Beneficial effects of endoscopic screening on gastric cancer and optimal screening interval: a population-based study

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ABSTRACT

Background The effectiveness of endoscopic screening on gastric cancer has not been widely investigated in China and the screening interval of repeated screening has not been determined.

Methods In a population-based prospective study, we included 375,800 individuals, 14,670 of whom underwent endoscopic screening (2012–2018). We assessed the associations between endoscopic screening and risk of incident gastric cancer and gastric cancer-specific mortality, and examined changes in overall survival and disease-specific survival following screening. The optimal screening interval for repeated endoscopy for early detection of gastric cancer was explored.

Results Ever receiving endoscopic screening significantly decreased the risk of invasive gastric cancer (age- and sex-adjusted relative risk [RR] 0.69, 95 % confidence interval [CI] 0.52–0.92) and gastric cancer-specific mortality (RR 0.33, 95 %CI 0.20–0.56), particularly for noncardia gastric cancer. Repeated screening strengthened the beneficial effect on invasive gastric cancer-specific mortality of one-time screening. Among invasive gastric cancers, screening-detected individuals had significantly better overall survival (RR 0.18, 95 %CI 0.13–0.25) and disease-specific survival (RR 0.18, 95 %CI 0.13–0.25) than unscreened individuals, particularly for those receiving repeated endoscopy. For individuals with intestinal metaplasia or low grade intraepithelial neoplasia, repeated endoscopy at an interval of <2 years, particularly within 1 year, significantly enhanced the detection of early gastric cancer, compared with repeated screening after 2 years (P-trend = 0.02).

Conclusion Endoscopic screening prevented gastric cancer occurrence and death, and improved its prognosis in a population-based study. Repeated endoscopy enhanced the effectiveness. Screening interval should be based on gastric lesion severity.

Introduction

Gastric cancer remains a major public health concern worldwide, with half of new gastric cancer cases and deaths occurring in China [1, 2]. Most cases are diagnosed at advanced stages, leading to unfavorable overall prognosis in China [3].

Endoscopic screening can prevent gastric cancer by early detection and treatment of asymptomatic early-stage gastric cancers and its precursors, and has been shown to be a cost-effec-

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tive approach in Japan and Korea, which adopt nationwide screening programs [4, 5]. In China, the endoscopy-based national Upper Gastrointestinal Cancer Early Detection (UGCED) Program was launched and has been running in selected areas since 2012 [6]. Instead of one-time screening only, individuals diagnosed with advanced gastric lesions are advised to undergo annual endoscopic surveillance. Despite a previous study reporting the effect of one-time endoscopic screening on upper gastrointestinal cancers in areas at high risk for esophageal cancer [7], no such studies have been conducted in the real-world scenario for populations at high risk for gastric cancer, and the extra value of repeated endoscopy is unclear. It is worth noting that the current guidelines on the time intervals for repeated endoscopy for individuals with advanced gastric lesions were developed from limited expert experience [8]. Data need to be gathered to determine the optimal screening intervals for repeated endoscopy for different gastric lesions, so that the benefit of gastric cancer screening can be maximized.

To fill the knowledge gap, we conducted a population-based prospective study to evaluate the effectiveness of endoscopic screening in Linqu county, a rural area in northeastern China that has one of the highest gastric cancer mortality rates worldwide [9]. We examined the changes in gastric cancer incidence and gastric cancer-specific mortality associated with one-time or repeated endoscopy, as well as gastric cancer prognosis. We also examined screening intervals for repeated endoscopy for individuals with endoscopy-detected gastric lesions of different stages.

Methods

Study population

This study was performed based on the ongoing National UGCED Program in Linqu, China, in which residents aged 40–69 years undergo endoscopic screening for early diagnosis of gastric cancer free of charge. High grade intraepithelial neoplasia (HGIN) and invasive gastric cancer were collectively defined as gastric cancer.

A standardized protocol for gastric cancer screening solely based on gastroendoscopy was introduced to the program in January 2012. Following this protocol, around 3000 eligible individuals (including those attending the first or repeated endoscopy during follow-up) undergo the examination annually. For the current study, villages were chosen based on cluster random sampling, and potential participants were invited via rural broadcasting and brochures. Individuals diagnosed with severe chronic atrophic gastritis (CAG), intestinal metaplasia (IM), or low grade intraepithelial neoplasia (LGIN) were advised to undergo repeated examination the following year. Individuals providing informed consent were interviewed using standardized questionnaires and underwent physical examinations to identify any contraindications to endoscopy.

A total of 375 800 permanent residents aged 40–69 years and without a history of cancer were documented in January 2012 by accessing the household registration (hukou) system in Linqu. Among them, 14 670 individuals who underwent endoscopy between January 2012 and December 2018 were classified as the screened group. The remaining participants were classified as the unscreened group (▶ **Fig. 1**). None of the study subjects participated in the interventional trials using *Helicobacter pylori* eradication or nutritional supplementation that we previously conducted in Linqu [10, 11].

The study was approved by the Institutional Review Board of Peking University Cancer Hospital (PUCH).

