancer deaths in non–high-risk areas, the absolute reduction is smaller, and the difference is not statistically significant. Nonetheless, endoscopic screening can be considered a population-based screening test in regions with a high burden of upper gastrointestinal cancers. Further research, including longer follow-up and real-world studies, is needed in non–high-risk areas and specific subgroups.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.11.025.

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Conflicts of interest
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Data Availability
Upon publication, researchers whose proposed use of the data has been approved will have access to the data. The data will be made available for meta-analysis and pooled-analysis, allowing for meaningful quantitative syntheses of research on the effects of public health interventions, as well as guiding future directions for cancer guidelines. The data will be accessible if the following criteria are fulfilled: (1) support from the investigator or organization is obtained; (2) the proposal for data use has been approved by the corresponding author (W. Chen); and (3) a data access agreement has been signed.