Clinical Gastroenterology and Hepatology 2023;21:653–662

ENDOSCOPY

Endoscopic Surveillance for Premalignant Esophageal Lesions: A Community-Based Multicenter, Prospective Cohort Study

He Li,[1,*] Shaokai Zhang,[2,*] Jinyi Zhou,[3,*] Feng Tong,[4,*] Jiyong Gong,[4,*] Zhenqiu Zha,[5,*] Ni Li,[1] Changfa Xia,[1] Jiang Li,[1] Liyang Zheng,[2] Pengfei Luo,[3] Renqing Han,[3] Hengmin Ma,[4] Yili Lv,[5] Hongmei Zeng,[6] Rongshou Zheng,[6] Maomao Cao,[1] Fan Yang,[1] Xinxin Yan,[1] Dianqin Sun,[1] Siyi He,[1] Shaoli Zhang,[1] Wanqing Chen,[1] and Jie He[7]

[1]Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College/Chinese Academy of Medical Sciences Key Laboratory for National Cancer Big Data Analysis and Implement, Beijing, China, [2]Department of Cancer Epidemiology, Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Henan Engineering Research Center of Cancer Prevention and Control, Henan International Joint Laboratory of Cancer Prevention, Zhengzhou, China, [3]Department for Chronic Non-communicable Diseases Control, Jiangsu Provincial Center for Disease Control and Prevention (Public Health Research Institute of Jiangsu Province), Nanjing, China, [4]Department of Preventive Management, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [5]Institute of Chronic Non-communicable Diseases Prevention and Control, Anhui Provincial Center for Disease Control and Prevention, Hefei, China, [6]Office of Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, and [7]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

BACKGROUND & AIMS: **Mild and moderate dysplasia are major premalignant lesions of esophageal squamous cell carcinoma (ESCC); however, evidence of the progression risk in patients with these conditions is extremely limited. We aimed to assess the incidence and risk factors for advanced neoplasia in patients with mild–moderate dysplasia.**

METHODS: **This prospective cohort study included patients with mild–moderate dysplasia from 9 regions in rural China. These patients were identified from a community-based ESCC screening program conducted between 2010 and 2016 and were offered endoscopic surveillance until December 2021. We estimated the incidence of advanced esophageal neoplasia, including severe dysplasia, carcinoma in situ, or ESCC, and identified potential risk factors using the Cox regression model.**

RESULTS: **The 1183 patients with mild–moderate dysplasia were followed up over a period of 6.95 years. During follow-up evaluation, 88 patients progressed to advanced neoplasia (7.44%), with an incidence rate of 10.44 per 1000 person-years. The median interval from the progression of mild–moderate dysplasia to advanced neoplasia was 2.39 years (interquartile range, 1.58–4.32 y). A total of 74.47% of patients with mild–moderate dysplasia experienced regression to nondysplasia, and 18.09% showed no lesion progression. Patients with mild–moderate dysplasia who had a family history of esophageal cancer and were age 55 years and older showed 97% higher advanced neoplasia yields than all patients with mild–moderate dysplasia.**

*Authors share co-first authorship.

Abbreviations used in this paper: CICAMS, Chinese Academy of Medical Sciences; EC, esophageal cancer; EDET, early detection and early treatment; ESCC, esophageal squamous cell carcinoma; IQR, interquartile range.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2022.04.039

CONCLUSIONS: **In a country with a high incidence of ESCC, patients with mild–moderate dysplasia showed an overall risk of advanced neoplasia progression of 1.04% per year. Patients with mild–moderate dysplasia would be recommended for endoscopic surveillance during the first 2 to 3 years.**

Keywords: Esophageal Dysplasia; Endoscopic Surveillance; Risk Factors; Progression Rate.

Approximately 84% of esophageal cancer (EC) cases diagnosed worldwide are esophageal squamous cell carcinoma (ESCC), and China has the highest disease burden.[1] ESCC is characterized by a poor prognosis, with a 5-year age-standardized net survival of 10% to 30% in most countries.[2] Prospective cohort studies of endoscopic screening for ESCC have reported significant reductions in ESCC incidence and mortality.[3] The decrease in incidence is owing primarily to the treatment of curable precursors and the detection of EC cases at an early stage. Thus, patients with advanced neoplasia, including those with severe dysplasia, carcinoma in situ, or ESCC, are recommended for immediate clinical treatment.[4]

The development of ESCC has been presumed to be a multistage process that progresses from the conversion of the normal squamous epithelium to basal cell hyperplasia, intraepithelial neoplasia, and, finally, invasive carcinoma.[5] A prospective study with a 13-year follow-up period including 682 participants from high-risk areas of ESCC in China found that compared with those with pathologically diagnosed normal tissues, those with mild dysplasia or moderate dysplasia had a high risk of developing ESCC, with relative ratios of 2.9 (95% CI, 1.6–5.2) and 9.8 (95% CI, 5.3–18.3), respectively.[6] Based mainly on this evidence, the current expert consensus for ESCC screening and surveillance in China recommends that patients with mild-to-moderate dysplasia undergo surveillance endoscopy to prevent ESCC.[4]

Determining the risk of progressing to advanced neoplasia or ESCC alone in patients with mild or moderate dysplasia is essential for developing ESCC surveillance guidelines, but the related evidence is extremely limited. To the best of our knowledge, only 4 cohort studies have reported a risk of advanced neoplasia or ESCC alone in these patients.[6–9] These studies were limited to high-risk areas of China, and most of them were single-center studies with sample sizes of fewer than 300 (summarized in Supplementary Table 1). In addition, the existing available evidence has shown a low advanced neoplasia yield in all patients with premalignant lesions.[6–9] Therefore, identifying potential risk factors influencing the progression to advanced neoplasia in patients with mild–moderate dysplasia appears to be important for improving yields of advanced neoplasia.

To fill these knowledge gaps, this multicenter prospective cohort study estimated the risk of progression to advanced neoplasia during a 6.95-year surveillance endoscopy period among patients with mild or moderate dysplasia in the Chinese population. We further aimed to assess the potential risk factors for developing advanced neoplasia in patients with mild–moderate dysplasia. These findings may provide high-grade evidence for the development of ESCC surveillance guidelines regarding the management of patients with premalignant esophageal lesions.

Methods

Study Design and Participants

This community-based multicenter, prospective cohort study was conducted based on an ongoing ESCC screening and Early Detection and Early Treatment (EDET) program in China. This program has been conducted in 4 provinces of China (Jiangsu Province, Anhui Province, Shandong Province, and Henan Province) since 2007, and the study design has been described in detail previously.[10] In this screening program, endoscopic surveillance has been provided since 2012 (see the *Surveillance Procedures and Outcomes* section). The research protocol was approved independently by the Institutional Review Board of the Cancer Institute/Hospital, Chinese Academy of Medical Sciences (CICAMS) (NCC1788).

Considering the year in which surveillance endoscopy started, the inclusion criteria in the present study were as follows: (1) participants who had a baseline endoscopy with a pathologic diagnosis of mild dysplasia or moderate dysplasia from January 2010 to December 2016; and (2) participants who underwent at least 1 surveillance endoscopy up to December 2021. The exclusion criteria were as follows: (1) participants diagnosed with any cancer before enrollment; (2) participants who were not in the age range of 40 to 69 years at baseline; (3) participants who were diagnosed with ESCC before the first surveillance endoscopy; (4) participants without complete baseline information; and (5) patients with advanced neoplasia diagnosed within 12 months from baseline endoscopy. These participants resided in 9 rural regions across 4 provinces of China, including 3 regions (Hongze County, Jinhu County, and Yandu District) in Jiangsu Province, 3 regions (Wenshang County, Tengzhou District, and Mudan District) in Shandong Province, 2 regions (Xiangfu District and Yuzhou City) in Henan Province, and 1 region (Panji County) in Anhui Province.

Baseline Procedures and Data Collection

In the included study centers, women and men aged 40 to 69 years without a history of cancer were approached through personal contact and telephone invitation by trained local medical staff. After explaining the study and obtaining written informed consent, all eligible participants were administered a baseline questionnaire by trained staff, which included age, sex, socioeconomic status, cigarette smoking, alcohol consumption, and family history of cancer (if yes, the cancer type). In addition, anthropometric measurements, such as height and weight, were obtained for each individual, and body mass index was calculated.