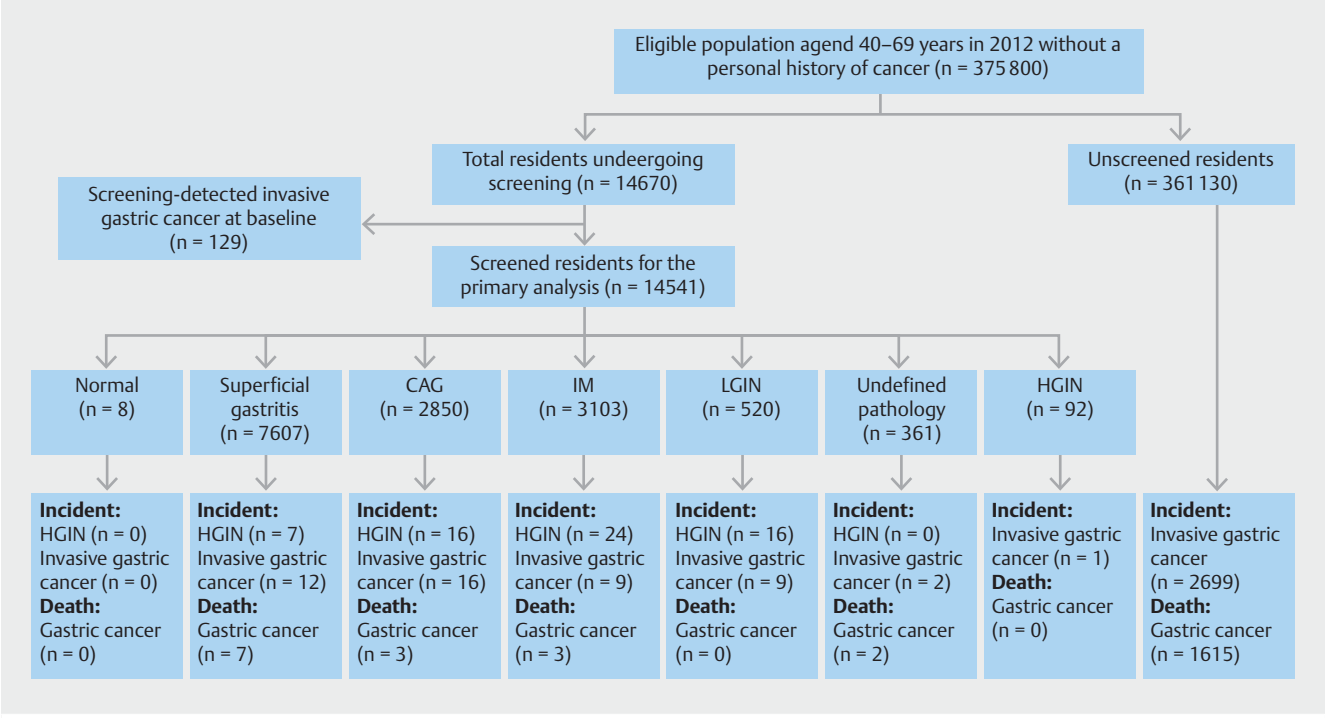
Gastroendoscopy and histopathology

Gastroscopic examinations were conducted by two experienced gastroenterologists using video endoscopes (Olympus, Tokyo, Japan). Biopsies were taken at five standardized sites, with one each from the antrum 3 cm above the pylorus at the lesser curvature, angulus at the lesser curvature, middle of the body at the anterior wall, cardia at the squamocolumnar junction at the lesser curvature, and the esophagus 2 cm above the squamocolumnar junction. In addition, any other suspicious lesion detected during endoscopy were biopsied. According to the criteria proposed by the Chinese Association of Gastric Cancer and updated Sydney System [12, 13], each participant was given a global diagnosis of normal, superficial gastritis, CAG (mild, moderate, or severe), IM (mild, moderate, or severe), LGIN, HGIN (pathologically including severe dysplasia and gastric cancer in situ), or invasive gastric cancer, based on the most severe histology among all biopsies. In Linqu, superficial gastritis represents the least abnormal type of mucosa that could be detected, and few individuals had completely normal histology [10, 12].

Assessment of gastric cancer outcomes

The primary outcomes were invasive gastric cancer incidence and gastric cancer-specific mortality. Among invasive gastric cancer cases, we also examined the overall survival and disease-specific survival.

During follow-up from the date of first endoscopy (screened individuals) or 1 January 2012 (unscreened individuals) to 31 December 2019, invasive gastric cancers were identified through cancer registry or autopsy reports and repeated endoscopies, and confirmed by reviewing medical records. The Linqu registry has gained a reputation for providing consistently high quality data, as recognized by the National Central Cancer Registry of China [2]. HGIN cases were identified through endoscopies. HGIN or early-stage invasive gastric cancer cases were collectively defined as early gastric cancer (EGC), in which the primary tumor was confined to mucosa or submucosa, regardless of the presence or absence of lymph node metastasis. Gastric cancer-specific death was obtained from the reporting system managed by the Chinese Center for Disease Control and Prevention, which integrates death certificates from hospitals, police, and judicial departments. To avoid missed records from delayed reporting, active clinical follow-up was conducted by village physicians, local program coordinators, and staff from PUCH. We did not record any drop-out cases during follow-up.



▶ **Fig. 1** Flow chart for the study populations. CAG, chronic atrophic gastritis; HGIN, high grade intraepithelial neoplasia; IM, intestinal metaplasia; LGIN, low grade intraepithelial neoplasia. In the National Upper Gastrointestinal Cancer Early Detection Program, HGIN and invasive gastric cancer were both classified as gastric cancer and were treated immediately. In the unscreened group, the Linqu cancer registry, in which only invasive gastric cancer cases were reported and not HGIN cases, was the main resource for assessing gastric cancer.

