An initial screening strategy based on epidemiologic information in esophageal cancer screening: a prospective evaluation in a community-based cancer screening cohort in rural China

Wanqing Chen, PhD,[1,*] He Li, BCh,[1,*] Rongshou Zheng, MPH,[2] Jiansong Ren, PhD,[1] Jufang Shi, PhD,[1] Maomao Cao, BCh,[1] Dianqin Sun, BCh,[1] Xibin Sun, BCh,[3] Xiaoqin Cao, PhD,[3] Jinyi Zhou, MPH,[4] Pengfei Luo, MPH,[4] Jialin Wang, BCh,[5] Hengmin Ma, MPH,[5] Tiantang Shao, BCh,[6] Chunling Zhao, BCh,[6] Shilin He, BCh,[7] Daokuan Sun, BCh,[7] Yuluan Xu, BCh,[8] Pengli Wu, BCh,[8] Hongmei Zeng, PhD,[2] Jiang Li, PhD,[1] Jie He, MD[9,*]

Beijing, Zhengzhou, Nanjing, Jinan, Zhu Madian, Huai'an, Tengzhou, China

Background and Aims: In China, regional organized esophageal cancer screening programs have been implemented since 2005. However, the implementation of these screening programs is still facing some urgent challenges, especially concerning identifying high-risk individuals. This study aimed to evaluate the risk stratification potential of the current initial assessment strategy used in a mass esophageal squamous cell carcinoma (ESCC) screening program in China.

Methods: A total of 43,875 participants without a previous cancer history enrolled in a mass ESCC screening program in China from 2007 to 2010 who had initial assessment results were included in this study and were followed until December 31, 2015. Eight potential risk factors for ESCC were evaluated in the initial assessment strategy. A comprehensive evaluation of the association of the initial assessment results with ESCC risk was performed by propensity score matching and Cox regression analysis.

Results: During a median follow-up of 5.5 years, 272 individuals developed ESCC. The high-risk population assessed at baseline had a higher risk of ESCC than the non-high-risk population, with a hazard ratio (HR) of 3.11 (95% confidence interval (CI), 2.33-4.14) after adjustment for sex, age, education level, income level, and body mass index. In addition, the initial assessment results of the high-risk population were significantly associated with the risk of all esophageal cancers (HR, 3.30; 95% CI, 2.51-4.33) and upper gastrointestinal cancers (HR, 3.03; 95% CI, 2.43-3.76).

Conclusions: The initial screening tool in a mass ESCC screening program in China, consisting of 8 accessible variables in epidemiologic surveys, could be helpful for the selection of asymptomatic individuals for priority ESCC screening. (Gastrointest Endosc 2021;93:110-8.)

(footnotes appear on last page of article)

INTRODUCTION

Esophageal cancer is associated with a major disease burden worldwide, and it was estimated that 572,000 new cases and 509,000 deaths caused by esophageal cancer occurred worldwide in 2018, making esophageal cancer ranked seventh in cancer incidence and sixth in cancer mortality.[1] Esophageal squamous cell carcinoma (ESCC) is the major histologic type, and more than 50% of new cases and deaths occur in China.[1,2]

The tumor stage at diagnosis is considered the strongest prognostic factor, and most cases of ESCC are clinically diagnosed at an advanced stage, with a population-based overall 5-year survival rate of approximately 30% in China.[3,4] However, findings from some observational studies in high-risk regions of China supported a mortality benefit associated with ESCC screening.[5,6] Endoscopy with iodine staining is the criterion standard for the diagnosis of esophageal cancer and its precursor lesions,[7,8] and it has been used as the clinical screening technique in regional organized esophageal cancer screening programs in

China since 2005,[9] including the Early Diagnosis and Early Treatment (EDET) program in rural China launched in 2005; the Esophageal, Stomach, Liver Cancer Screening Program (ESLCSP) in Jiangsu, Anhui, Shandong, and Henan Provinces in rural China launched in 2007; and the Cancer Screening Program in Urban China (CanSPUC) launched in 2012.

In the practice of esophageal cancer screening, the identification of high-risk individuals in the general population has remained an important and difficult challenge, and to our knowledge, prediction tools that could be implemented in mass screening programs for the Chinese population have been limited. The questionnaire-based risk assessment tool (ie, the initial screening strategy) in the ESLCSP was the first to be used in an organized esophageal cancer screening program in China to select the high-risk population for further endoscopic examinations;[10] however, its effectiveness needs to be evaluated.

Thus, in this study, we quantified the statistical association of the initial screening assessment results with the risk of developing ESCC during a median follow-up of 5.5 years to evaluate the effectiveness of the present initial screening strategy in the ESLCSP.

