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The optimal starting age of endoscopic screening for esophageal squamous cell cancer in high prevalence areas in China

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Abstract

Background and Aim—This study aimed to evaluate effects of endoscopic screening method in different starting age groups and further confirm the optimum starting age for ESCC screening.

Methods—This study received IRB approval, and 6,825 residents aged 40 to 69 years in high prevalence communities were assigned to the screening group or the control (non-screening) group from Hebei province, China. Cumulative mortalities during the 14-year period, relative risks (RR) for participants underwent screening, numbers needed to invite for screening (NNS) to save one life were compared between the screening group and the control group of different starting age groups at 14-year follow-up.

Results—The 14-year risks of ESCC mortality were one in 55, one in 17 and one in 9 for a person screened in the starting age group of 40, 50 and 60 years old. The cumulative mortalities of ESCC in screening groups were significantly lower than control groups in starting age groups of 40 years (1.42% vs 2.38%, $p=0.0331$) and 50 years (4.18% vs 7.13%, $p=0.0053$). RR for participants underwent screening were 0.60 and 0.59 for the starting age groups of 40 years and 50 years. NNS to save one life were 104 and 34 for participants aged in 40 years old group and 50 years old group, respectively.

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Conclusions—In conclusion, people in high prevalence area of ESCC should have endoscopy screening once at their 50 years. 40 years will be preferable defined as the starting age for screening in areas with sufficient health resources.

Keywords

Cohort Study; Cancer Screening; Esophageal Squamous Cell Cancer

Introduction

Esophageal cancer is a serious malignancy with poor prognosis and fatal outcome in a great majority of cases [1-3]. In China, esophageal cancer accounted for 11.19% of the total cancer deaths [4, 5]. After standardized by the age structure of the world population, the age-standardized mortality and incidence rate of esophageal cancer in China were 13.73 and 14.81 per 100,000 person, respectively [4, 5]. Both of them were much higher than the estimated age-standardized incidence rate and mortality rate (5.9 and 5.0 per 100,000 person) of the world [1].

In western, the incidence rate of esophageal squamous cell cancer (ESCC) was decreasing [6-10]. However, ESCC is particularly common in a so-called “esophageal cancer belt” which stretches from northern China through the central Asian republics to Northern Iran [11, 12]. In China, ESCC accounts for about 90% of the total esophageal cases [13]. Cixian County has the highest age-standardized incidence and mortality rate of esophageal cancer in China [5]. Esophageal cases accounted for 32.37% of the total cancer deaths and 38.25% of the total cancer incidents, respectively in this area [5].

Previous study has shown that early detection and early treatment for ESCC in high prevalence areas of China can reduce the mortality [14]. Endoscopic examination has been proved to be the best screening method with high sensitivity and specificity [15, 16] and up to date has been applied widely in high prevalence areas in China. Widespread use of this screening method followed by the appropriate treatment for all advanced lesions could significantly reduce the disease burden of esophageal cancer [17]. Although this screening method has been carried out for many years, to our knowledge, there is still no global normative screening recommendation in China. The optimum starting age of endoscopic screening based on population evidence has not been defined yet.

In our study, we explored the optimum starting age of endoscopic screening for esophageal cancer in high prevalence areas of China, and provided evidence of the current technical proposal for early detection and early treatment based on a population-based cohort study in high prevalence areas.

Material and Methods

Study Population

In this study, the cohort is a community assignment endoscopic screening cohort conducted in the high prevalence areas of esophageal cancer in Cixian, Hebei province, China [17]. Details on the cohort have been previously published [17]. In brief, forty villages in this

region were divided into intervention communities, control communities and buffer regions according to their geographic characters. This study only focuses on targeted population from the intervention communities (Figure 1). Local residents aged 40 to 69 years from the intervention communities with no contraindications for endoscopic examinations (e.g. history of reaction to iodine or lidocaine, serious cardiovascular disease, poor health status) and competent to provide written informed consent were eligible for this study and received esophageal cancer prevention and treatment education. In total 6,827 targeted population were invited to receive endoscopic screening after education. Targeted subjects were assigned to screening group (n=3,319) if they agreed and received the endoscopic screening, while other subjects refused endoscopic screening were assigned to control (non-screening) group (n=3,508). The study was approved by the Institutional Review Board of the Cancer Foundation of China.