Statistical analysis

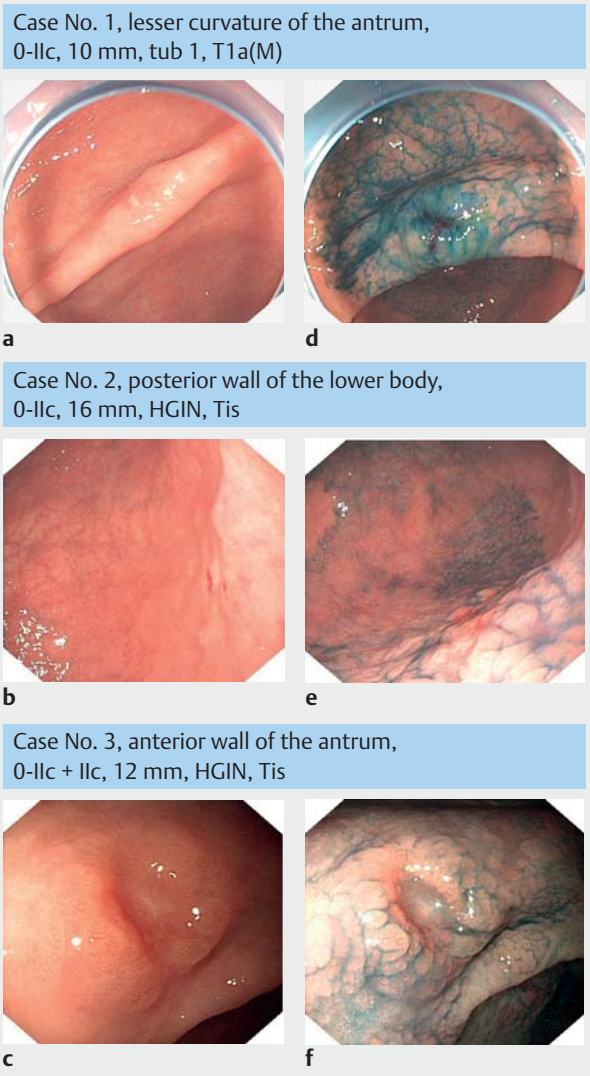
Detailed methods are shown in the online-only **Supplementary Material**. First, we evaluated the effectiveness of endoscopic screening on the risk of incident invasive gastric cancer and gastric cancer-specific mortality. Age- and sex-adjusted relative risks (RRs) and 95 % confidence intervals (CIs) were calculated using Poisson regression models by comparing the screened and unscreened groups. Analyses were also conducted for one-time or repeated screening, respectively. In addition, we performed stratified analyses by age and sex. The Nelson–Aalen method was used for the calculation of cumulative hazards [14]. To satisfy the requirement of prospective study design, we excluded invasive gastric cancer cases that were diagnosed at the initial screening (n = 129) for the primary analyses, with 14 541 remaining in the screened group (n = 3802 receiving repeated screening).

Second, we restricted the analyses to invasive gastric cancer cases only and assessed the changes in overall survival and disease-specific survival of invasive gastric cancers between cases in the screened and unscreened groups. Survival curves were plotted and crude rates of overall survival and disease-specific survival were estimated using the Kaplan–Meier method, and the age- and sex-adjusted RRs (95 %CIs) were calculated using Poisson regression models.

Third, in an exploratory analysis, we examined the odds of EGC associated with screening interval. Focusing on individuals who were diagnosed with gastric cancer by endoscopy and had undergone previous endoscopy, we defined the screening interval as the interval between the preceding endoscopy and the subsequent endoscopy that detected gastric cancer. Unconditional logistic regression analyses were conducted to calculate the odds ratios (ORs) and 95 %CIs for the associations of screening interval (≤ 1, 1–2, or > 2 years) and the odds of being diagnosed with EGC compared with non-EGC.

Results

We included 14 670 individuals who underwent endoscopic screening and 361 130 unscreened individuals. Among screened individuals, 129 were diagnosed with invasive gastric cancer at first screening (69 detected at an early stage), and 92 had HGIN. Representative endoscopic images of selected cases diagnosed with HGIN or early-stage invasive gastric cancer in the UGCED program are shown in ▶ **Fig. 2**. The screened group were slightly younger (53.9 [SD 7.5] years) than the unscreened group (52.9 [SD 8.0] years), and included fewer men (47.7 % vs. 50.7 %) (**Table 1 s**). The median follow-up time was 5.1 years (interquartile range [IQR] 3.1–6.6) for the screened group. During follow-up, we documented 49 incident invasive gastric cancers and 63 HGINs among screened individuals, and 2699 new invasive gastric cancers among unscreened individuals. At the diagnosis of invasive gastric cancer or HGIN, affected individuals had been followed for a median time of 2.0 years (IQR 1.2–3.8). One HGIN case at the first screening developed invasive gastric cancer during follow-up, despite immediate treatment for screening-detected HGIN in the UGCED Program (▶ **Fig. 1**).



▶ **Fig. 2** Representative endoscopic images of three selected cases with high grade intraepithelial neoplasia (HGIN) or early-stage invasive gastric cancer diagnosed in the National Upper Gastrointestinal Cancer Early Detection Program. **a–c** White-light imaging. **d–f** Indigo carmine imaging. The location of HGIN or invasive gastric cancer, Paris classification, diameter, and clinical staging for each case are shown. Case No. 1: male, age 64 years (**a, d**); Case No. 2: male, age 61 years (**b, e**); Case No. 3: female, age 66 years (**c, f**).