METHODS

Study design and study population

This cohort study used prospective data from the esophageal cancer screening component of the ESLCSP. The ESLCSP is an ongoing regional organized multicenter cancer screening program for esophageal cancer, stomach cancer, and liver cancer in 4 provinces (Jiangsu, Anhui, Shandong, and Henan) in rural China that was implemented in 2007. All women and men aged 40 to 69 years without a cancer history in the selected villages (the smallest unit) of the participating counties were approached through personal contact and phone invitation by trained local medical staff. Supplementary Figure 1 (available online at www.giejournal.org) shows the overview of the screening procedure in the esophageal cancer screening component of the ESLCSP. Briefly, after explaining the study and obtaining written informed consent, all eligible participants were administered a baseline questionnaire by trained staff to gather information about their exposure to potential risk factors, and the high-risk individuals identified by an initial assessment strategy were recommended for further endoscopic examination. Research protocols for the ESLCSP were independently approved by the Institutional Review Board of the Cancer Institute/Hospital, Chinese Academy of Medical Sciences (CICAMS, NCC1788).

The criteria for inclusion in the present study were as follows: (1) participants who were enrolled in the esophageal cancer screening component of the ESLCSP from 2007 and 2010 and who completed the questionnaire investigations; (2) participants who had no history of cancer confirmed by cancer registry data; and (3) participants who signed an informed consent form. For the present study, 44,098 participants who completed the face-to-face interview and the epidemiology questionnaire were recruited between 2007 and 2010. Participants who were diagnosed with cancer (n = 99) before recruitment or who had invalid questionnaires with any missing data needed for the risk assessment (n = 124) were excluded. Ultimately, a population of 43,875 was included in the analysis, covering 3 counties, namely, Jinhu County of Jiangsu Province, Tengzhou County of Shandong Province, and Xiping County of Henan Province, as indicated in Figure 1.

Data collection and definition of the high-risk population

The baseline questionnaires included age at enrollment, sex, socioeconomic status (education level, number of household members, household income per capita, etc), source of drinking water, cigarette smoking, consumption of alcohol, family history of cancer and cancer type, dietary habits (consumption frequency of fresh vegetables, fresh fruit, meat and eggs, soy foods, garlic, rice or flour, dried vegetables, salted food, fried food, high-temperature food, and moldy food), self-reported current clinical symptoms of esophageal cancer, medicine use history, and disease history. In addition, all participants underwent anthropometric measurements, including height, weight, pulse rate, and blood pressure, at baseline. Body mass index (BMI) was calculated for each individual.

The tool to identify the target population for endoscopic examinations was developed by an expert panel led by the National Cancer Center of China. The candidate variables were selected from up-to-date reviews and meta-analyses focusing on the Chinese population, as well as evidence from population-attributable factors for esophageal cancer, and the Chinese expert consensus on early esophageal cancer screening and endoscopic diagnosis before 2007.[11-15] The assessment variables in this tool included tobacco smoking; alcohol consumption; salted food consumption; high-temperature food consumption; moldy food consumption; family history of cancer of the digestive system; any symptoms of dysphagia, odynophagia, chest pain, back pain, or neck pain; and any disease history of esophageal reflux or peptic or duodenal ulcer (Appendix 1, available online at www.giejournal.org). The risk score for each assessment variable was determined by an expert advisory panel based on the available evidence and expertise, resulting in the development of the initial assessment tool with 8 environmental variables (Supplementary Table 1, available online at www.giejournal.org). People who had risk scores of 2 or more were deemed high-risk individuals, that is, the target population for endoscopic examinations (Supplementary Table 1).

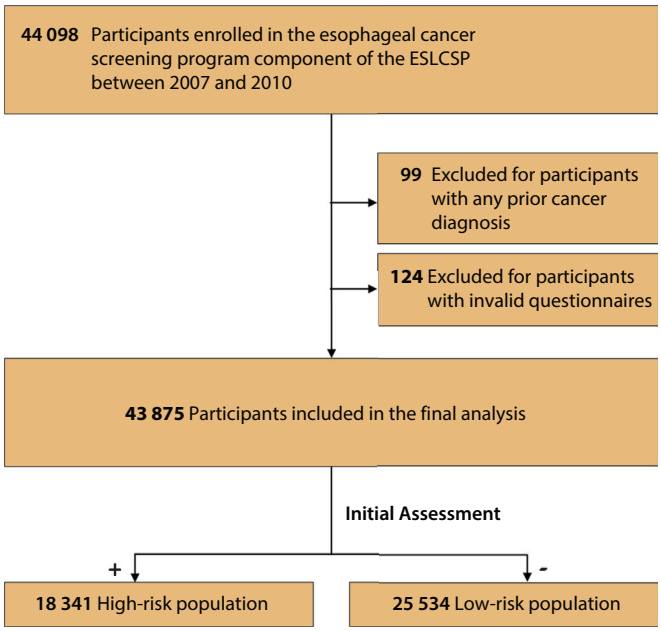

Figure 1. Definition of the study population.