Participants were assigned to either screening group or control group between

Endoscopy Procedure

November 1999 and May 2000 and endoscopy screening was accomplished from June 2000 to November 2001. Endoscopy with Lugol's iodine staining with biopsies of the unstained lesions was the screening methodology for the screening group. All endoscopic examinations and therapies were conducted by local doctors after training by and under the supervision of experienced doctors from the Cancer Institute^[17]. Lugol's iodine (1.2%) solution was used to stain the full length of the esophagus, and biopsy was used for unstained foci.

Treatment Procedure

Two independent pathologists read the biopsy slides without knowledge of the visual endoscopic findings. After diagnosis of early lesions, participants were recalled to the clinic with appropriate intervention methods. Endoscopic mucosal resection (EMR) and/or argon plasma coagulation (APC) treatments were used as local therapies for severe dysplasia/carcinoma in situ or intramucosal carcinomas. Patients will be endoscopic followed up 6 and 12 months after the first therapy. Esophagectomy, radiotherapy, and other conventional treatments were used for submucosal cancers and advanced esophageal cancers.

Outcomes

The primary outcomes of this cohort were mortality of ESCC. The Only patients with esophageal cancer were calculated as ESCC incident cancers. Others with normal biopsy, mild dysplasia, moderate dysplasia and severe dysplasia or carcinoma in situ were not classified as incident cancers^[18].

Data collection and management

The participants were followed up for 14 years from January 1, 2000 to December 31, 2013. Basic demographic information including name, sex, age and ID number were collected by the household registration system of local police station. The local cancer registration system provided data on cancer mortality and incidence. Furthermore, date of onset, disease code, diagnostic hospital, diagnostic materials, date of death, death code, hospital of death

diagnosis, and other information were collected by investigators during the monthly follow-up process.

Information on village doctors visiting and cancer incidence and death records were collected and then checked by investigators. Verification of the diagnoses report and case report form were conducted by interviewing the case family. All data of this study were double entered and logic checked to ensure accurate information.

Statistical analysis

Cases of incidents and deaths of ESCC occurring between 1st January 2000 and 31st December 2013 were included in the analysis. SAS version 9.2 software (SAS Institute, Cary, NC) was used for statistical analysis.

Chi-square test was used in the analysis of demographic characteristics. The absolute numbers of residents with ESCC incidents and deaths were calculated during the 14-year period. The mortality was calculated by dividing absolute numbers with the total numbers of residents at each age group. Cumulative mortalities in screening group and control group were compared using the PROC Life test and PROC Phreg in SAS. Mortality reduction and “life-years gained” were both considered important outcomes of screening in forming recommendation [19]. The number needed to invite for screening (NNS) to save one life was used as the metric of the “life-years gained” [20]. NNS was calculated as the reciprocal of the relative risk (RR) reduction. An alpha of 0.05 and two-sided test was used throughout the statistical analysis.

Results

Demographic characteristics of participants from screening and control communities

The demographic characteristics of participants from screening communities that received endoscopy and a 10% sample of the population from the control communities [17] were compared to verify the demographic difference. No significant differences were found for gender, number of household members, drinking water source, smoking tobacco, alcohol drinking, and history of diseases of the digestive system in these participants (Table 1). Participants from the screening communities that received endoscopy had younger age, higher education, were more likely to report a family history of cancer and had less household income than people from control communities that not received endoscopy. Among the 3,311 subjects received screening and biopsy, 163 subjected were diagnosed with severe dysplasia or carcinoma in situ, and 38 were diagnosed with esophageal cancer.

Absolute deaths

During the 14 years follow up, the final analysis consisted 3,311 in the screening group and 3,514 in the control (non-screening) group. There were 108 deaths of ESCC in the screening group while 217 deaths in the control group between 1st January 2000 and 31th December 2013. In screening group, the absolute numbers of ESCC deaths were 29, 36 and 43 in 40, 50 and 60 years old age groups respectively. In control group, the absolute numbers of ESCC deaths were 36, 78 and 103 in different age groups respectively (Figure 1).

The cumulative mortality and 14-year risk of deaths in starting age of screening

As shown in Table 2, cumulative mortality of ESCC were 4.76% (325/6,825) in the target population. It also demonstrated that the 14-year risk of deaths due to ESCC in different starting age groups: the 14-year risks of mortality for ESCC was one in 55 for a person in the starting age group of 40 years, one in 17 in the starting age group of 50 years, and one in 9 in the starting age group of 60 years. The results of cumulative incidence in starting age of screening showed in Supplementary Table 1.