Associations between endoscopic screening and risk of incident invasive gastric cancer

Individuals receiving at least one endoscopic screening (ever screening) had a lower incidence of invasive gastric cancer than unscreened individuals (age- and sex-standardized cumulative incidence 70.16 [95 %CI 50.24–90.07] vs. 95.81 [95 %CI 92.19–99.42], per 100 000 person–years). We found a significant inverse association between endoscopic screening and risk of invasive gastric cancer (age- and sex-adjusted RR 0.69, 95 %CI 0.52–0.92), particularly for noncardia invasive gastric cancer (age- and sex-adjusted RR0.64, 95 %CI 0.47–0.87) (▶ **Table 1**). Further analysis found that compared with unscreened individuals, one-time screening significantly reduced the risk of developing gastric cancer during follow-up (age- and sex-adjusted RR 0.38, 95 %CI 0.24–0.60). Interestingly, those receiving repeated screening had significantly increased risk of gastric cancer (age- and sex-adjusted RR 1.44, 95 %CI 1.00–2.06) (▶ **Table 1**), which may be explained by the identification of additional gastric cancer cases during repeated endoscopic examinations. Among 30 invasive gastric cancers recorded in the repeated screening group, only 6 were identified from regular cancer registry or autopsy reports (the same approach for accruing cases in the unscreened group), while 24 cases were detected by endoscopic examinations during follow-up. In sensitivity analysis including only cancer registry or autopsy reports, we observed significantly decreased risk of invasive gastric cancer associated with repeated screening (age- and sex-adjusted RR 0.30, 95 %CI 0.13–0.66).

Associations between endoscopic screening and risk of incident invasive gastric cancer-specific mortality

We identified 14 deaths due to gastric cancer (all noncardia) in the ever-screened group and 1615 deaths from gastric cancer in the unscreened group (age- and sex-adjusted cumulative gastric cancer-specific mortality 21.15 [95 %CI 9.90–32.40] vs. 57.24 [95 %CI 54.45–60.03], per 100 000 person–years, respectively), revealing significantly decreased risk of gastric cancer-specific deaths among screened individuals (age- and sex-adjusted RR 0.33, 95 %CI 0.20–0.56) (▶ **Table 1**). A significantly lower risk of gastric cancer-specific mortality was observed for participants receiving one-time (age- and sex-adjusted RR 0.37, 95 %CI 0.20–0.67) or repeated screening (age- and sex-adjusted HR 0.24, 95 %CI 0.08–0.74) compared with unscreened individuals. We did not document any death from cardia gastric cancer in the screened group. The inverse association was statistically pronounced for noncardia gastric cancer (▶ **Table 1**). We analyzed the temporal patterns and found that the cumulative incidence of and cause-specific mortality from invasive gastric cancer both seemed immediately lower in the screened group compared with the unscreened group (**Fig. 1 s a, b**). In the sensitivity analysis without excluding invasive gastric cancers identified at the first screening, despite the obviously higher reported incidence for screened individuals (**Fig. 1 s c**), a reduction in invasive gastric cancer-specific mortality in the screened group was reached after 4 years' follow-up (**Fig. 1 s d**). Similar patterns were observed for noncardia invasive gastric cancer (**Fig. 1 s e–h**).

Associations between endoscopic screening and risk of incident invasive gastric cancer and gastric cancer-specific mortality, stratified by age and sex

In stratified analyses, the association of the risk of invasive gastric cancer and gastric cancer-specific mortality with ever or one-time endoscopic screening differed among age groups, and was statistically significant for individuals aged 50–59 years and 60–69 years, but not for those aged < 50 years (*P*-heterogeneity 0.005 for gastric cancer occurrence and 0.001 for

▶ **Table 1** Incident invasive gastric cancer and gastric cancer-specific mortality associated with endoscopic screening.[1]

	Screened													
	Total (n = 14 541)		One-time screened (n = 10 739)		Repeated screened (n = 3802)		Unscreened (n = 361 130)		Screened vs. unscreened		One-time screened vs. unscreened		Repeated screened vs. unscreened	
	Cases	Person-years	Cases	Person-years	Cases	Person-years	Cases	Person-years	RR[2]	95 %CI	RR[2]	95 %CI	RR[2]	95 %CI
Incidence														
Invasive gastric cancer	49	70 614	19	51 091	30	19 523	2699	2 820 272	0.69	0.52–0.92	0.38	0.24–0.60	1.44	1.00–2.06
▪ Cardia invasive gastric cancer	7	70 625	3	51 080	4	19 545	192	2 824 433	1.41	0.66–2.99	0.86	0.28–2.71	2.66.	0.99–7.15
▪ Noncardia invasive gastric cancer	42	70 630	16	51 094	26	19 536	2507	2 820 639	0.64	0.47–0.87	0.35	0.21–0.56	1.34	0.91–1.97
Mortality														
Invasive gastric cancer	14	70 718	11	51 111	3	19 607	1615	2 824 799	0.33	0.20–0.56	0.37	0.20–0.67	0.24	0.08–0.74
▪ Cardia invasive gastric cancer	0	70 718	0	51111	0	19 607	70	2 824 799	–	–	–	–	–	–
▪ Noncardia invasive gastric cancer	14	70718	11	51111	3	19 607	1545	2 824 799	0.35	0.20–0.58	0.38	0.21–0.70	0.25	0.08–0.78

RR, relative risk; CI, confidence interval; HGIN, high grade intraepithelial neoplasia.

[1] High grade intraepithelial neoplasia (HGIN) was not examined here because cancer registry was the main resource for assessing gastric cancer in the unscreened group, in which only invasive gastric cancer cases, but not HGIN, were reported.