High-risk individuals identified by an initial assessment strategy were recommended to undergo a standard upper gastrointestinal endoscopic examination and biopsy with iodine staining. Detailed descriptions for each evaluated variable and estimations of the effectiveness of the initial assessment strategy have been reported previously.[10] The protocol for the endoscopic examination and pathologic diagnosis in this ESCC screening and EDET program was formulated based on the official endoscopy protocol of EDET.[11] The endoscopists and pathologists participating at each study center were well trained by experts from CICAMS to use the protocol. The participants were first administered a local anesthetic orally (5 mL of a 1%–2% slurry of lidocaine) before the procedure. The entire esophagus and stomach were examined visually; the esophagus was sprayed with 10 to 15 mL of 1.2% Lugol's iodine solution.[12,13] Suspicious lesions were removed for a biopsy, and the number of biopsy specimens taken depended on the size of the lesion. Biopsy specimens were fixed with 10% to 13% formaldehyde, embedded in paraffin, and stained with H&E. Two experienced pathologists independently reviewed the biopsy slides, and diagnostic discrepancies were adjudicated by consultation. The agreement of precancerous esophageal lesions identified by the 2 pathologists in each study center ranged from 85% to 90% after training. In addition, an expert team including pathologists from CICAMS performed routine quality control, and if a disagreement occurred, those sections were reviewed again to achieve consensus. Histologic criteria were based on the official protocol of EDET in China.[11]

Surveillance Procedures and Outcomes

In this ESCC screening and EDET program, endoscopic surveillance has been provided since 2012, and patients diagnosed with mild dysplasia and moderate dysplasia are recommended for triennial and annual surveillance endoscopy, respectively. The surveillance intervals were determined according to the official endoscopy protocol of EDET in China.[11] During endoscopic surveillance, we still provided endoscopic surveillance for patients with mild dysplasia or moderate dysplasia who did not follow recommended surveillance intervals to prevent EC incidence as much as possible. The procedures and protocols for the endoscopic examination and biopsy during surveillance endoscopy were the same as those used at baseline. In addition, endoscopists were informed of the position of any lesions identified at baseline to ensure a careful review of the endoscopy images. All participants in this study underwent at least 1 surveillance endoscopy from January 2012 to December 2021.

All study participants also were followed up via door-to-door visits by village doctors and by linking with local cancer registry data until the date of death or December 31, 2021, whichever occurred first. The primary outcome of this study was incident esophageal advanced neoplasia, including cases of severe dysplasia, carcinoma in situ, or ESCC, and the secondary outcome was the incidence of ESCC alone.

Statistical Analysis

Continuous variables are presented as the means ± SD or median with interquartile range (IQR), and categoric variables are reported as counts and percentages. The progression rates of advanced neoplasia and ESCC alone identified within the study period were calculated as the number of patients who had progressed to advanced neoplasia and ESCC alone divided by all study participants. Person-years of follow-up evaluation were calculated from the date of enrollment to the date of

What You Need to Know

Background

Determining the risk of advanced neoplasia progression in patients with mild–moderate dysplasia is essential for developing esophageal squamous cell carcinoma surveillance guidelines, but the related evidence is extremely limited.

Findings

In an analysis of surveillance endoscopy data from a multicenter community-based prospective cohort in China, only 7.44% of patients with mild–moderate dysplasia progressed to advanced neoplasia during a median follow-up period of 6.95 years, with an incidence rate of 10.44 per 1000 person-years. The median time to develop advanced neoplasia was 2.39 years after detection of mild–moderate dysplasia.

Implications for patient care

These findings have implications for managing patients with premalignant esophageal lesions and will provide supportive evidence for the establishment of screening and surveillance guidelines for esophageal squamous cell carcinoma.

diagnosis of advanced neoplasia or the date of December 31, 2021, whichever occurred first. Cumulative incidences of advanced neoplasia and ESCC alone were calculated as the number of cases divided by the person-years of follow-up evaluation. In addition, we performed Kaplan–Meier analyses to calculate the cumulative incidence of advanced neoplasia with 95% CIs at 3 and 5 years, respectively. We compared the cumulative incidences of advanced neoplasia in patients with different factors of dysplasia, sex, age, family history of EC, cigarette smoking, and alcohol consumption using the Kaplan–Meier method with the log-rank test. Cox proportional hazards models were used to identify independent risk factors for developing advanced neoplasia by calculating the hazard ratios and 95% CIs. In the sensitivity analyses, we additionally included cases of advanced neoplasia diagnosed within 12 months and calculated the main index to avoid this exclusion criterion impacting the main results of this study.

Analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Participant Characteristics

A total of 2835 individuals were diagnosed with mild–moderate dysplasia at the baseline endoscopic screening between 2010 and 2016. After reviewing the inclusion and exclusion criteria, 1183 individuals were included in the final analysis (Supplementary Figure 1). Major baseline characteristics were similar between patients who were included and those who were excluded (Supplementary Table 2). In 1652 excluded patients, 95 developed incident ESCC (7.43 per 1000 person-years) and 19 died of ESCC (1.43 per 1000 person-years), which was higher than the included patients (Supplementary Table 3).

The main baseline characteristics of the included study population are summarized in Table 1. The median age of the participants was 60 years (IQR, 55–64 y), and 646 (54.61%) were men. Among all included participants, 976 (82.50%) were diagnosed with mild dysplasia, and the other 207 (17.50%) were diagnosed with moderate dysplasia at the baseline endoscopy screening. No significant differences in the distribution of sex, age, education status, family history of EC, cigarette smoking, alcohol consumption, or body mass index were observed between patients with mild dysplasia and those with moderate dysplasia (Table 1).

Follow-Up Evaluation and Endoscopic Surveillance

Table 2 summarizes the main follow-up information among the whole cohort. The median follow-up time was 6.95 years (IQR, 5.79–8.30 y), with a maximum of

Table 1. Baseline Characteristics of the 1183 Participants Included in This Study

Characteristics	Total (n = 1183), n (%)	Mild dysplasia (n = 976), n (%)	Moderate dysplasia (n = 207), n (%)	*P* value
Sex				.359
Male	646 (54.61)	527 (54.00)	119 (57.49)	
Female	537 (45.39)	449 (46.00)	88 (42.51)	
Age, *y*				.957
Means ± SD	58.84 (6.58)	58.78 (6.58)	59.10 (6.59)	
Median (IQR)	60 (55–64)	60 (55–64)	60 (56–64)	
Education				.385
Primary school and below	775 (65.51)	634 (64.96)	141 (68.12)	
Middle school and above	408 (34.49)	342 (35.04)	66 (31.88)	
Family history of EC				.590
No	991 (83.77)	815 (83.50)	176 (85.02)	
Yes	192 (16.23)	161 (16.50)	31 (14.98)	
Cigarette smoking				.891
No	765 (64.67)	632 (64.75)	133 (64.25)	
Yes	418 (35.33)	344 (35.25)	74 (35.75)	
Alcohol consumption				.943
No	814 (68.81)	672 (68.85)	142 (68.60)	
Yes	369 (31.19)	304 (31.15)	65 (31.40)	
Body mass index, kg/m^2				.463
Means ± SD	24.16 (2.69)	24.19 (2.67)	24.01 (2.78)	

EC, esophageal cancer; IQR, interquartile range; SD, standard deviation.