Follow-up and outcome definition

The ESLCSP is linked annually to the cancer registry data and death registry data from the county-level Center for Disease Control and Prevention. Cancer data were provided to December 31, 2015. Newly diagnosed cancers were classified by site according to the International Classification of Diseases, version 10 (ICD-10), and by histology based on International Classification of Disease for Oncology, version 3 (ICD-O-3). Primary ESCC (ICD-10 C15, with ICD-O-3 M8050-M8078 or M8083-M8084) diagnosed after baseline was the main outcome of interest. Secondary outcomes included all primary esophageal cancers (ICD-10 C15, regardless of histology codes) and upper gastrointestinal (UGI) cancers (ICD-10 C15 and C16) that were diagnosed after enrollment. Information on the tumor stage was not available.

Statistical analysis

Cause-specific incidence rates were compared between the high-risk and the non-high-risk groups. Person-years of follow-up in each group were calculated from the date of enrollment to the date of diagnosis of cancer incidence or December 31, 2015, whichever occurred first, which was based on the assumption that there were no participants lost to follow-up. Cumulative incidence rates in each group were calculated as the number of cancer cases divided by the person-years of follow-up, based on the participants in the full cohort. Cumulative incidence rates for ESCC, esophageal cancer, and UGI cancer were compared between the 2 groups using the Kaplan-Meier method with the log-rank test, based on the participants in the full cohort. These rates were also estimated in a subgroup of participants identified through propensity score matching (PSM). PSM was conducted to balance demographic factors (sex, age, education level, income level, and BMI status) and to generate comparable study arms; 1:1 participant matching without replacement was used to pair each participant in the high-risk group with a participant in the non-high-risk group who had a propensity score within the designated caliper size. The Cox proportional hazard model was established among participants before PSM. We used the technique of –ln(–ln) graphical survival curves to evaluate the proportional hazards assumption for candidate variables in multivariable analysis. For each estimated variable, plots of the ln (-ln(S(t))) curves of different groups have reasonably parallel lines; therefore, there was no significant problem with the assumption for the model. The outcomes were presented as hazard ratios (HRs) and 95% confidence intervals (CIs) with stratification by sex and adjustment for age, education level (primary school and lower, junior high school and above), income level (<5000 RMB yearly per household unit; ≥5000 RMB yearly per household unit), and BMI levels (<22 kg/m^2; ≥22 kg/m^2). For the sensitivity analysis, we reanalyzed the association of the initial assessment results with the risk of developing ESCC, esophageal cancer, and UGI cancer after excluding 13,461 participants who underwent endoscopic examination from the full cohort. In addition, there was multiple testing of outcome data arising from individual participants. Correction by Bonferroni's method did not change the statistical significance for any of the main findings regarding comparisons between groups, and the *P* values for the preliminary analyses are given for descriptive purposes only, so all *P* values presented are not corrected for multiple testing.

RESULTS

Demographic characteristics of the analysis cohort

The demographic characteristics listed in Table 1 were compared between the high-risk group and the non-high-risk group based on the initial assessment results. The results show that females accounted for a higher proportion of the high-risk population, and the proportion increased with increasing age. In addition, individuals with lower educational levels (no more than primary school), those with higher yearly incomes per household unit, and those with relatively higher BMI values (≥22 kg/m^2) accounted for a higher proportion of the high-risk population than did participants with higher education levels (junior high school and above), individuals with lower income levels, and those with BMI values less than 22 kg/m^2.

Cumulative incidence by initial assessment results

Table 2 shows the incidence rates of ESCC, esophageal cancer, and UGI cancer among the cohort population. During approximately 240,672.67 person-years of follow-

TABLE 1. Demographic comparisons between those in the non-high-risk group and those in the high-risk group assessed at baseline

Characteristic	Before propensity score matching			After propensity score matching		
	Non-high-risk group (n, %)	High-risk group (n, %)	*P* value	Non-high-risk group (n, %)	High-risk group (n, %)	*P* value
Total	25,534 (58.20)	18,341 (41.80)		17,375 (50.00)	17,375 (50.00)	
Gender			.0056			.7036
Male	11,310 (58.94)	7880 (41.06)		7313 (42.09)	7278 (41.89)	
Female	14,224 (57.62)	10,461 (42.38)		10,062 (57.91)	10,097 (58.11)	
Age			<.0001			1.0000
40-49 years	10,827 (62.48)	6501 (37.52)		6492 (37.36)	6492 (37.36)	
50-59 years	8967 (55.70)	7133 (44.30)		6468 (37.23)	6468 (37.23)	
60-69 years	5740 (54.94)	4707 (45.06)		4415 (25.41)	4415 (25.41)	
Education level			<.0001			.6008
No more than primary school	14,607 (57.04)	11,000 (42.96)		10,429 (60.03)	10,380 (59.75)	
Junior high school and above	10,923 (59.82)	7337 (40.18)		6945 (39.97)	6992 (40.25)	
Missing	4	4		1	3	
Income level			<.0001			1.0000
<5000 RMB	19,216 (63.40)	11,093 (36.60)		11,084 (63.79)	11,084 (63.79)	
≥5000 RMB	6291 (46.54)	7227 (53.46)		6291 (36.21)	6291 (36.21)	
Missing	27	21		0	0	
Body mass index			<.0001			.925
<22 kg/m^2	8032 (59.85)	5388 (40.15)		5122 (29.48)	5114 (29.43)	
≥22 kg/m^2	17,488 (57.47)	12,944 (42.53)		12,253 (70.52)	12,261 (70.57)	
Missing	14	9		0	0	

RMB, Renminbi.