[2] RRs were calculated using Poisson regression models, adjusting for age and sex.

gastric cancer-specific mortality) (▶ **Table 2**). We also found a stronger association with risk of invasive gastric cancer occurrence, but not with gastric cancer-specific mortality, for women compared with men (*P*-heterogeneity 0.06 for gastric cancer occurrence and 0.36 for gastric cancer-specific mortality) (▶ **Table 2**). Similar heterogeneity by age was found for noncardia gastric cancer (**Table 2 s**).

Associations of endoscopic screening with overall survival and disease-specific survival: invasive gastric cancer cases only

We assessed the overall survival and disease-specific survival of invasive gastric cancers between the screened group (n = 178, including 129 identified at first screening and 49 incident cases at repeated screening during follow-up) and the unscreened group (n = 2699) (▶ **Fig. 3**, **Table 3 s**). During follow-up, we recorded 36 deaths (n = 34 gastric cancer-specific deaths) in the screened group and 1706 deaths (n = 1615 gastric cancer-specific deaths) in the unscreened group. The 5-year overall survival rate was 77.7 % (95 %CI 70.1–83.6) and 5-year disease-specific survival rate was 78.4 % (95 %CI 70.8–84.2) for invasive gastric cancer cases in the screened group and 29.2 % (95 %CI 27.2–31.2) and 31.9 % (95 %CI 29.8–34.0), respectively, in the unscreened group. Screening-detected cases had a significantly more favorable overall survival (age- and sex-adjusted RR 0.18, 95 %CI 0.13–0.25) (▶ **Fig. 3a**) and disease-specific survival (age- and sex-adjusted RR 0.18, 95 %CI 0.13–0.25) (▶ **Fig. 3e**). Despite the apparently higher percentage of early invasive gastric cancer in the screened group (**Table 3 s**), subgroup analysis by early or advanced stage found consistently favorable prognoses for the screened group (▶ **Fig. 3b, c, f, g**). The effect on improved overall survival or disease-specific survival was particularly stronger for those undergoing repeated screening compared with those receiving one-time screening (▶ **Fig. 3d, h**). Restricting analysis to cases with surgical resection yielded similar findings (**Fig. 2 s**).

Sensitivity analysis excluding 129 cases identified at the first screening did not materially change the findings (**Fig. 3 s**).

Screening interval associated with the odds of EGC detection

We documented a total of 97 endoscopy-detected gastric cancers that had defined gastric histopathology in the preceding endoscopy, 85 of which were EGCs, including 63 HGINs and 22 early-stage invasive gastric cancers. Compared with endoscopy-detected gastric cancers that had the preceding endoscopy performed more than 2 years previously, individuals undergoing preceding endoscopy 1–2 years previously or < 1 year previously were more likely to be EGCs (▶ **Table 3**). For endoscopy-detected gastric cancers that were diagnosed with IM or LGIN at the preceding endoscopy, having the following endoscopy within 1–2 years (age- and sex-adjusted OR 14.9, 95 %CI 1.8–121.6) or within 1 year (age- and sex-adjusted OR 19.9, 95 %CI 1.6–248.4) significantly improved the odds of detecting EGC, compared with repeated screening after 2 years (*P*-trend = 0.02). No significant findings were found for those with superficial gastritis or CAG at the preceding endoscopy.

Discussion

In our prospective study of individuals residing in a recognized high-risk area, ever receiving endoscopic screening led to significantly decreased risk of incident invasive gastric cancer occurrence and gastric cancer-specific mortality. The beneficial effect on gastric cancer-specific mortality was enhanced by repeated endoscopy and particularly notable among those aged ≥ 50 years. A favorable prognosis for invasive gastric cancer was found for endoscopy-detected cases, particularly for those undergoing repeated endoscopy. For individuals diagnosed with IM or LGIN by endoscopy, repeated endoscopy at an interval of < 2 years, particularly within a year, significantly boosted the odds of detecting EGC.

Since 2012, the government-funded UGCED Program has operated with continuous funding for endoscopic screening in selected rural areas, including Linqu [6]. However, to date, only limited studies have evaluated the benefit of this program on gastric cancer prevention [7, 15] and no studies have been conducted on its effectiveness in areas at high risk for gastric cancer, or the potentially extra value of repeated screening. Our findings in an area at high risk for gastric cancer are consistent with a previous study covering six areas at high risk for esophageal cancer, including Cixian, Feicheng, Linzhou, Yancheng, Yanting, and Yangzhong [7], and reported similar magnitudes of effect for noncardia invasive gastric cancer. We further found a stronger beneficial effect on gastric cancer-specific mortality by repeated screening compared with only one-time screening, stressing the necessity for repeated endoscopic surveillance of gastric cancer.

We observed significantly decreased risk of developing invasive gastric cancer by one-time screening, similarly to Chen et al. [7], but a significantly increased risk of incident invasive gastric cancer by repeated screening. The results should be interpreted with caution. In the primary analyses, the identification of incident invasive gastric cancers was solely based on cancer registry or autopsy reports for those undergoing only one-time endoscopy or unscreened individuals, while individuals undergoing repeated screening may also have had gastric cancer diagnosed by endoscopic examinations, leading to surveillance bias. Therefore, the seemingly contradictory results may be understandable in practice given the different approaches to the accrual of incident invasive gastric cancers during follow-up. A previous study from Korea also found that individuals undergoing gastroendoscopy screening had a higher risk of incident gastric cancer (screened once hazard ratio 2.19, 95 %CI 1.45–3.31; screened more than twice hazard ratio 2.06, 95 %CI 1.30–3.28) than unscreened individuals [16]. Nevertheless, the current study, and a previous study [4], consistently yielded reduced risk of gastric cancer-specific deaths by one-time or repeated screening, corroborating the favorable effect of endoscopic screening.