Table 2. Follow-Up Evaluation and Outcomes of Advanced Neoplasia and Esophageal Squamous Cell Carcinoma Alone in the 1183 Participants With Mild–Moderate Dysplasia

Variables	Total (n = 1183)	Mild dysplasia (n = 976)	Moderate dysplasia (n = 207)
Follow-up time			
Median (IQR), *y*	6.95 (5.79–8.30)	6.94 (5.84–8.13)	7.21 (5.35–9.10)
Person-years	8427.08	6992.40	1434.68
Intervals to the first endoscopy screening, median (IQR), *y*	2.86 (1.62–3.62)	3.03 (1.88–3.67)	1.86 (1.27–2.87)
Cases, n			
Advanced neoplasia	88	48	40
ESCC	34	17	17
Progression rate, %			
Advanced neoplasia	7.44	4.92	19.32
ESCC	2.87	1.74	8.21
Incidence rate per 1000 person-years			
Advanced neoplasia	10.44	6.86	27.88
ESCC	4.03	2.43	11.85
Time to diagnosis of cases, median (IQR), *y*			
Advanced neoplasia	2.39 (1.58–4.32)	2.60 (1.58–4.41)	2.39 (1.59–3.88)
ESCC	4.44 (1.79–5.82)	4.84 (3.05–6.30)	3.48 (1.69–5.42)

ESCC, esophageal squamous cell carcinoma; IQR, interquartile range.

11.72 years, contributing a total of 8427.08 person-years. The median interval between baseline and first surveillance endoscopy was 2.86 years (IQR, 1.62–3.62 y). According to the program protocol of surveillance endoscopy, the surveillance intensity differed for patients with baseline dysplasia, and the median interval between the baseline endoscopy and first surveillance for patients with moderate dysplasia (1.86 y; IQR, 1.27–2.87 y) was shorter than that for patients with mild dysplasia (3.03 y; IQR, 1.88–3.67 y).

Progression and Regression of Dysplastic Lesions

Figure 1 shows the progression and regression of patients with mild–moderate dysplasia. During follow-up evaluation, 88 patients with mild–moderate dysplasia progressed to advanced neoplasia (7.44%) with an incidence rate of 10.44 per 1000 person-years, including 34 incident ESCC cases (2.87%) with an incidence rate of 4.03 per 1000 person-years (Figure 1, Table 2). Among the patients with advanced neoplasia diagnosed by surveillance endoscopy, 92.31% were at curable stages, including lesions with severe dysplasia, carcinoma in situ, intramucosal carcinoma, and submucosal carcinoma. During the follow-up period, 6 died of ESCC, with a mortality rate of 0.67 per 1000 person-years. Patients with moderate dysplasia showed a higher rate of progression to advanced neoplasia than those with mild dysplasia (19.32% vs 4.92%; $P < .0001$) (Figure 1). In addition, 214 patients with mild–moderate dysplasia (18.09%) diagnosed at baseline showed no lesion progression, and 881 patients (74.47%) showed regression to nondysplasia (Figure 1).

In all included patients with mild–moderate dysplasia, the median interval from the baseline diagnosis to the development of the first event of advanced neoplasia was 2.39 years (IQR, 1.58–4.32 y), with a median interval of developing ESCC alone of 4.44 years (IQR, 1.79–5.82 y). In addition, patients with moderate dysplasia had a slightly shorter time to progression to advanced neoplasia (median interval, 2.39 vs 2.60 y) and ESCC alone (median interval, 3.48 vs 4.84 y) than those with mild dysplasia (Table 2). The median intervals of developing advanced neoplasia were shorter in those aged 55 years or older and in those with a family history of EC (Supplementary Table 4). Supplementary Table 5 presents further analyses of the participants who underwent 2 surveillance endoscopies and had a pathologic diagnosis of nondysplasia or mild–moderate dysplasia at the first surveillance endoscopy (n = 231). More patients progressed to advanced neoplasia among those with mild–moderate disease than among those without dysplasia (3.74% vs 0.81%; $P < .0001$), over a median surveillance endoscopy interval of 2.02 years (IQR, 1.23–3.02 y). The sensitivity analyses found that slightly higher incidence rates in advanced neoplasia and ESCC were observed, with slightly shorter intervals to advanced neoplasia, after including cases of advanced neoplasia diagnosed within 12 months (Supplementary Table 6). However, this variation did not affect the main results and conclusion.

The cumulative incidences for advanced neoplasia or ESCC alone gradually increased from 1 to 5 years

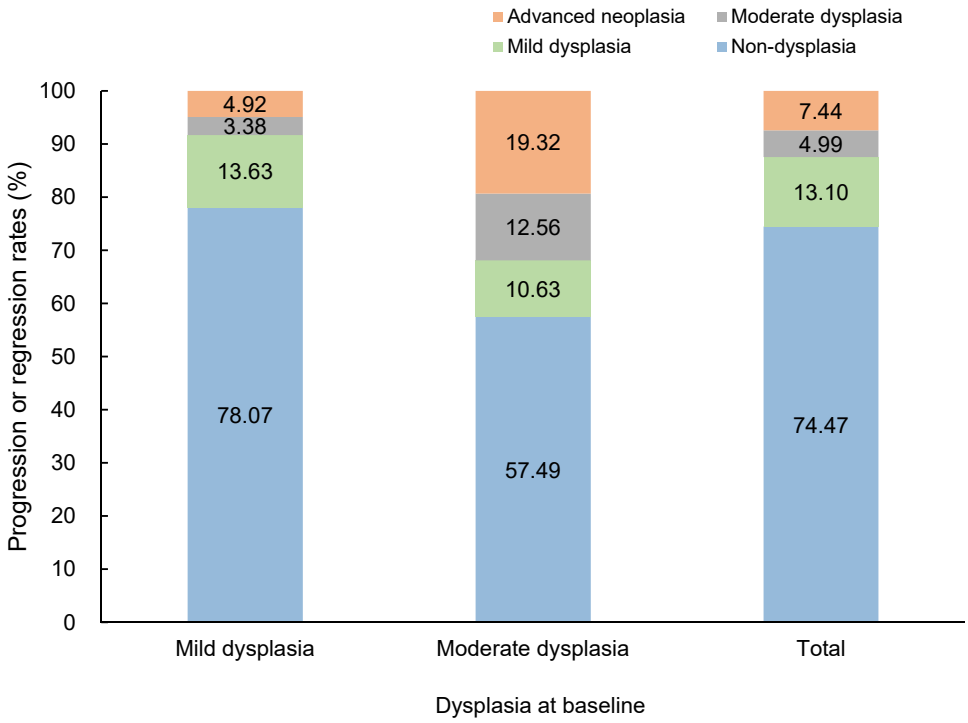


Figure 1. Regression and progression of 1183 patients with mild–moderate esophageal dysplasia over a median follow-up time of 6.95 years.

and then increased slowly. For all patients with mild–moderate dysplasia, the cumulative incidence of advanced neoplasia or ESCC alone at 5 years was 6.02% (95% CI, 4.66%–7.37%) (Figure 2*A*) and 1.74% (95% CI, 0.99%–2.50%) (Figure 2*B*), respectively. In addition, the time-specific cumulative incidences of advanced neoplasia or ESCC alone for patients with mild dysplasia and moderate dysplasia are shown in Supplementary Figures 2 and 3, respectively.

Progression to Advanced Neoplasia According to the Risk Profile

The univariate and multivariable analyses of developing advanced neoplasia are shown in Supplementary Figure 4 and Table 3, respectively. Patients with moderate dysplasia, those with a family history of EC, and those aged 55 years or older were associated independently with progression risk. All patients with mild–moderate dysplasia were subdivided further into 4 groups based on a family history of EC and age at enrollment (Table 4). The progression rate of advanced neoplasia during the follow-up period varied substantially for different combinations of risk factors (log-rank test, $P = .0002$) (Supplementary Figure 5). For patients with a family history of EC (profile group 3 or 4), the progression rate of advanced neoplasia was 12.24% (95% CI, 4.63%–24.77%) in those younger than age 55 years and 14.69% (95% CI, 9.33%–21.57%) in those aged 55 years or older. The advanced neoplasia yield in these 2 subgroups reached 1.65 and 1.97 times that of the overall study population (7.44%; 95% CI, 6.01%–9.08%).

Discussion

In this community-based, multicenter, prospective, cohort study conducted in the Chinese population, we found that most patients with mild or moderate dysplasia stabilized or regressed to nondysplasia, with only 7.44% developing advanced neoplasia over a median follow-up time of 6.95 years. Patients with moderate dysplasia had a higher risk and shorter time interval for developing advanced neoplasia than those with mild dysplasia. In addition, risk stratification based on a family history of EC and age might help improve the advanced neoplasia yield.