TABLE 2. Incidence rates of ESCC, esophageal cancer, and upper GI cancer in the cohort population

Initial assessment results at baseline	Follow-up (person-years)	ESCC		Esophageal cancer		Upper GI cancer	
		No. of incidence cases	Incidence rate (1/10^5 person-years)	No. of incidence cases	Incidence rate (1/10^5 person-years)	No. of incidence cases	Incidence rate (1/10^5 person-years)
Total	240,672.67	235	97.64	272	113.02	411	170.77
Non-high-risk group	143,491.38	66	46.00	72	50.18	115	80.14
High-risk group	97,181.29	169	173.90	200	205.80	296	304.59

ESCC, Esophageal squamous cell carcinoma.

up (median follow-up time of 5.5 years), 235 newly diagnosed cases of ESCC were identified, with 66 patients in the non-high-risk group assessed at baseline (incidence rate of 46.00/10^5 person-years) and 169 patients in the high-risk group (incidence rate of 173.90/10^5 person-years). The incidence rates for esophageal cancer were 50.18/10^5 and 205.80/10^5 in the non-high-risk and high-risk groups, respectively, and the incidence rates were 80.14/10^5 and 304.59/10^5, respectively, for UGI cancer (Table 2).

Univariate analysis showed that participants in the high-risk group had higher incidence rates of ESCC (Fig. 2A, $P < .0001$), esophageal cancer (Figure 2C, $P < .0001$), and UGI cancer (Fig. 2E, $P < .0001$) than the population in the non-high-risk group. Analysis of the well-balanced PSM cohort (17,375 participants in each group; Table 1) also demonstrated that participants in the high-risk group had higher risk of ESCC (Fig. 2B, $P < .0001$), esophageal cancer (Fig. 2D, $P < .0001$), and UGI cancer (Fig. 2F, $P < .0001$).

In the multivariable analysis, the initial assessment result remained an independent factor influencing the development of ESCC, esophageal cancer, and UGI cancer (Table 3). Compared with those in the non-high-risk group at baseline, participants in the high-risk group had HRs of 3.11 (95% CI, 2.33-4.14) for ESCC, 3.30 (95% CI, 2.51-4.33) for esophageal cancer, and 3.03 (95% CI, 2.43-3.76) for UGI cancer. These associations were observed in both males and females (Table 3).