Cumulative mortality of ESCC between screening group and control group

The crude cumulative ESCC mortalities in the cohort population of three starting age groups by time since entered into the cohort were showed in Figure 2. Results of log-rank tests showed that the differences in cumulative mortality rates of starting age group of 40 years and 50 years were statistically significant (starting age group of 40 years: $p=0.033$; starting age group of 50 years: $p=0.005$). In each panel, a reduction in mortality of the screening group was apparently since subjects joined the cohort, and the reduction of cumulative mortalities seemed larger with year's increasing. Figure 2C showed the curves of the starting age group of 60 years diverged in the first five years of follow-up but then had a trend to gather together. In the last four years of follow-up, cumulative mortality rates in the screening group and control group were almost same. The differences in cumulative mortality rates in the screening group and control group were not statistically significant ($p=0.681$) which meant no reduction of mortality was found in the screening group than the control group among the starting age group of 60 years. The results of cumulative incidence and the results of subjects divided into 5-year age groups between screening and control group showed in Supplementary Figure 1 and Supplementary Figure 2.

RR and NNS in starting age groups of screening

NNS to extend one person's life was calculated as the metric of life-years gained in Table 3. For the starting age group of 40 years old, results indicated the RR for ESCC mortality of 0.60 (95% confidence interval, 95% CI 0.37-0.97) for people assigned to screening group, indicating a 40% reduction in ESCC mortality in favor of screening, and the NNS to extend one person's life over 14 years of 104 (95% CI 51-1,520). For subjects in the starting age group of 50 years, results indicated the RR of 0.59 (95% CI 0.40-0.86) for ESCC mortality for people assigned to screening, which indicated a 41% reduction in ESCC mortality in favor of screening. This corresponded to the NNS to extend one person's life of 34 (95% CI 20-114) over 14-years of follow-up. For people in the starting age group of 60 years, results provided the RR of 0.94 (95% CI 0.67-1.31) for ESCC mortality for people assigned to endoscopic screening. The NNS to extend one person's life over 14-years of follow-up was 146.

Discussion

Esophageal cancer is the sixth most common cause of death from cancer with an estimated 400,000 deaths [21]. In our result, the cumulative incidence of the population with both screening and non-screening group were 388 cancers, with the cumulative incidence rate of about 5%. This high cumulative incidence rate is in line with the reported cumulative

incidence from the total cohort [17], 367/6,200 in control communities and 285/6,827 in intervention communities respectively. The instant incidence rate of esophageal cancer was about 2% based on 110 sites in 29 provinces from the population-based endoscopy screening program launched by the Ministry of Health of China [22]. The cumulative incidence rate would be higher than the instant incidence rate if the population were followed up with a period. In another high prevalence area of esophageal cancer in Linxian, China, similar esophageal cancer incidence was reported. After a 15-year follow-up among 29,584 individuals aged 40-69 years from general population, 1,958 ESCC were diagnosed [23]. The overall age-specific incidence and mortality rates also showed that both rates were relatively low before 45 years old (0-5.79/100,000 in 2009), and then gradually increased with age (15.11/100,000 in 50-54 years old in 2009), reached peak in the age group of 80-84 (145.31/100,000 in 80-84 years old group) [24]. The age-specific mortality rates were relatively low before 50 years old and then increased promptly with age after 50 years old [25].

In our study, the risk of incidents and deaths for ESCC increased with age apparently. Compared with the age group of 50 years and 60 years, the 14-year risks of incidents and deaths for ESCC were relative lower in the age group of 40 years. These figures indicated that the burden of esophageal cancer in this population aged 50 years or older is much higher than that in younger people. The elder population is the major group with heavy burden of esophageal cancer.

Mortality reduction and life-years gained were both considered important outcomes of screening in forming recommendation [19]. Therefore the outcomes of mortality reduction and “life-years gained” were both showed to express the benefits of screening in each age group. The survival rates could be increased by early detection and early treatment of esophageal cancer [26,27]. The effectiveness of endoscopic screening in our study has been confirmed in the previous published article [17]. It showed screening by endoscopic examination with iodine staining and biopsy could decrease mortality due to ESCC in a short period, within one or two years after the initiation of screening. After 10 years’ follow-up, cumulative incidence of ESCC in the screening group was lower than the control group (4.17% vs 5.92%, $p<0.0001$) and a reduction in cumulative mortality in the screening group versus the control group was apparent and significant (3.35% vs 5.05%, $p<0.0001$).