The finding that most patients with mild–moderate dysplasia did not progress to advanced neoplasia in this study is consistent with observations from 4 previously published prospective cohort studies.[6–9] Our data showed an average risk of advanced neoplasia progression of 1.04% per year in patients with mild–moderate dysplasia. This progression risk was lower than that in the other 2 single-center surveillance endoscopy cohort studies, which showed an average annual risk of advanced neoplasia progression of 4.00% in participants from Shexian (n = 91)[7] and 2.22% in participants from Huaxian (n = 246).[8] Similarly, the risk of progression to ESCC alone in our study, with an average annual incidence rate of 0.40%, also was lower than that reported in another surveillance endoscopy cohort (2.39% per year) in Linxian.[6] These 3 cohort studies all were conducted in areas of China with extremely high ESCC incidence and mortality rates, which might have contributed to the increased risk of progression to advanced neoplasia or ESCC alone compared with our study. In contrast, the

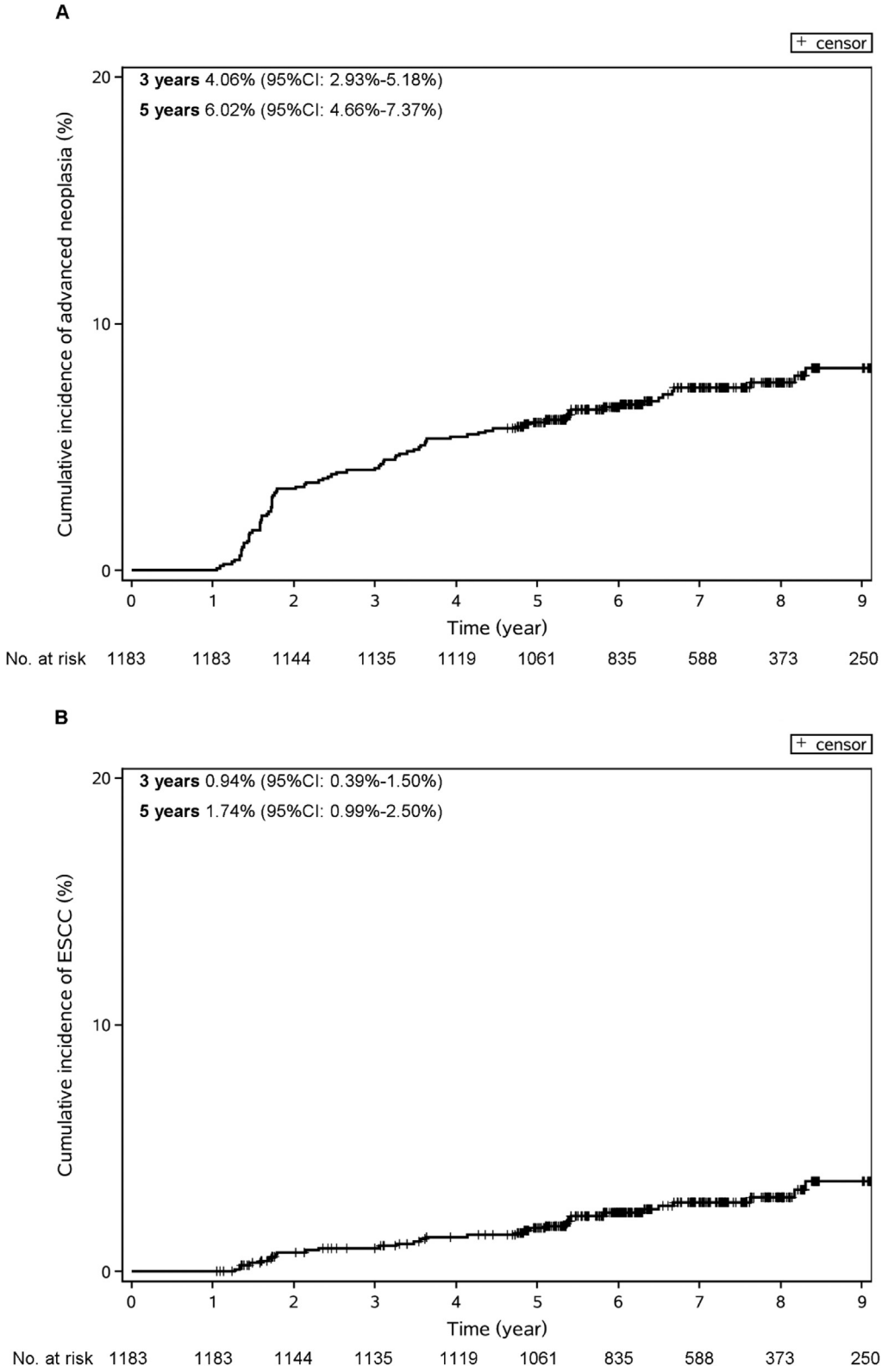


Figure 2. Cumulative incidence of developing advanced neoplasia or esophageal squamous cell carcinoma (ESCC) alone in patients with mild–moderate esophageal dysplasia. (*A*) Cumulative incidence of advanced neoplasia. (*B*) Cumulative incidence of ESCC alone.

risk of progression to ESCC in our study was higher than that reported in another prospective cohort study (0.23% per year) conducted on 2977 patients with mild–moderate dysplasia from 3 high-risk ESCC areas in China.[9] The difference in follow-up measures might mainly explain this discrepancy. In the study conducted by Wei et al,[9] patients with ESCC mainly were identified by nonendoscopic surveillance, such as in cancer

Table 3. Adjusted Risk of Progression to Advanced Neoplasia Over a Median Follow-Up Period of 6.95 Years

Variables	Participants, n	Advanced neoplasia, n	Multivariable HR[a] (95% CI)	*P*	Multivariable HR[b] (95% CI)	*P*
Pathologic diagnosis				<.0001		<.0001
Mild dysplasia	976	48	Ref		Ref	
Moderate dysplasia	207	40	4.13 (2.71–6.29)		3.98 (2.61–6.08)	
Family history of EC				.0003		.0005
No	991	61	Ref		Ref	
Yes	192	27	2.34 (1.48–3.68)		2.25 (1.42–3.55)	
Age, *y*				.0176		.0311
<55	285	11	Ref		Ref	
≥55	898	77	2.15 (1.14–4.05)		2.04 (1.07–3.91)	

CI, confidence interval; EC, esophageal cancer; HR, hazard ratio.
[a]HRs were driven from the Cox regression model, adjusted by pathologic diagnosis (mild dysplasia; moderate dysplasia), family history of EC (no; yes), and age (<55 y; ≥55 y).
[b]HRs were driven from the Cox regression model, adjusted by pathologic diagnosis (mild dysplasia; moderate dysplasia), family history of EC (no; yes), age (<55 y; ≥55 y), gender (male; female), cigarette smoking (no; yes), alcohol consumption (no; yes), education status (primary school and below; middle school and above), and visits for surveillance endoscopy (continuous).

registries or by home visits. In our study, patients with mild–moderate dysplasia underwent at least 1 surveillance endoscopy, which would help detect more cases during the same period.

The current expert consensus in China recommends repeat surveillance endoscopy within 3 years for patients with mild–moderate dysplasia.[4] Our findings showed that the median interval of progression from mild–moderate dysplasia to advanced neoplasia and ESCC alone was 2.39 years (IQR, 1.58–4.32 y) and 4.44 years (IQR, 1.79–5.82 y), respectively. In addition, compared with patients who regressed to nondysplasia at the first surveillance endoscopy, patients with persistent mild–moderate dysplasia had a higher progression risk to advanced neoplasia, with a median interval of 2.02 years. These findings support the recommendation of surveillance endoscopy for patients with persistent mild–moderate dysplasia during the first 2 to 3 years, whereas longer surveillance intervals might be considered for those showing regression to nondysplasia during surveillance. A previous study suggested prolonging the endoscopic surveillance intervals for patients with moderate dysplasia and mild dysplasia to 3 and 5 years, respectively.[9] This difference in the surveillance interval can be explained by the differences in pathologic end points; that is, the surveillance end point in the earlier-described study was ESCC, whereas the surveillance end point in our study was advanced neoplasia. In the future, more high-quality evidence is required to help health care providers decide the appropriate interval for surveillance endoscopy.