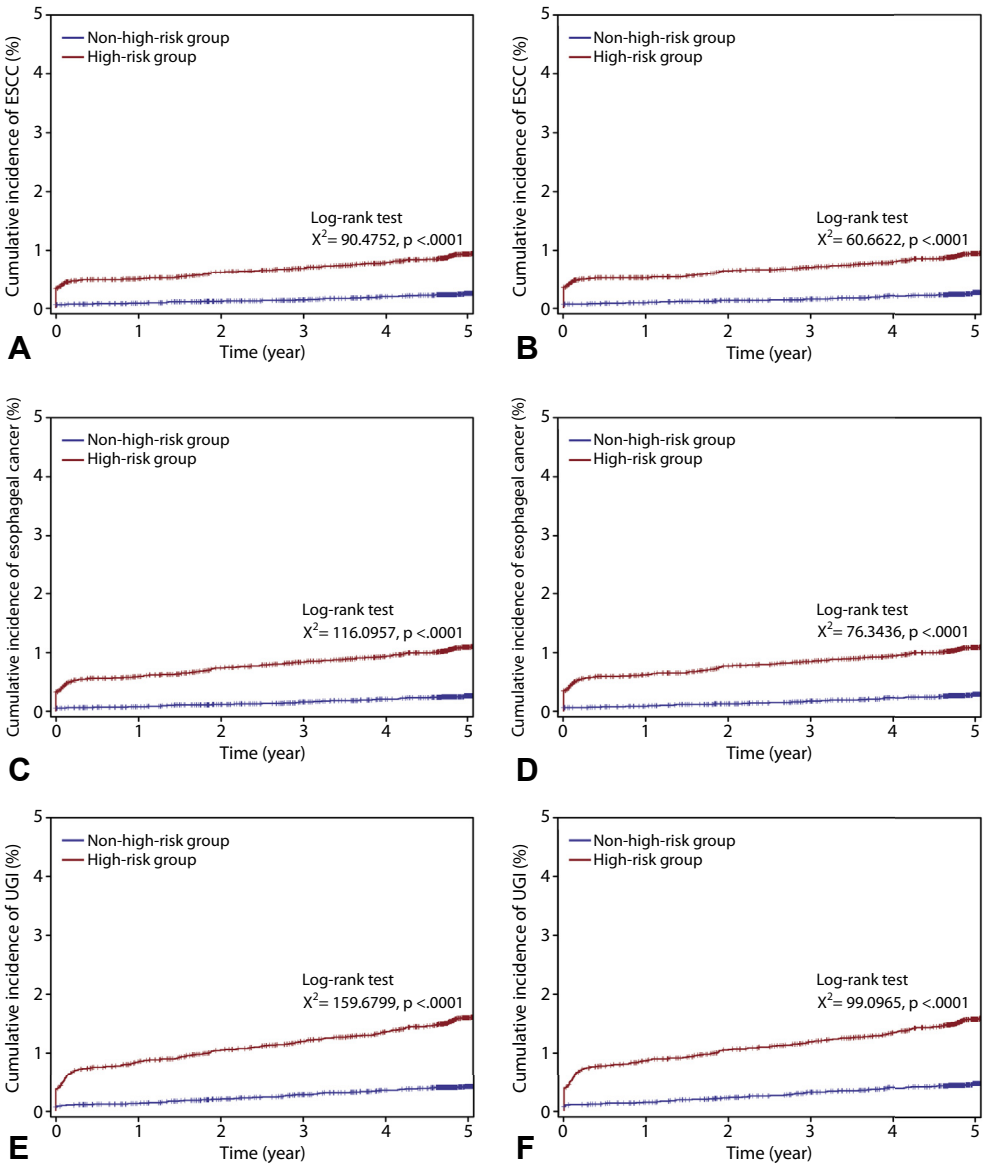

Figure 2. Comparison of the cumulative incidence of esophageal squamous cell carcinoma (ESCC), esophageal cancer and upper gastrointestinal (UGI) cancer based on high-risk assessment results at baseline. (**A**) Cumulative incidence of ESCC among all participants before match stratification (n=43 875). (**B**) Cumulative incidence of ESCC among all participants after match stratification (n=34 750). (**C**) Cumulative incidence of esophageal cancer among all participants before match stratification (n=43,875). (**D**) Cumulative incidence of esophageal cancer among all participants after match stratification (n=34 750). (**E**) Cumulative incidence of UGI among all participants before match stratification (n=43 875). (**F**) Cumulative incidence of UGI among all participants after match stratification (n=34 750).

Sensitivity analysis

After excluding participants who underwent endoscopic examinations from the full cohort (n = 13,461), we found that participants in the high-risk group in the initial assessment still had a higher risk of developing ESCC (HR, 2.34; 95% CI, 1.56-3.51), esophageal cancers (HR, 2.34; 95% CI, 1.60-3.43), and all UGI cancers (HR, 2.61; 95% CI, 1.95-3.48) than participants in the non-high-risk group (Table 4). In addition, the positive associations between the initial assessment result and the risks of developing ESCC, EC, and UGI cancer were observed in both males and females (Table 4).

DISCUSSION

This large population-based, esophageal cancer screening cohort study in China prospectively evaluated the effectiveness of the current initial assessment strategy used in a mass screening program in terms of predicting the risk of developing ESCC. The results showed that the cumulative risk of developing ESCC in the high-risk group based on the initial screening assessments was higher than that in the non-high-risk group; these results were slightly affected by sex, age, education, income levels, and BMI status. In addition, the initial assessment results also

TABLE 3. Multivariable associations between risk assessment results and the risk of ESCC, esophageal cancer, and upper GI cancer by sex

Stratified variables	ESCC			Esophageal cancer			UGI cancer		
	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)
All									
Non-high-risk group	143,491.38 (66)	Reference	Reference	143,491.38 (72)	Reference	Reference	143,491.38 (115)	Reference	Reference
High-risk group	97,181.29 (169)	3.63 (2.73-4.83)	3.11 (2.33-4.14)	97,181.29 (200)	3.94 (3.01-5.16)	3.30 (2.51-4.33)	97,181.29 (294)	3.66 (2.95-4.53)	3.03 (2.43-3.76)
Men									
Non-high-risk group	64,203.61 (37)	Reference	Reference	64,203.61 (39)	Reference	Reference	64,203.61 (69)	Reference	Reference
High-risk group	41,613.58 (98)	3.88 (2.66-5.66)	3.12 (2.12-4.58)	41,613.58 (115)	4.31 (3.00-6.20)	3.42 (2.37-4.95)	41,613.58 (178)	3.77 (2.85-4.98)	2.95 (2.23-3.92)
Women									
Non-high-risk group	79,287.77 (29)	Reference	Reference	79,287.77 (33)	Reference	Reference	79,287.77 (46)	Reference	Reference
High-risk group	55,567.70 (71)	3.39 (2.20-5.22)	3.07 (1.99-4.75)	55,567.70 (85)	3.57 (2.39-5.34)	3.14 (2.09-4.70)	55,567.70 (118)	3.52 (2.50-4.95)	3.08 (2.18-4.35)

ESCC, Esophageal squamous cell carcinoma; *HR*, hazard ratio; *CI*, confidence interval.

