

Precision screening for esophageal squamous cell carcinoma in China

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Abstract

Esophageal squamous cell carcinoma (ESCC) is the predominant subtype of esophageal cancer in China, and this neoplasm is associated with high morbidity and mortality as well as clear geographical heterogeneity. Since primary prevention for ESCC lacks a clear intervention target, secondary prevention, also known as screening and early diagnosis and early treatment, has become the mainstay of ESCC prevention and control in China. ESCC screening in China has been subject to decades of evaluation and practice. However, the ESCC screening strategy currently adopted in China has encountered a developmental bottleneck. In this review, we have summarized studies and significant findings for ESCC screening and proposed advancement of screening strategies as follows: 1) evidence from randomized controlled trials is needed to support the effectiveness and health economic value of endoscopic screening for ESCC; 2) the current traditional screening and surveillance strategies warrant reform, and a risk-prediction-based precision strategy should be established; and 3) a deeper understanding of the value of opportunistic screening in the prevention and control of ESCC in China is called for. Due to the low absolute prevalence of precancerous lesions, substantial investment of resources and nonnegligible risks of invasive screening techniques, precision and individualization should be the main direction of cancer screening programs for the future. We advocate cooperation on the part of Chinese scientists to solve this major China-specific health problem in the next decades.

Keywords: Esophageal cancer; organized screening; opportunistic screening; cost-effectiveness; risk stratification

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Esophageal cancer (EC) is a malignancy of the esophageal epithelium that can be divided into two subtypes, including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). These subtypes have clear differences in tissue origin, etiology, epidemiology and treatment prognosis (1). EAC predominates in Western populations, however, over 90% of EC cases in China are ESCC. In China, EC ranks as the sixth most frequent cancer and the fourth leading cause of cancer death, and cases originating in China account for about 53% of new EC cases in the world (2). The prevalence of

ESCC in China has clear geographical heterogeneity, and the Taihang mountain area at the junction of Henan, Hebei and Shanxi provinces is a well-known high-risk area, with a mortality rate 5 times of the national average (3).

As with most other cancers, the occurrence and progression of ESCC is a multistage process which can be generally divided into an etiologic exposure stage, together with preclinical (asymptomatic or with mild symptoms), clinical treatment (obvious symptoms), and prognostic stages. Over the past half century or more, scientists have conducted multiple epidemiologic and etiologic studies in

populations living in regions of high ESCC incidence in China, and these studies have reported associated risk factors, including environmental exposures and genetic susceptibility (4-11). However, the main cause of the high incidence of ESCC in China has not been determined. Primary prevention for ESCC, that is to say etiologic prevention, lacks a clear intervention target. Secondary prevention, also known as “screening” and “early diagnosis and early treatment”, has thus become the mainstay of ESCC prevention and control in China.

Secondary prevention of ESCC consists of targeted early screening in individuals who have not yet sought clinical treatment to identify patients at the early stage of esophageal malignancy (e.g., severe dysplasia, carcinoma *in situ*) or at precancerous stages with malignant transformation potential (e.g., mild or moderate dysplasia). Timely and effective clinical management may be initiated in these patients, including endoscopic treatment, surgical treatment, endoscopic surveillance, and so on. The ultimate goal is to alter the natural progression of the disease and prevent or decrease the risk of occurrence of advanced ESCC and death.

Population-level screening for ESCC in high-incidence areas in China, such as Lin County in Henan province, began in the 1960s. A number of professionals in cancer prevention and treatment have been devoted to ESCC screening and related scientific research in these areas. The central government of China has continuously invested resources for early diagnosis and early treatment of cancer including ESCC, and has established a series of national cancer screening programs, such as the “Taihang Project”, the “Central Government Transfer the Payment for Local Cancer Prevention and Control Program” and the “Huai River Basin Cancer Early Diagnosis and Treatment Project”. By the end of 2018, more than 2.16 million people had undergone upper gastrointestinal endoscopy in 194 program sites nationwide, and more than 34,000 patients with malignant lesions were diagnosed, with an early diagnostic rate of more than 70% (12). These programs have played an important role in the prevention and treatment of major malignant tumors, and have helped China accumulate great experience in the organization and implementation of population-based cancer prevention and treatment programs.

However, with the advancement of evidence-based and value-based medicine concepts (13), the ESCC screening strategy currently employed in China has encountered a series of developmental bottlenecks.

It is time to provide evidence from randomized controlled trials to support effectiveness and health economic value of population-level endoscopic screening for ESCC

Conventional endoscopic ESCC screening has a direct economic cost (14) as well as potential for physical and emotional harm, including complications of endoscopic examination such as bleeding, perforation, or allergic reaction to iodine, and unnecessary psychologic stress brought about by false-positive screening results. Before recommending ESCC screening for generalized public, two questions must first be addressed: 1) Can such screening in fact save lives? In other words, from a population perspective, can early diagnosis and treatment definitively change the natural progression of precancerous lesions in esophagus and reduce the risk of advanced ESCC and death? 2) Is such screening cost-effective? That is, from a health economic perspective, would conducting large-scale population screening be in accordance with the principles of health economics, and what kind of screening modalities are most cost-effective under specific conditions of health resource allocation?