Our findings showed that approximately 2 times the advanced neoplasia yield was obtained in the subgroup of patients aged 55 years or older and with a family history of EC compared with all study patients. In addition, in these subgroups a shorter median time of progression to advanced neoplasia was observed. These findings indicated that patients with mild–moderate dysplasia aged 55 years or older and those with a family history of EC should be prioritized for endoscopic

Table 4. Estimated Progression Rates of Advanced Neoplasia Based on 2 Main Risk Factors (Family History of Esophageal Cancer and Age) in the 1183 Participants With Mild–Moderate Dysplasia

	Risk factors			Outcome index	
Profile group	Age, *y*	Family history of EC	Participants	Advanced neoplasia	Progression rate, % (95% CI)
1	<55	No	236	5	2.12 (0.69–4.87)
2	≥55	No	755	56	7.42 (5.65–9.52)
3	<55	Yes	49	6	12.24 (4.63–24.77)
4	≥55	Yes	143	21	14.69 (9.33–21.57)
5	40–69	No or yes	1183	88	7.44 (6.01–9.08)

CI, confidence interval; EC, esophageal cancer.

surveillance. Since the World Health Organization revised its classification, mild dysplasia and moderate dysplasia now are classified as low-grade intraepithelial neoplasia,[14] and recommendations for surveillance endoscopy in China tend to focus on low-grade intraepithelial neoplasia.[4,15] However, our data showed that patients with moderate dysplasia had a higher risk of developing advanced neoplasia and tended to progress within a short period compared with those with mild dysplasia. These findings suggested that health care providers must fully consider these differences in patients with mild dysplasia and moderate dysplasia when creating guidelines for ESCC surveillance.

Some strengths and limitations should be mentioned when interpreting the results of this study. The primary strength of this study is that it was a large, community-based, multicenter, prospective cohort study on surveillance endoscopy among patients with mild or moderate esophageal dysplasia. Some findings in our study provide supporting evidence for establishing guidelines for ESCC surveillance in China and other countries with an increased incidence of ESCC. However, our study also had several limitations. First, selection bias may have existed, although similar baseline characteristics were observed between the included and excluded patients with mild–moderate dysplasia. Second, although this study analyzed a large and representative population, the individuals all resided in rural China; thus, the progression risk to advanced neoplasia in other populations remains unknown. A corresponding estimation will be conducted using a large-scale, population-based, prospective cohort study for upper gastrointestinal cancer screening when data are available in the future.[16] Third, some information on the potential risk factors for advanced neoplasia in the endoscopic images was not sufficiently detailed, such as the size of Lugol-unstained lesions, and, thus, the confounders were unable to be assessed more precisely. In our ongoing ESCC screening and surveillance program, sufficient information on endoscopic images has been collected since 2019. Therefore, a more comprehensive analysis integrating endoscopic images could be conducted in the future. Finally, in terms of surveillance intervals, this study considered only the median interval time and cumulative incidence of progression to advanced neoplasia during a median follow-up period of 6.95 years. In the future, modeling studies also are needed to explore optimal surveillance intervals, and randomized controlled trials will be required to provide robust evidence for this field.

In conclusion, in a country with a high incidence of ESCC, patients with mild–moderate dysplasia showed an overall risk of advanced neoplasia progression of 1.04% per year. Our findings indicated that patients with mild–moderate dysplasia should be recommended for endoscopic surveillance during the first 2 to 3 years, especially older patients or those with a family history of EC. In the future, more studies, including modeling studies, high-quality cohort studies, and randomized controlled trials, are needed to determine the optimal surveillance intervals for patients with premalignant esophageal lesions.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.04.039.

References

1. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut 2020;69:1564–1571.
2. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391:1023–1075.
3. Chen R, Liu Y, Song G, et al. Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. Gut 2021;70:251–260.
4. National Digestive Endoscopy Improvement System, National Clinical Research Center for Digestive Disease. National Early Gastrointestinal-Cancer Prevention & Treatment Center Alliance, et al. Experts' consensus on the endoscopic screening of early esophageal cancer and precancerous lesions in China (2019 Xinxiang). Chin J Gastroenterol 2019;36:793–801.
5. Lin DC, Wang MR, Koeffler HP. Genomic and epigenomic aberrations in esophageal squamous cell carcinoma and implications for patients. Gastroenterology 2018;154:374–389.
6. Wang GQ, Abnet CC, Shen Q, et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. Gut 2005;54:187–192.
7. Wen D, Zhang L, Wang X, et al. A 5.5-year surveillance of esophageal and gastric cardia precursors after a population-based screening in China. J Gastroenterol Hepatol 2015;30:1720–1725.
8. Liu M, Zhou R, Guo C, et al. Size of Lugol-unstained lesions as a predictor for risk of progression in premalignant lesions of the esophagus. Gastrointest Endosc 2021;93:1065–1073.e3.
9. Wei WQ, Hao CQ, Guan CT, et al. Esophageal histological precursor lesions and subsequent 8.5-year cancer risk in a population-based prospective study in China. Am J Gastroenterol 2020;115:1036–1044.
10. Chen W, Li H, Zheng R, et al. An initial screening strategy based on epidemiological information in esophageal cancer screening: a prospective evaluation in a community-based cancer screening cohort in rural China. Gastrointest Endosc 2021;93:110–118.e2.
11. Cancer Early Detection and Treatment Expert Group, Bureau of Disease Control, Ministry of Health. Technology scheme for cancer early detection and treatment. Beijing: People's Medical Publishing House, 2011.
12. Dawsey SM, Fleischer DE, Wang GQ, et al. Mucosal iodine staining improves endoscopic visualization of squamous

dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. Cancer 1998;83:220–231.
13. Muto M, Minashi K, Yano T, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010;28:1566–1572.
14. Stanley R, Hamilton LAA. Pathology and genetics of tumours of the digestive system. Lyon: International Agency for Research on Cancer (IARC), 2000.
15. National Health Commission of the People's Republic of China, Cancer Foundation of China. Cancer Early Detection and Treatment (rural China) Expert Group. Technology scheme of screening and early detection and treatment for upper gastrointestinal cancer (trial version in 2020). Beijing: People's Medical Publishing House, 2020.
16. Zeng H, Sun K, Cao M, et al. Initial results from a multi-center population-based cluster randomized trial of esophageal and gastric cancer screening in China. BMC Gastroenterol 2020; 20:398.

Correspondence
Address correspondence to: Wanqing Chen, PhD, Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 17 Pan-jia-yuan South Lane, Chaoyang District, Beijing 100021, China. e-mail: chenwq@cicams.ac.cn; fax: (86) 10-67718227.

Acknowledgments
The authors gratefully acknowledge all participants in their program and all staff who have made a great contribution to the data collection, auditing, database management, and verification. The authors thank all the individuals who contributed to this study for their important and much-appreciated contributions to the preparation of this report.