TABLE 4. Sensitivity analysis of multivariable associations between risk assessment results and the risk of ESCC, esophageal cancer, and upper GI cancer by sex

Stratified variables	ESCC			Esophageal cancer			Upper GI cancer		
	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)	Person-years (cases)	Crude HR (95% CI)	Adjusted HR (95% CI)
All									
Non-high-risk group	121,779.69 (46)	Reference	Reference	121,779.69 (51)	Reference	Reference	121,779.69 (84)	Reference	Reference
High-risk group	44,879.75 (53)	3.05 (2.05-4.53)	2.34 (1.56-3.51)	44,879.75 (61)	3.15 (2.17-4.58)	2.34 (1.60-3.43)	44,879.75 (112)	3.51 (2.64-4.66)	2.61 (1.95-3.48)
Men									
Non-high-risk group	55,998.51 (22)	Reference	Reference	55,998.51 (23)	Reference	Reference	55,998.51 (46)	Reference	Reference
High-risk group	20,746.07 (30)	3.52 (2.03-6.12)	2.36 (1.33-4.17)	20,746.07 (37)	4.14 (2.46-6.98)	2.73 (1.60-4.68)	20,746.07 (71)	3.99 (2.75-5.78)	2.72 (1.86-4.00)
Women									
Non-high-risk group	65,781.18 (24)	Reference	Reference	65,781.18 (28)	Reference	Reference	65,781.18 (38)	Reference	Reference
High-risk group	24,133.68 (23)	2.59 (1.46-4.60)	2.17 (1.21-3.88)	24,133.68 (24)	2.32 (1.34-4.00)	1.88 (1.08-3.27)	24,133.68 (41)	2.90 (1.86-4.51)	2.29 (1.46-3.59)

ESCC, Esophageal squamous cell carcinoma; *HR*, hazard ratio; *CI*, confidence interval.

predicted the risks of developing esophageal cancer and UGI cancer.

There are no guidelines for ESCC, although endoscopy with iodine staining is the reference standard technique for the diagnosis of esophageal cancer and its precursor lesions.[9,16] In China, regional organized ESCC screening programs have been implemented in the last 10 years; however, the implementation of screening programs is still facing some urgent challenges, such as identifying the high-risk population.[9] Risk prediction models based on information on risk factors have shown promising usefulness in selecting individuals at high risk of developing esophageal cancer; however, most of these models were built for esophageal adenocarcinoma (EAC).[17-22] In a population-based cohort of 62,576 participants in Norway, an EAC model including predictors of sex, age, gastroesophageal reflux symptoms, BMI, and tobacco smoking supported a positive association between the risk thresholds and the risk of developing EAC. The results showed that 72% of cases of EAC occurred in the 20%

of the population with the highest risk within 15 years, whereas none of the cases of EAC occurred in participants in the 60% of the population with the lowest estimated risk.[17] In another cohort of 355,034 individuals in the United Kingdom, an EAC model based on the predictors of age, sex, smoking, BMI, and history of esophageal conditions or treatments showed that the high-risk population had a higher risk of developing EAC within 5 years (odds ratio, 8.17; 95% CI, 5.97–11.18).[18] Similarly, the findings in the present study supported that the high-risk population had a higher risk of developing ESCC (in both multivariable and PSM analyses). In the unadjusted population, the cumulative incidence rate of ESCC was much higher in the high-risk group (173.90/10^5) than in the non-high-risk group (46.00/10^5), and a significant difference in terms of the incidence of ESCC existed between the 2 groups in the adjusted population ($P < .0001$). Similar significant differences in the risk of all esophageal cancers and UGI cancers between the 2 groups were also observed (Fig. 2). Our findings in the multivariate analysis showed that compared with participants in the non-high-risk group, the high-risk population had a higher risk of developing ESCC (HR, 3.11; 95% CI, 2.33-4.14), and the initial assessment results could also predict the development of all esophageal cancers (HR, 3.30; 95% CI, 2.51-4.33) and UGI cancers (HR, 3.03; 95% CI, 2.43-3.76). In addition, to avoid the disturbance caused by screening tests for ESCCs, we conducted a sensitivity analysis to exclude all participants who underwent endoscopic examinations in our program, with unchanged results. The results of the present study showed that the current initial assessment strategy used in the ESLCSP could be an effective triage method for stratification of the general population.