In our study, the outcomes of survival analysis showed significant reductions in ESCC mortality in people who received endoscopic screening than those in the control group at the age of 40 years and 50 years. Besides, we found that the improvements in the RR for deaths due to ESCC for persons aged 40 to 49 years and 50 to 59 years were similar. However, the NNS to prevent one ESCC death over 14 years of follow up of people aged 50 to 59 years (NNS=34) was much smaller than people aged 40 to 49 years (NNS=104). Larger numbers of endoscopic screening were required when screening started at age 40 years compared with age 50 years. For people aged 60 to 69 years, results with an RR of 0.94 (95% CI 0.67-1.31) for ESCC death associated with screening people and the NNS to extend one person’s life was 146, which indicated no significant mortality reduction. This could be explained by the following reasons: 1) due to the old age, a large percentage of people in this age group could not survive long enough to show the benefits of screening after endoscopic

screening; 2) people at this age group were more likely to die from other conditions that would not be affected by endoscopic screening than the younger age groups; 3) the limited sample size and lower screening rate compared with other age groups might diminish the screening benefit. In future study, the balance of the screening rates in different age groups should be considered and the effect of endoscopic screening in a larger population scale should be evaluated.

A review summarized the recent advances of the screening for esophageal squamous cell carcinoma [28]. They found that Asian or African area was an important risk factor for esophageal squamous cell carcinoma despite the other risk factors such as achalasia and injury. One-time endoscopy beginning at the age of 40 was recommended with lower ESCC incidence and mortality rates. However, the widespread endoscopic screening is not possible or cost-effective in most high prevalence areas in Asia and Africa [28]. Our study showed that one-time endoscopy screening at age 50 years old is of high cost-effectiveness, while starting at 40 years old could be preferable in areas with sufficient health resources. Simple, inexpensive, and minimally invasive tests that are acceptable to unstated asymptomatic adults and can specifically distinguish those with moderate to severe dysplasia are desperate [28]. In addition to above outcomes, some other factors should be considered when choose reasonable screening strategy in different conditions. Almost all high prevalence regions for esophageal cancer such as Cixian and Yanting county are rural or less-developed regions in China. Policy makers should also consider the cost-benefit, population acceptance, willingness to pay and local economic status together. Some cost-benefit analysis studies had been evaluated the economic benefit of endoscopic screening. The health economic evaluation proved that endoscopic screening, early diagnosis and treatment for esophageal cancer could provide great cost savings [29]. Other studies also showed the high benefits to cost ratios [30,31]. In the first comprehensive model-based cost-effectiveness assessment for the ESCC screening strategies using endoscopic examination in high prevalence areas of China [32], there were twelve cost-effective strategies considering start age, screening interval and screening times. Among these strategies, screening once at age 50 years yielded the most appropriate benefit-cost ratio. This cost-effective study provided recommended screening program based on cost-effectiveness analysis. It was consisted with the results of the NNSs which indicated in this study.

Our results showed that one-time lifetime endoscopy screening can provide long lasting benefits by reducing cumulative mortality among screening group. However, the implement of one-time endoscopy screening in the national screening guideline should be carefully considered in terms of the effect of one-time screening, the target population selected, the screening frequency and the screening interval.

The lead time bias might be a limitation in this study. The mortality rate would be affected by the length of follow-up time. However, as the observation time increases, the less survival of the screened patients, the differences in the annual mortality rate between the screened and unscreened patients is reduced. Therefore, mortality as an indicator can reflect the screening effect with a long-term observation [33]. On the other hand, lead time bias can be avoided by calculating the survival time at the starting point of the cohort. Which allowed the survival time of screening and no screening can be compared directly. The survival of the

non-screening group is not calculated from the time of clinical diagnosis, but is calculated together with the screening group from the beginning of the establishment of the cohort. In this study, the mortalities of the screening group and non-screening group were calculated since the starting point, which will control the lead time bias [34].