CRediT Authorship Contributions

He Li, MPH (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Methodology: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

Shaokai Zhang, PhD (Data curation: Equal; Investigation: Equal; Supervision: Equal; Writing – review & editing: Equal)

Jinyi Zhou, MPH (Data curation: Equal; Investigation: Equal; Supervision: Equal; Writing – review & editing: Equal)

Feng Tong, MPH (Data curation: Equal; Investigation: Equal; Supervision: Equal; Writing – review & editing: Equal)

Jiyong Gong, MPH (Data curation: Equal; Investigation: Equal; Supervision: Equal; Writing – review & editing: Equal)

Zhenqiu Zha, PhD (Data curation: Equal; Investigation: Equal; Supervision: Equal; Writing – review & editing: Equal)

Ni Li, PhD (Project administration: Supporting; Writing – review & editing: Supporting)

Changfa Xia, PhD (Project administration: Supporting; Writing – review & editing: Supporting)

Jiang Li, PhD (Project administration: Supporting; Writing – review & editing: Supporting)

Liyang Zheng, PhD (Investigation: Supporting; Supervision: Supporting; Writing – review & editing: Supporting)

Pengfei Luo, MPH (Investigation: Supporting; Supervision: Supporting)

Renqiang Han, MPH (Supervision: Supporting)

Hengmin Ma, MPH (Investigation: Supporting; Supervision: Supporting; Writing – review & editing: Supporting)

Yili Lv, MPH (Supervision: Supporting)

Hongmei Zeng, PhD (Project administration: Supporting; Writing – review & editing: Supporting)

Rongshou Zheng, MPH (Project administration: Supporting; Writing – review & editing: Supporting)

Maomao Cao, MPH (Project administration: Equal; Supervision: Equal; Writing – review & editing: Supporting)

Fan Yang, MPH (Writing – review & editing: Supporting)

Xinxin Yan, BCH (Writing – review & editing: Supporting)

Dianqin Sun, BCH (Writing – review & editing: Supporting)

Siyi He, BCH (Writing – review & editing: Supporting)

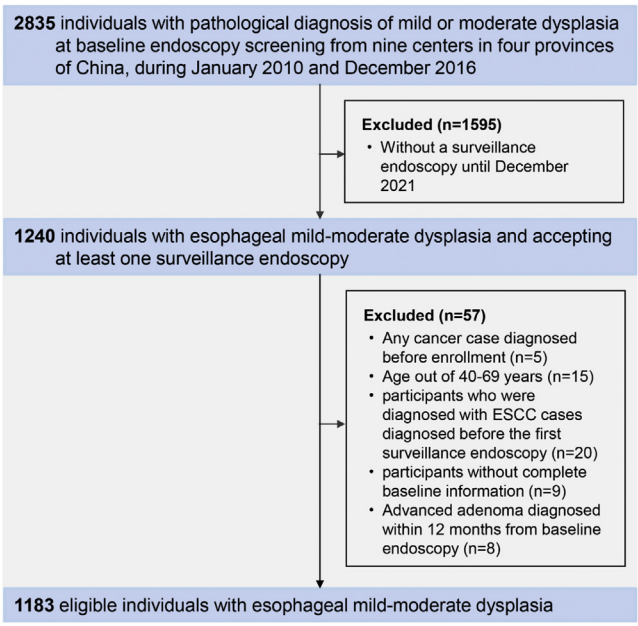
Shaoli Zhang, BCH (Writing – review & editing: Supporting)

Wanqing Chen, PhD (Conceptualization: Lead; Funding acquisition: Lead; Resources: Lead; Writing – review & editing: Lead)

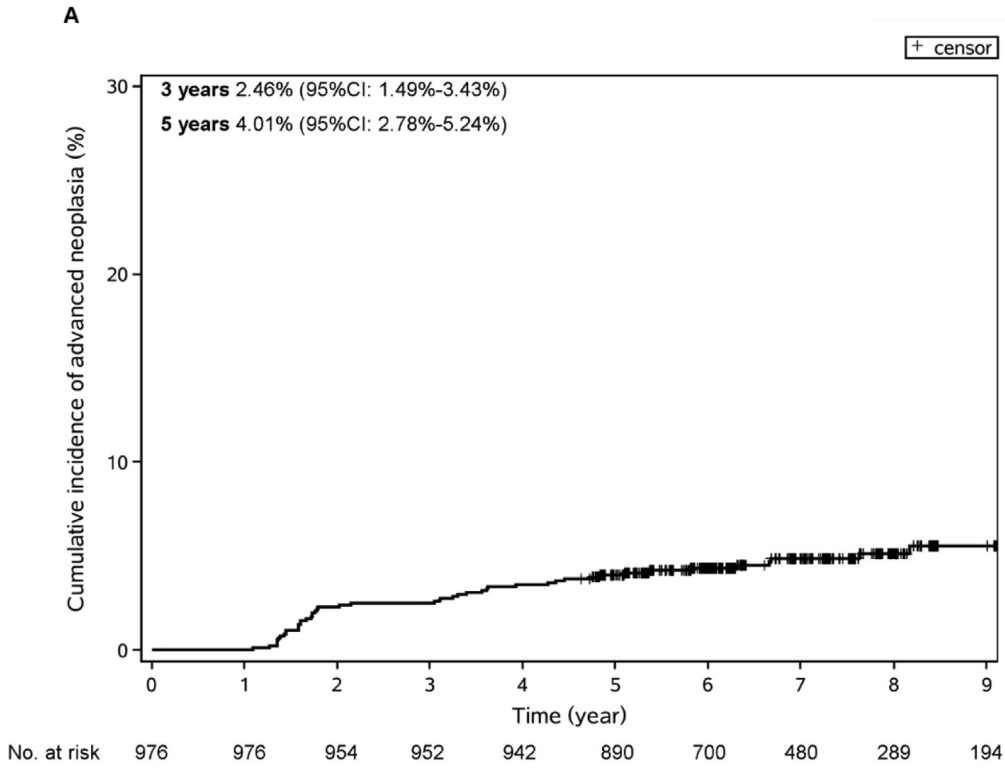
Jie He, PhD (Resources: Lead)

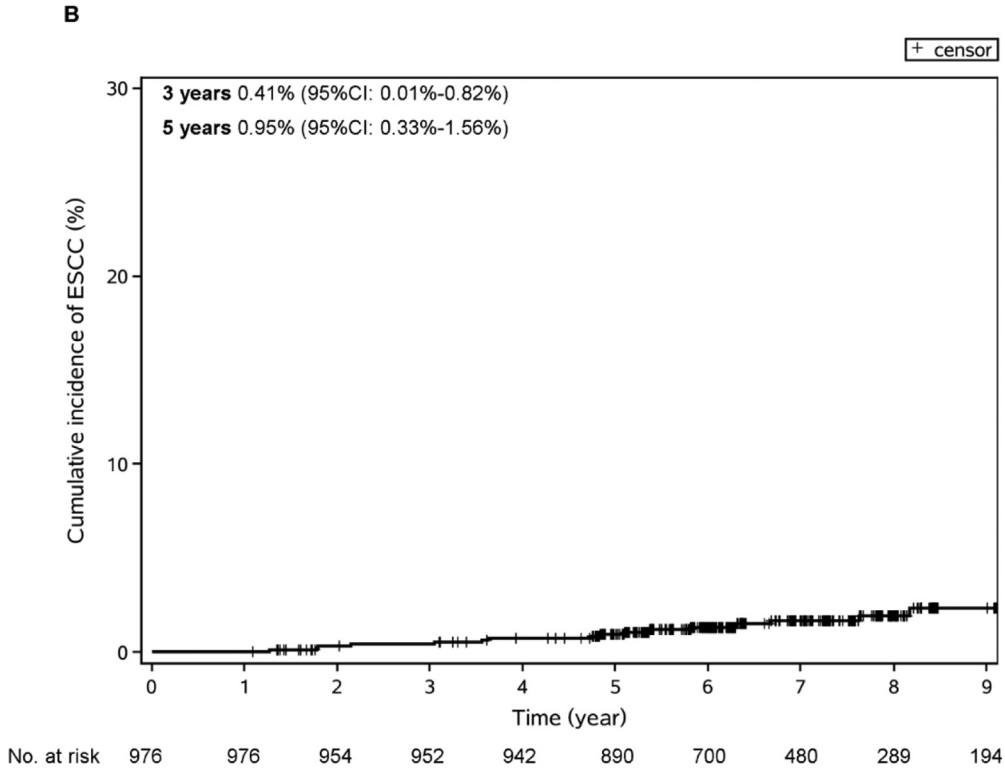
Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by the National Key R&D Program of China (2018YFC1313100), Sanming Project of Medicine in Shenzhen (SZSM201911015), the Cooperation Project in Beijing, Tianjin, and Hebei of China (J200017), and the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences (2019PT320027). The funding source of the study had no role in the study design, data collection, analysis, interpretation, or writing of the report.