The effectiveness of endoscopic screening was further supported by its benefit on gastric cancer survival, which appeared even stronger for repeated screening and remained for individuals undergoing surgical resection. Screening tended to detect early-stage tumors that were smaller in size and yet asympto-

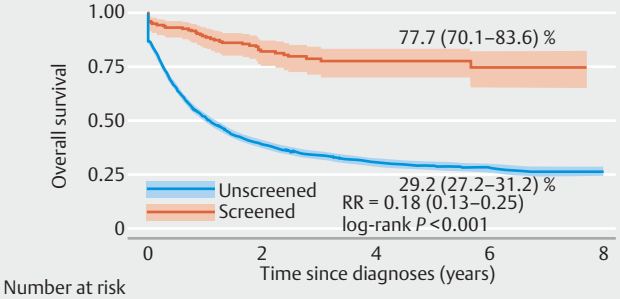
▶ **Table 2** Incident invasive gastric cancer and gastric cancer-specific mortality associated with endoscopic screening: analyses stratified by age and sex.

	Screened						Unscreened (n = 361 130)		Screened vs. unscreened			One-time screened vs. unscreened			Repeated screened vs. unscreened		
	Total (n = 14 541)		One-time screened (n = 10 739)		Repeated screened (n = 3802)												
	Cases	Person-years	Cases	Person-years	Cases	Person-years	Cases	Person-years	RR[1]	95 %CI	$P_{heterogeneity}$[2]	RR[1]	95 %CI	$P_{heterogeneity}$[2]	RR[1]	95 %CI	$P_{heterogeneity}$[2]
Incidence																	
Sex											0.06			0.35			0.17
▪ Male	43	33 427	16	23 360	27	10 068	2082	1 419 243	0.80	0.59–1.08		0.43	0.26–0.71		1.63	1.11–2.38	
▪ Female	6	37 186	3	27 731	3	9455	617	1 401 029	0.35	0.16–0.79		0.24	0.08–0.73		0.70	0.22–2.16	
Age											0.005			< 0.001			0.34
▪ 40–49	13	25 449	8	18 912	5	6537	450	1 220 825	1.46	0.84–2.53		1.21	0.60–2.44		2.12	0.88–5.13	
▪ 50–59	18	28 457	6	19 945	12	8512	1063	980 997	0.60	0.38–0.96		0.29	0.13–0.66		1.27	0.72–2.24	
▪ 60–69	18	16 708	5	12 234	13	4473	1186	618 450	0.56	0.35–0.90		0.22	0.09–0.53		1.43	0.83–2.47	
Mortality																	
Sex											0.36			0.53			–
▪ Male	12	33 522	9	23 380	3	10 142	1232	1 422 819	0.38	0.21–0.67		0.41	0.21–0.79		0.31	0.10–0.95	
▪ Female	2	37 197	2	27 732	0	9465	383	1 401 980	0.19	0.05–0.75		0.25	0.06–1.01		–	–	
Age											0.001			0.03			0.02
▪ 40–49	6	25 463	4	18 914	2	6548	252	1 221 632	1.21	0.54–2.71		1.09	0.41–2.94		1.52	0.38–6.11	
▪ 50–59	4	28 502	4	19 953	0	8549	587	982 873	0.24	0.09–0.65		0.35	0.13–0.95		–	–	
▪ 60–69	4	16 754	3	12 244	1	4510	776	620 294	0.19	0.07–0.51		0.20	0.06–0.62		0.17	0.02–1.19	

RR, relative risk; CI, confidence interval.
[1] RRs were calculated using Poisson regression models, adjusting for age and sex.
[2] Heterogeneity tests were conducted using Q statistics for meta-analysis.

Overall survival

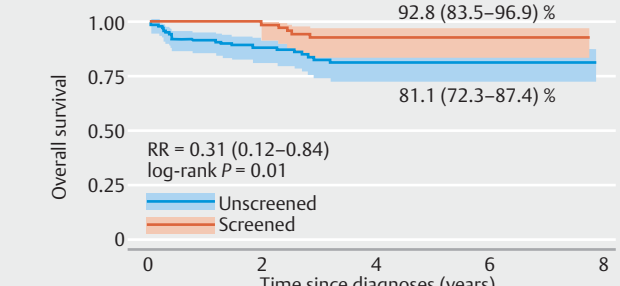
All invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	2699	774	397	190	0
screened	178	118	64	19	0

a

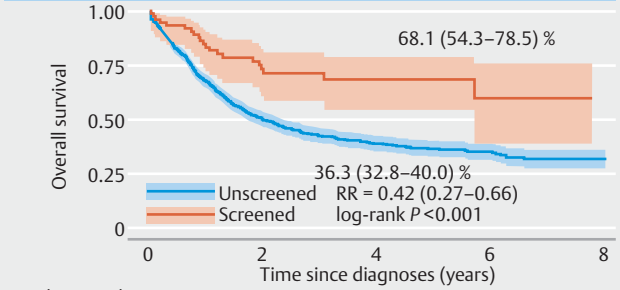
Early stage invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	147	91	47	26	0
screened	92	79	42	12	0

b

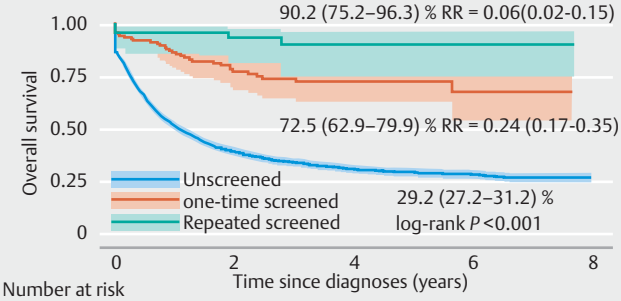
Advanced stage invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	891	365	184	74	0
screened	72	38	21	5	0

c

All invasive gastric cancer cases (repeated vs. one-time endoscopy vs. unscreened)