Several large prospective population cohort studies in China have reported that early endoscopic screening decreases the incidence of advanced ESCC and ESCC-specific mortality (15-17). However, due to the limitations of the observational or non-randomized design of these studies, even large multicenter studies with long-term follow-up cannot avoid the influence of lead-time bias, length-time bias, and confounding bias (18). The presence of these biases makes it difficult to accurately demonstrate the effectiveness of screening by merely comparing risks of outcome events of cases detected by screening and clinically diagnosed cancer cases, or even by comparing a screened group and a non-randomized control group. “One-step” population-based randomized controlled trial (RCT) is the only way to evaluate screening effectiveness without such shortcomings, by comparing the probability of outcome events (e.g., advanced ESCC incidence and ESCC-specific death rate) for an entire screening group with a randomized control group.

Although a population-based randomized trial is extremely difficult to implement, it is an essential prerequisite for cancer screening strategy which is intended for eventual inclusion in guidelines and recommended in public health and clinical medicine settings. For example, the American Cancer Society (ACS) guidelines for cervical

cancer, lung cancer, colorectal cancer, and breast cancer screening are all based on the results of large RCTs (19). Because some of the results of the respective RCTs did not support effectiveness of the screening, or because conclusions were controversial, a series of well-known cancer screening programs were gradually withdrawn or had their recommendation level reduced. These included programs such as X-ray screening for lung cancer (20), transvaginal ultrasound and cancer antigen 125 (CA125) screening for ovarian cancer (21), and prostate-specific antigen (PSA) screening for prostate cancer (22). For this reason, the Cochrane Library concluded that RCTs are needed to provide definitive evidence in EC screening (23).

Due to the high-quality control group setting and screening practices that are similar to real-world practices, the RCT design is also the optimal choice for assessment of health economic value of screening. By considering basic socioeconomic conditions of population in which the screening is conducted, optimal screening strategy can be established based on available resources, which should ensure feasibility of population-level screening program.

Based on this, we initiated the Endoscopic Screening for Esophageal Cancer in China (ESECC) trial (ClinicalTrials.gov: NCT01688908) in 2012 (24). In this study, 668 target villages in a county with a high incidence of ESCC were randomly selected and divided into screening and control groups (334 villages/group). The screening group received standard endoscopic screening with iodine staining, while the control group did not receive any screening. A follow-up of more than 10 years was designed to compare indicators of effectiveness and health economic value of ESCC screening, including the incidence of advanced ESCC, ESCC-specific mortality, all-cause mortality, cost-effectiveness, and cost-utility in the two groups to draw conclusions about the effectiveness and cost-effectiveness of population-level endoscopic screening for ESCC. The ESECC trial is still in the follow-up phase, and final conclusions are not yet available. Therefore, ESCC screening has not yet been included in the international cancer screening guidelines for clinical and public health practice based on high-grade evidence. Considering the invasive nature of ESCC screening and its associated risks, experts should be relatively cautious about recommending early endoscopic ESCC screening to the public. Although it is not always necessary to obtain evidence from RCTs before recommending screening, RCT is the *sine qua non* for achieving approval for efficacy and effectiveness of a screening program. In the real world,

professional advice can be given based on high-quality evidence from prospective observational studies, but the strength of recommendation must be lowered accordingly until supporting evidence from RCT is available.

Traditional screening and surveillance strategies warrant reform, and a risk-prediction-based precision strategy should be established

Although the effectiveness of screening has been demonstrated in RCTs, it is time for a change in traditional screening strategy.

First, as noted above, screening for ESCC at the population level requires extensive resources and has nonnegligible risks (18). In addition, the actual effects of screening in the real world often have high interpersonal heterogeneity. That is, even when identical technology and procedures are used to screen for a given disease, the effectiveness may still vary significantly among individuals. In other words, a given screening program may have a protective effect for some people but nonetheless be ineffective for, or even harmful to others. For example, in some patients, precancerous ESCC lesions (e.g. moderate or severe dysplasia) will not progress to cancer except after a very long interval, or may possibly even remain in a precancerous stage for the remaining life of the patient. These patients will not benefit from early endoscopic diagnosis and subsequent clinical treatment, and may even suffer serious damage to their physical and mental health as well as to quality of life as a result of unnecessary diagnostic and therapeutic intervention. Such heterogeneity is presented even in areas of high prevalence.

A recent follow-up study of a large-scale screening cohort in a high-incidence area in China (25) showed that among asymptomatic subjects from a natural population of over 20,000 people, 73.7% of the subjects underwent endoscopic mucosal biopsy to evaluate Lugol-unstained lesions (LULs) at the baseline endoscopic examination. However, severe dysplasia and above lesions (SDA, requiring immediate clinical care) were found in fewer than 3% of individuals, which means 97% of the subjects did not immediately benefit from the initial endoscopic screening. In addition, among the subjects with mild and moderate dysplastic lesions for whom endoscopic surveillance is recommended under the current pathology-based guidelines, only 1.4% and 4.5% of cases progressed to ESCC over a period of 8.5 years. This suggests that at least

95% of the subjects did not benefit from repeated endoscopic reexamination after the initial screening test. Another follow-up study conducted in a neighboring high-incidence area revealed that as compared with over screening and reexamination as noted above, a more serious problem was insufficient diagnosis. During the median 4-year follow-up, 40%–50% of newly diagnosed ESCC patients were not positive for dysplastic lesions at the baseline screening examination, and these individuals would have been missed under the tenets of current surveillance practice. (26). The sensitivity of the screening in these two studies is almost identical (96.0% vs. 96.5%, taking the malignant lesions diagnosed at baseline screening and within 1 year after screening as true positives).