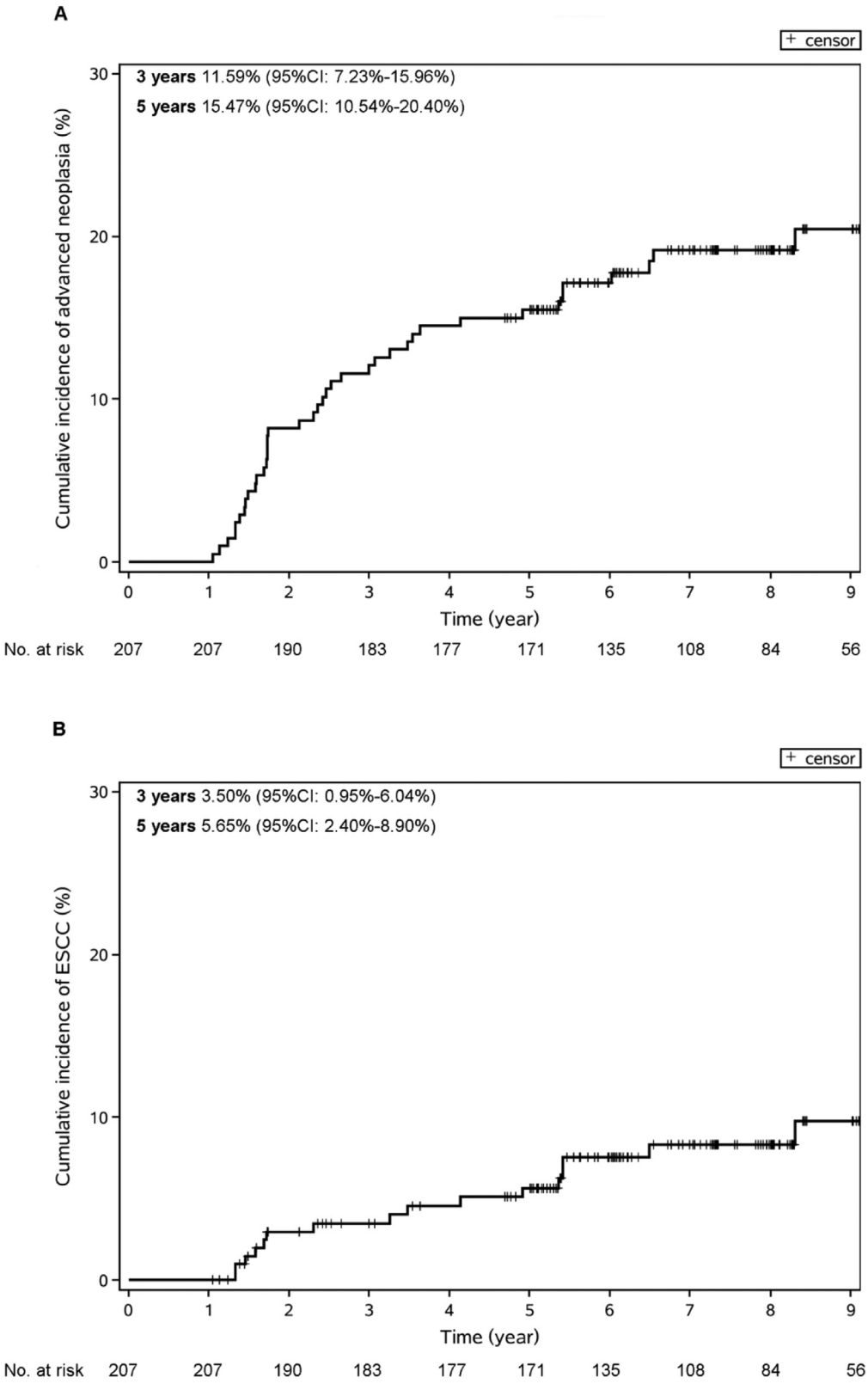


Supplementary Figure 1. Flow diagram of the study participants. ESCC, esophageal squamous cell carcinoma.