The initial screening strategy reported in the present study is the first easy-to-use, initial screening tool applied in a mass esophageal cancer screening program in China, which was constructed based on potential environmental risk factors in the literature and then assessed by experts. The assessment variables were tobacco smoking; alcohol consumption; salted food intake; high-temperature food intake; moldy food intake; family history of digestive system cancer; any symptom of dysphagia, odynophagia, chest pain, back pain, or neck pain; and any disease history of esophageal reflux, peptic or duodenal ulcer, which are usually used to establish ESCC models.[21-24] A model of the absolute 5-year risk of ESCC was developed from a nationwide Swedish population-based, case-control study using 6 potential demographic and environmental predictors, namely, age, sex, tobacco smoking, alcohol overconsumption, education, duration of living with a partner, and place of residence during childhood.[21] A model for severe esophageal dysplasia and higher-grade lesions (severe dysplasia and above [SDA]) was developed based on a population-based cross-sectional endoscopic screening study in a high-risk region in China.[22] For participants aged more than 60 years, the SDA model was generated from 9 variables: age, family history of ESCC, cigarette smoking, BMI, pesticide exposure, regularity of eating, intake of high-temperature foods, eating speed, and ingestion of leftover food during summer; for participants aged 60 and younger, the SDA model was developed with 5 variables: age, exposure to cooking fumes, BMI, unexplained epigastric pain, and eating speed. In addition, a prediction model of ESCC that included known environmental risk factors (age, sex, tobacco smoking, and alcohol consumption) together with genetic information (25 single-nucleotide polymorphisms) was developed in the Chinese population[23]; another ESCC model was developed based on the genotype of aldehyde dehydrogenase-2 and the environmental variables of alcohol consumption, tobacco smoking, and consumption of green-yellow vegetables and fresh fruit in a Japanese population.[24] These ESCC or SDA models had many predictors similar to those included in the present study. However, some key predictors, such as age, sex, and BMI, were not included in the current initial screening strategy of the ESLCSP.

Some strengths and limitations of the present study should be considered. The main strength of this study is that it was the first study to prospectively estimate the stratification value of the current initial screening tool developed based on epidemiological information in the ESLCSP. Furthermore, detailed epidemiologic information was collected by questionnaire in a standardized manner by trained study staff to ensure the quality of the data. A sound annual passive follow-up mechanism was established and implemented in our program based on the cancer registration system. The follow-up information is updated using linked data once a year for the entire cohort population, as each screening center involved in this study conducted population-based cancer registration at least in the first year of enrollment. Therefore, we could obtain information on cancer incidence for each participant in the cohort. Some limitations must be mentioned. First, the assessment variables in the current initial screening strategy and the corresponding scores and cutoff values to define the target population for endoscopic examinations were reviewed and determined by experts because there was no useful prediction tool in 2007. Other key factors, such as age, sex, and BMI, were not included in the current initial assessment strategy, although many potential and known risk factors related to ESCC were considered. In the next study, we will develop prediction models for ESCC based on the prospective screening cohort population to provide a quantitative individual risk score system for ESCC and to optimize the current initial screening strategy. Second, this study only estimated the associations between the initial assessment results and the risk of developing ESCC, without assessing the sensitivity and specificity of the initial screening strategy, because

endoscopic examinations were only conducted in high-risk individuals identified by the initial screening strategy. We will conduct a further screening test study based on an ongoing randomized controlled trial of endoscopic screening for UGI cancer when data are available in the future, including endoscopic examinations for all community residents aged 40 to 69 years in 3 rural regions of China. From these data, we will be able to assess the sensitivity and specificity of the current initial screening strategy for the detection of ESCC and SDA.

CONCLUSIONS

In conclusion, the data obtained in this prospective cohort of mass esophageal cancer screening in the Chinese population illustrate that the initial screening tool in the ESLCSP, consisting of 8 accessible variables in epidemiologic surveys, is helpful for the selection of asymptomatic individuals for priority ESCC screening. More comprehensive studies are warranted to further evaluate the value of the initial screening strategy in esophageal cancer screening programs.

ACKNOWLEDGMENTS

We sincerely appreciate the funding from the National Health Commission of the People's Republic of China and the National Key R&D Program of China (grant number 2018YFC1313100) and the Special Fund for Health Research in the Public Interest, China (grant number 2016-I2M-2-004). The funding source of the study had no role in the study design; data collection, analysis, interpretation; or writing of the report. The first author and corresponding authors have full access to all the study data and assume final responsibility for submission for publication. We gratefully acknowledge all participants in our program and all staff who have made substantial contributions to the data collection, auditing, database management and verification.

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Abbreviations: BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ESLCSP, Esophageal, Stomach, Liver Cancer Screening Program; HR, hazard ratio; PSM, propensity score matching; SDA, severe dysplasia and above; UGI, upper gastrointestinal.

DISCLOSURE: *All authors disclosed no financial relationships.*

*Drs Chen and Li contributed equally to this article.

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2020.05.052

Received January 9, 2020. Accepted May 17, 2020.