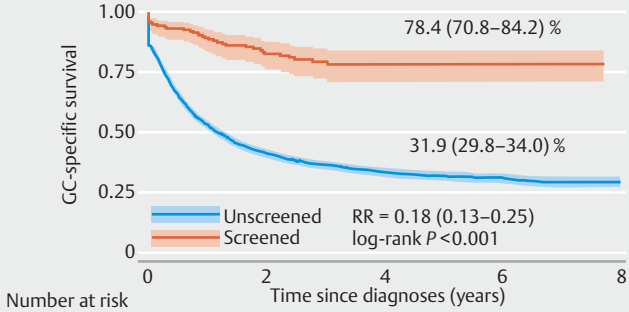


Number at risk					
unscreened	2699	774	397	190	0
one-time screened	128	78	43	10	0
repeated screened	50	40	21	8	0

d

GC-specific survival

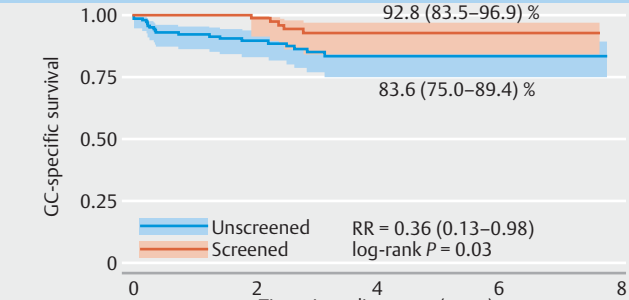
All invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	2699	774	397	190	0
screened	178	118	64	19	0

e

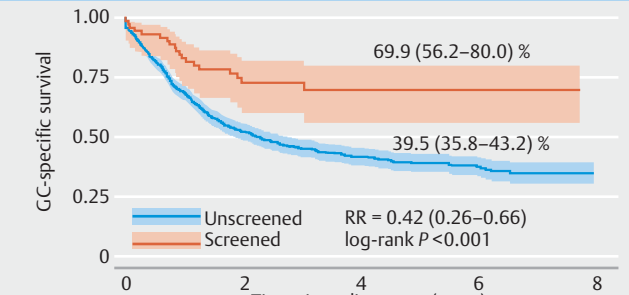
Early stage invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	147	91	47	26	0
screened	92	89	42	12	0

f

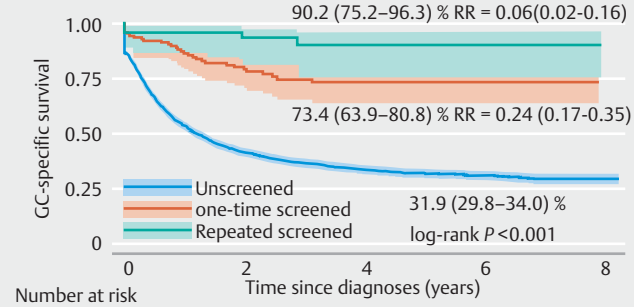
Advanced stage invasive gastric cancer cases (screened vs. unscreened)



Number at risk					
unscreened	891	365	184	74	0
screened	72	38	21	5	0

g

All invasive gastric cancer cases (repeated vs. one-time endoscopy vs. unscreened)



Number at risk					
unscreened	2699	774	397	190	0
one-time screened	128	78	43	10	0
repeated screened	50	40	21	8	0

h

▶ **Table 3** The odds ratios of detecting early gastric cancer associated with the endoscopic screening intervals stratified by the preceding endoscopy-detected pathology.*

Preceding pathology and screening interval	EGC, n (%)	Gastric cancer of other stages, n (%)	OR	95 %CI
Total				
▪ >2 years	16 (70)	7 (30)	1.0	
▪ 1–2 years	38 (93)	3 (7)	5.6	1.2–25.5
▪ Within 1 year	31 (94)	2 (6)	7.5	1.3–42.1
▪ *P* for trend			0.02	
Superficial gastritis/CAG				
▪ >2 years	12 (80)	3 (20)	1.00	
▪ 1–2 years	6 (86)	1 (14)	3.0	0.1–70.5
▪ Within 1 year	8 (89)	1 (11)	3.1	0.2–45.6
▪ *P* for trend			0.39	
IM/LGIN				
▪ >2 years	4 (50)	4 (50)	1.00	
▪ 1–2 years	32 (94)	2 (6)	14.9	1.8–121.6
▪ Within 1 year	23 (96)	1 (4)	19.9	1.6–248.4
▪ *P* for trend			0.02	

EGC, early gastric cancer; OR, odds ratio; CI, confidence interval; CAG, chronic atrophic gastritis; IM, intestinal metaplasia; LGIN, low grade intraepithelial neoplasia.

* No cases of gastric cancer were identified for those with normal mucosa at the first screening so that the subgroup analyses were confined to those with superficial gastritis or other gastric lesions. ORs were calculated using unconditional logistic regression model, adjusting for age and sex.

matic, and screening-detected gastric cancer would receive early treatment, improving the prognosis. A previous study also reported fewer metastatic lymph nodes for the screened group [17], which may lead to improved prognosis as well. Lead time bias or length bias was also possible, as indicated by the nonsignificant results for analysis of one-time screening including only incident gastric cancers during follow-up (**Fig. 3 s d**). However, favorable survival by endoscopy was found for analyses restricted to early or advanced stage gastric cancer, which partly addresses these concerns. For gastric cancers, even at equivalent stages, variations in the anatomical distribution of metastatic lymph nodes and other clinical characteristics between screened and unscreened groups may also affect outcomes [17], but data in this regard are lacking.