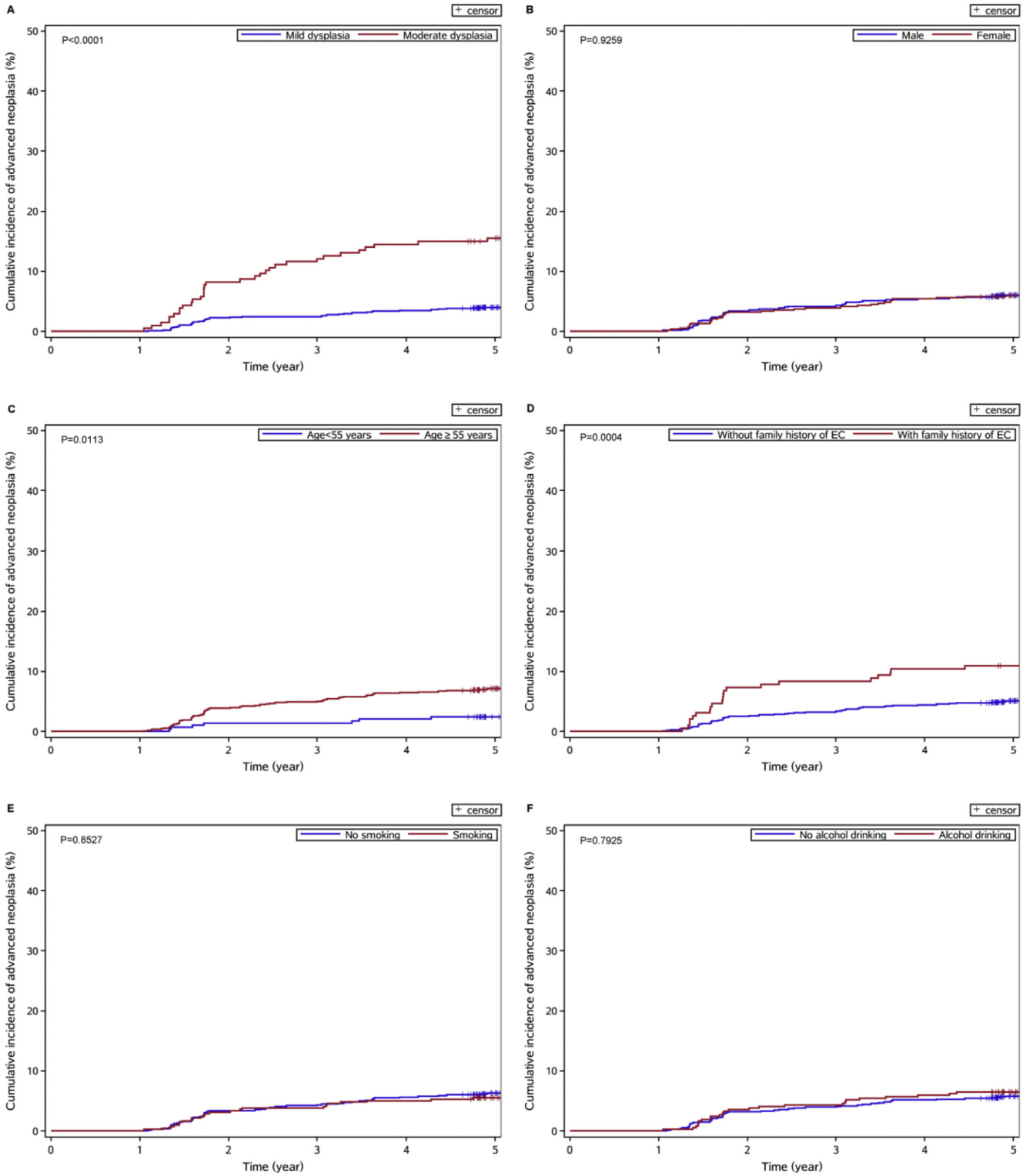




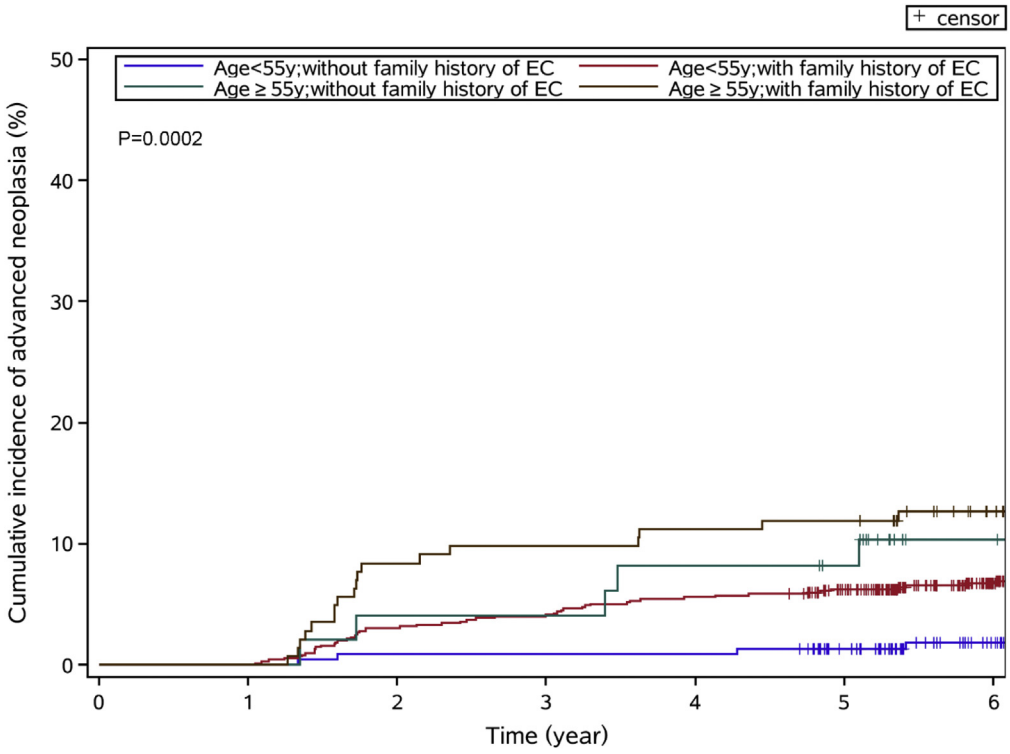
Supplementary Figure 2. Cumulative incidence of developing advanced neoplasia or esophageal squamous cell carcinoma (ESCC) alone in patients with mild esophageal dysplasia. (*A*) Cumulative incidence of advanced neoplasia. (*B*) Cumulative incidence of ESCC alone.



Supplementary Figure 3. Cumulative incidence of developing advanced neoplasia or esophageal squamous cell carcinoma (ESCC) alone in patients with moderate esophageal dysplasia. (*A*) Cumulative incidence of advanced neoplasia. (*B*) Cumulative incidence of ESCC alone.



Supplementary Figure 4. Cumulative incidence of advanced neoplasia stratified by different patient characteristics and risk factors. (*A*) Dysplasia (mild dysplasia; moderate dysplasia); (*B*) sex (male; female); (*C*) age (<55 y; ≥55 y); (*D*) family history of esophageal cancer (EC) (no; yes); (*E*) cigarette smoking (no; yes); and (*F*) alcohol consumption (no; yes).



Supplementary Figure 5. Cumulative incidence of advanced neoplasia stratified by the risk factors for a family history of esophageal cancer and age. EC, esophageal cancer.

Supplementary Table 1. Summary of the Published Studies Investigating the Natural History of Mild–Moderate Esophageal Dysplasia

Study	Study setting	Country	Study centers, n	Year of cohort	Age at baseline, *y*	Median time of follow-up evaluation, *y*	Participants	Sample sizes	Outcomes			
									Definition	Regression to nondysplasia	Stable in mD or MD	Progression to ESCC or advanced neoplasia
Wang et al,[6] 2005	Community-based	China	1	1987	40–69	13	All mD MD	106 76 30	ESCC	NG NG NG	NG NG NG	33 18 15
Wen et al,[7] 2017	Community-based	China	1	1998–2002	40–69	5.5	All mD MD	91 55 36	Advanced neoplasia	NG NG NG	5 5 NG	20 5 15
Wei et al,[9] 2020	Community-based	China	3	2005–2009	40–69	8.5	All mD MD	2977 2422 555	ESCC	NG NG NG	NG NG NG	59 34 25
Liu et al,[8] 2021	Community-based	China	1	2012	45–69	4.4	All mD MD	246 205 41	Advanced neoplasia	NG NG NG	NG NG NG	24 15 9

ESCC, esophageal squamous cell carcinoma; mD, mild dysplasia; MD, moderate dysplasia; NG, not given.

Supplementary Table 2. Baseline Characteristics of the 1183 Included Patients and 1652 Excluded Patients Diagnosed With Mild–Moderate Dysplasia

Characteristics	Included patients (n = 1183), n (%)	Excluded patients (n = 1652), n (%)	*P* value
Gender			.9304
Male	646 (54.61)	872 (54.77)	
Female	537 (45.39)	720 (45.23)	
Missing data	0	60	
Age, *y*			.0672
Means ± SD	58.84 (6.58)	58.76 (6.92)	
Missing data	0	60	
Education			.3726
Primary school and below	775 (65.51)	1068 (67.13)	
Middle school and above	408 (34.49)	523 (32.87)	
Missing data	0	61	
Family history of EC			.2032
No	991 (83.77)	1359 (85.53)	
Yes	192 (16.23)	230 (14.47)	
Missing data	0	63	
Cigarette smoking			.2245
No	765 (64.67)	1064 (66.88)	
Yes	418 (35.33)	527 (33.12)	
Missing data	0	61	
Alcohol consumption			.1044
No	814 (68.81)	1140 (71.65)	
Yes	369 (31.19)	451 (28.35)	
Missing data	0	61	
Body mass index, kg/m^2			.5401
Means ± SD	24.16 (2.69)	24.10 (2.65)	
Missing data	0	60	

EC, esophageal cancer.

Supplementary Table 3. Risk of Progression to ESCC Incidence and Mortality in Included Patients and Excluded Patients Over a Median Follow-Up Period of 6.95 Years

		ESCC incidence		ESCC mortality	
Study participants	Sample sizes	ESCC cases, n	Incidence rate per 1000 person-years	ESCC deaths, n	Incidence rate per 1000 person-years
Included patients	1183	34	4.03	6	0.67
Excluded patients	1652	95	7.43	19	1.43

ESCC, esophageal squamous cell carcinoma.

Supplementary Table 4. Intervals From Mild–Moderate Dysplasia to Advanced Neoplasia

Characteristics	Median (IQR), *y*
Family history of esophageal cancer	
No	2.53 (1.60–4.28)
Yes	1.76 (1.58–4.45)
Age, *y*	
<55	3.48 (1.59–5.42)
≥55	2.30 (1.58–3.93)

IQR, interquartile range.

Supplementary Table 5. Outcomes of the Second Surveillance Endoscopy in Patients Diagnosed With Nondysplasia or Mild–Moderate Dysplasia at the First Surveillance Endoscopy

	Outcomes by surveillance endoscopies		
Dysplasia at the first surveillance endoscopy	Nondysplasia, n (%)	Mild or moderate dysplasia, n (%)	Advanced neoplasia, n (%)
Nondysplasia (n = 124)	117 (94.35)	6 (4.84)	1 (0.81)
Mild–moderate dysplasia (n = 107)	75 (70.09)	28 (26.17)	4 (3.74)

Supplementary Table 6. Sensitivity Analyses When Including Cases of Advanced Neoplasia Diagnosed Within 12 Months

	Main analysis (n = 1183)	Additional including cases of advanced neoplasia diagnosed within 12 months (n = 1191)
Cases, n		
Advanced neoplasia	88	96
ESCC	34	39
Progression rate, %		
Advanced neoplasia	7.44	8.06
ESCC	2.87	3.27
Incidence rate per 1000 person-years		
Advanced neoplasia	10.44	11.39
ESCC	4.03	4.63
Time of diagnosis cases, median (IQR), *y*		
Advanced neoplasia	2.39 (1.58–4.32)	2.07 (1.45–4.03)
ESCC	4.44 (1.79–5.82)	3.56 (1.58–5.42)

ESCC, esophageal squamous cell carcinoma; IQR, interquartile range.