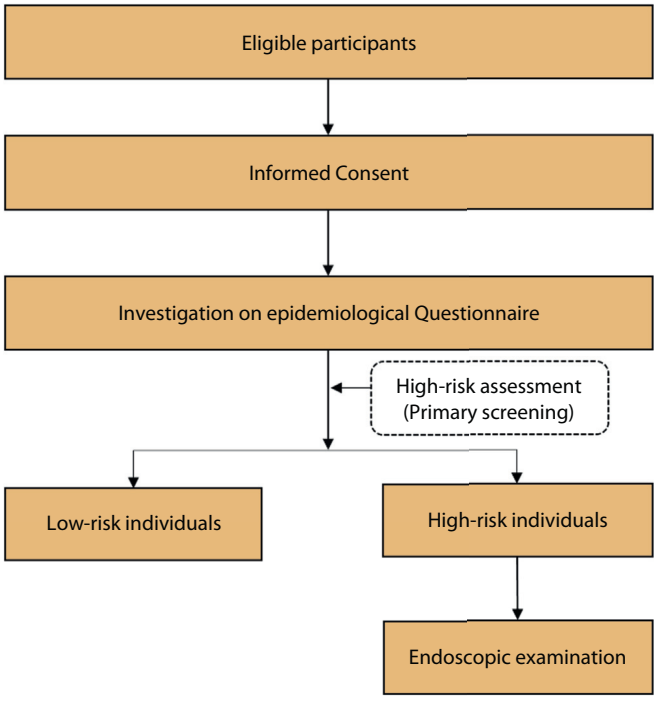
Current affiliations: Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021 (1); Office of Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021 (2); Department of Cancer Epidemiology, Henan Office for Cancer Control and Research, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, 450000 (3); Institute of Chronic Non-communicable Diseases Prevention and Control, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, 210009 (4); Department of Public Health, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, 250117 (5); Office of Chronic Non-communicable Diseases Prevention and Control, Xiping Center for Disease Control and Prevention, Zhu Madian, 463900 (6); Office of Chronic Non-communicable Diseases Prevention and Control, Jinhu Center for Disease Control and Prevention, Huai'an, 211600 (7); Office of Chronic Non-communicable Diseases Prevention and Control, Tengzhou Center for Disease Control and Prevention, Tengzhou, 277599 (8); Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China (9).

Reprint requests: Prof. Wanqing Chen, Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China or Prof. Jie He, Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No.17 Pan-jia-yuan South Lane, Chaoyang District, Beijing 100021, China.

If you would like to chat with an author of this article, you may contact Dr Chen at chenwq@cicams.ac.cn or Dr He at hejie@cicams.ac.cn.

APPENDIX 1. PROFILES OF ESTIMATED VARIABLES FOR THE PRESENT STUDY

1. Tobacco smoking: Participants were asked about their lifetime smoking. Current smokers were further asked the type (cigarette or tobacco leaf) and corresponding years they smoked.
2. Alcohol consumption: Participants were asked about their alcohol consumption history. Current drinkers were asked to report the frequency per week and last years when they consumed different classes of alcohol (beer, white spirit, and others).
3. Dietary habits: Dietary habits (salted food intake, high-temperature food intake, and moldy food intake) were included in this section. For each item, participants were asked about the frequency of intake with the following 4 options: (a) every day; (b) usually (>1 time per week); (c) sometimes (1-4 times per month); and (d) never.
4. Family history of cancer: Participants were asked about their family history of cancer, including cancer types and the relationship of the family member. Family history of digestive cancer was defined as any cancer of the esophagus or stomach or small intestine or liver or gallbladder or pancreas in the immediate family and relatives within 3 generations.
5. Clinical esophageal symptoms: Participants were asked 5 questions regarding their current for esophageal symptoms, which included unexplained dysphagia, unexplained odynophagia, unexplained chest pain, unexplained back pain, and unexplained neck pain. Each question had 2 options in this section: (a) no and (b) yes.
6. Disease history: Participants were asked about their disease history related to the digestive system, including peptic ulcer, esophagitis, gastroenteritis, hepatitis, cirrhosis, anemia, and self-reported cancer history. Each item had 2 options: (a) no and (b) yes.



Supplementary Figure 1. An overview of the workflow of the esophageal cancer screening program component of the ESLCSP.

SUPPLEMENTARY TABLE 1. Definition of the target population for endoscopic examination in the esophageal cancer program of the Esophageal, Stomach, Liver Cancer Screening Program

Assessment items	Assessed score
Smoking at least 20 cigarettes per day for last 10 years or more; or smoking tobacco leaf for 10 years or more	1
Drinking beer at least 5 L per week for last 10 years or more; or drinking white spirit at least 1 L per week and for last 10 years or more	1
Eating salted food at least once per week	1
Eating high-temperature food at least once per week	1
Eating moldy food at least once per week	1
Family history of digestive system cancer	2
Any current symptom of dysphagia, odynophagia, chest pain, back pain, or neck pain	2
Any disease history of esophageal reflux or peptic or duodenal ulcer	2
High-risk individual*	≥2

*Patients were asked to respond to each item, and a summary score was added up for identification of high-risk individuals (the target population for endoscopic examination).