Selection bias exist in cohort studies. In this study, participants with family history of cancer, young age, high education tend to show more endoscopy screening compliance, which would cause differences in the baseline risk of ESCC and impair the comparability between the screening and control group. However, the other demographic characteristics in this study showed of no significance in gender, number of household members, drinking water source, smoking tobacco, alcohol drinking, and history of diseases of the digestive system. Though smoking and drinking were evaluated, other ESCC related risk factors demonstrated by large population cohorts such as dietary intake should also be considered for the incidence and mortality of ESCC [35-38]. Large sample size randomization study should be performed in the future to verify the screening effects.

In conclusion, government should make policies depend on different conditions in different areas. The burden of disease in the population aged 50 years or older is much higher than the younger people. However, although the elder population is the major group with heavy burden of esophageal cancer according to the China cancer registry annual report, the effectiveness of screening for people 60 years has not confirmed yet in our study and needs to be evaluated in the further study. Moreover, the additional benefit gained by starting screening at age 40 years rather than at age 50 years is small relatively. And larger numbers of endoscopies will be required when screening is started at age 40 years compared with the start age of 50 years. Considering overall conditions of high prevalence regions of ESCC in China, we recommend people in high prevalence areas should have screening once at their 50 years. If screening policies were undertaken in certain developed areas, 40 years will be preferable defined as the starting age to screening, while it means much health resources needed to be provided.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure Statement

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Abbreviations

APC	argon plasma coagulation
CI	confidence interval

EMR	endoscopic mucosal resection
ESCC	esophageal squamous cell cancer
NNS	numbers needed to invite for screening
RR	relative risks

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Figure 1: Study profile of community assignment endoscopic screening cohort in Cixian, Hebei province, China.

ESCC: esophageal squamous cell cancer

Figure 2: Cumulative mortalities of ESCC in different starting age groups.

(A) Starting age group of 40 years. (B) Starting age group of 50 years. (C) Starting age group of 60 years.

ESCC: esophageal squamous cell cancer

Table 1.

The demographic characteristics of screening group and control group.

Demographic characteristics	Screening group		Control group*		chi-square	P
	No.	%	No.	%		
Age, years old					176.003	<0.001
40-49	2046	61.79	302	37.89		
50-59	862	26.03	281	35.26		
60-69	403	12.17	214	26.85		
Gender					1.757	0.185
Male	1625	49.08	412	51.69		
Female	1686	50.92	385	48.31		
Household members, No.					1.162	0.282
<6	2653	80.13	625	78.42		
6	658	19.87	172	21.58		
Household income, Chinese yuan					58.450	<0.001
5000	2699	81.52	552	69.26		
>5000	612	18.48	245	30.74		
Education					10.550	0.001
No primary education	1055	31.86	302	37.89		
Primary education or higher	2256	68.14	495	62.11		
Drinking water					2.140	0.144
Well or lake water	3274	98.88	783	98.24		
Piped water	37	1.12	14	1.76		
Smoking					0.659	0.417
No	2276	68.74	536	67.25		
Yes	1035	31.26	261	32.75		
Alcohol drinking					2.216	0.137
No	2871	86.71	675	84.69		
Yes	440	13.29	122	15.31		
Disease of digestive system					0.169	0.681
No	2958	89.34	716	89.84		
Yes	353	10.66	81	10.16		
Family history of cancer					79.730	<0.001
No	2021	61.04	621	77.92		
Yes	1290	38.96	176	22.08		

Note:

* A 10% sample (Number = 797) of the control communities.

Table 2:

The 14-year risk of incidence and mortalities for ESCC in cohort population (Jan/1/2000 -Dec/31/2013)

Age Group	Deaths	Total	Mortality (%)
40-49	65	3559	1 in 55 (1.83)
50-59	114	1956	1 in 17 (5.83)
60-69	146	1310	1 in 9 (11.15)
Total	325	6825	1 in 21 (4.76)

Table 3:

RRs for ESCC Mortality from Endoscopic Screening for All Ages

Age	RR for ESCC Mortality (95% CI)	NNS to Prevent one ESCC Death (95% CI)
40–49	0.60 (0.37-0.97)	104 (51-1520)
50–59	0.59 (0.40-0.86)	34 (20-114)
60–69	0.94 (0.67-1.31)	146 (NA)

Note: RR refers to relative risk compared with control group, RR was bold if $P < 0.05$. NA: Not applicable