The target age for endoscopic screening remains debatable. While screening in Korea is implemented for individuals aged ≥40 years [18], Japan drew up new guidelines in 2014 that included a new starting age of 50 years [5]. A stronger protective effect of endoscopic screening on gastric cancer for individuals aged 40–49 years was reported in a Korean study and a study based on an area at high risk for esophageal cancer in China [4, 7]. Our study found a particularly prominent effect of endoscopic screening among those aged ≥50 years, providing evidence to support the implementation of gastric cancer screening at an older age in areas of China at high risk for gastric cancer.

The multistep cascade of gastric cancer development is well recognized [19, 20]. The dynamic evolution of gastric lesions may result in variation in the estimated risk of developing gastric cancer. Periodic repeated screening and intensive surveillance for individuals with premalignant gastric lesions would be crucial to detect gastric cancer at an early stage [21]. The recommended frequency for repeated endoscopy in the UGCED Program was formulated empirically, following a "one-size-fits-all" approach. Indeed, several studies worldwide have suggested a screening interval of 2 or 3 years to optimize the benefit of EGC detection and improve survival [22–25]. However, these studies failed to provide evidence on screening intervals for different gastric lesions. Two Korean studies included gastric cancer cases with other concomitant gastric lesions at the gastric mucosa, and assessed the interval between self-reported prior endoscopic screening and time of gastric cancer diagnoses [26, 27]. One study concluded an optimum screening interval of 3 years for gastric cancer cases without IM at cancer-adjacent tissues, and an interval of 2 years for cases with IM to achieve a favorable disease-free survival of gastric cancer [26]. The other study involved gastric cancer cases with severe IM and reported a 1-year interval for early detection of gastric cancer [27]. In our study, based on clearly recorded endoscopic screening with prospective follow-up, although an interval of more than 2 years may be acceptable for those with superficial gastritis or CAG, repeated screening within 2 years is warranted for individuals with IM or LGIN, and within 1 year would be highly recommended when medical and health resources are available.

Some international guidelines, such as those of British Society of Gastroenterology [28] and the Management of Epithelial Precancerous Conditions and Lesions in the Stomach (MAPS-II) [29] have recommended endoscopic surveillance every 3 years for individuals with severe atrophy or IM and within 1 year for LGIN. In addition to investigation into cost-effectiveness, studies are warranted to optimize screening intervals by combining epidemiological and clinical features of targeted individuals, thus improving the effectiveness of secondary prevention of gastric cancer.

▶ **Fig. 3** Survival analyses of invasive gastric cancer cases between screened and unscreened groups. **a–d** Overall survival. **e–h** Disease-specific survival. Comparisons are for all invasive gastric cancer cases (**a, e**), early-stage invasive gastric cancer (**b, f**), and advanced-stage invasive gastric cancer (**c, g**). Comparison of repeated vs. one-time endoscopy vs. unscreened groups are also shown (**d, h**). Relative risk (RR) was calculated using Poisson regression models, adjusting for age and sex. *(previous page)*

We acknowledge several limitations to the study. First, we lack information on major characteristics and cannot directly evaluate the effects of socioeconomic status. However, participants all came from the Linqu rural area, with similar medical care and lifestyles, strengthening the comparability of screened and unscreened groups. In addition, the UGCED Program was free of charge for individuals, minimizing the effects of socioeconomic status on participation. Second, selection bias is possible because individuals undergoing endoscopic screening might be more health conscious and have a better health status than unscreened individuals. Individuals with subjective gastrointestinal symptoms may be more motivated to undertake the screening. In addition, those attending repeated endoscopy were not randomly sampled from those attending the preceding screening. Third, numbers of events (gastric cancer cases and cause-specific deaths) were only modest. Cardia gastric cancer and esophageal cancer are not as common as noncardia gastric cancer in Linqu [10]. During follow-up, we only identified 12 incident esophageal cancer cases and 4 cause-specific deaths in the screened group. These precluded detailed analyses with reasonable power. Fourth, we cannot directly extrapolate our findings to populations with moderate or low risk for gastric cancer. Fifth, we were not able to examine the changes in gastric cancer outcomes for residents of invited villages that did not participate in the screening, which were classified as the unscreened group. Sixth, due to the modest sample size, the analyses on screening intervals were exploratory in nature. Additional analyses are necessary to explore screening intervals for CAG, IM, and LGIN, respectively. Based on the Shandong Intervention Trial [10], we once estimated a mean sojourn time of 8.0 years (95 %CI 7.1–9.0) for CAG, 4.0 years (95 %CI 3.4–4.7) for IM, and 2.2 years (95 %CI 1.8–2.7) for LGIN by multistate Markov model (unpublished data), which stresses their heterogeneity in progression, and demonstrates the necessity of defining screening intervals with further refinement and amendment of national guidelines.

In conclusion, our study supports the effectiveness of endoscopic screening and the significance of repeated screening with suitable time intervals tailored to the severity of gastric lesions. Further large-scale studies are warranted to validate the findings on the starting age for endoscopic screening and time intervals for repeated surveillance, particularly considering individuals with gastric lesions of different stages, and to evaluate the related cost-effectiveness, before translation into public health strategies in large communities.

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Competing interests

The authors declare that they have no conflict of interest.

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