A high proportion of biopsies carried out in the endoscopic examination and low absolute progression risk in subgroups defined by only pathologic analysis characterize the real-world situation in ESCC screening in extremely high-risk areas of China. That is, endoscopists and pathologists who play key roles in screening, have reached their upper limit of work capacity under the current strategy. During endoscopic examination, endoscopists were not able to accurately distinguish malignant lesions from other unstained benign lesions. Moreover, pathologists were unable to precisely predict which patients were at high risk of progression warranting endoscopic surveillance. In addition to waste of resources, this also inevitably leads to various direct and indirect screening-related cost and potential harm. Therefore, precision screening strategy should be developed to eventually improve the cost-effectiveness of large-scale screening and reduce the risk of harm. The overall rationale of this precision screening strategy is to exclude low-benefit subgroups from initial screening and subsequent endoscopic surveillance as much as possible, through individualized risk prediction and stratification to improve the overall screening performance while reduce resource investment and potential harm. This would ultimately achieve the goal of cost reduction and effectiveness improvement. According to different phases in which risk stratification may be implemented, precision screening strategy would consist of the following three key steps (Figure 1).

First, a risk assessment of ESCC in the general population should be performed to identify individuals or subpopulations with a high risk of onset of ESCC and its precancerous lesions, and only subgroups or individuals

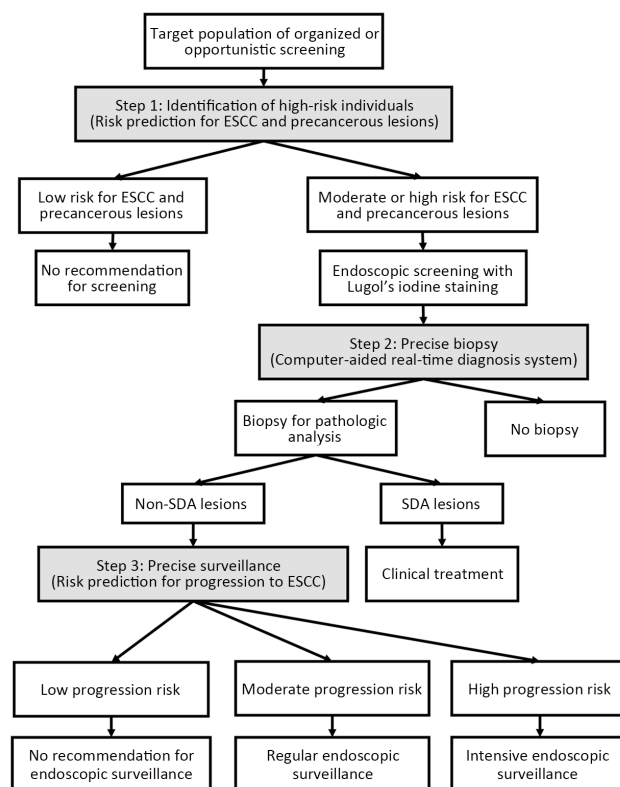


Figure 1 Precision screening strategy for ESCC in China. ESCC, esophageal squamous cell carcinoma.

identified as high risk for ESCC and precancerous lesions should undergo endoscopic screening. This will enrich the high-risk subgroup before screening, and thereby reduce the initial screening workload and increase the detection rate of malignant lesions.

Second, in order to improve the accuracy of endoscopic biopsy, that is, to reduce unnecessary biopsy and missed biopsy resulting from lack of experience and nonstandard operation at the same time, a computer-aided diagnosis system could be developed based on large-scale endoscopic images from real-world screening practice. Ideally, detection of all the malignant and precancerous lesions at the initial screening, and any newly detected malignant lesions during a specific follow-up period should be the outcome event when establishing the diagnostic model underlying this system. This system should be deeply integrated into the electronic endoscope operating system so as to dynamically display the predicted probabilities of different pathologic diagnoses for an unstained lesion during the process of endoscopy. For example, SDA lesions (90%), mild and moderate dysplasia (6%) and non-dysplastic lesions (4%) suggest a 90% of probability the

lesion of interest is an SDA lesion, and so on. This will help endoscopists in making a quick decision on whether to perform a biopsy or not.

Finally, a multidimensional comprehensive progression risk assessment should be performed for patients with abnormal esophageal mucosa found during screening. Regular or intensive endoscopic follow-up should be performed for patients with a moderate or high risk of progression to achieve personalized surveillance after screening.

For malignant tumors, the etiologic network is complex, and heterogeneity among the population is significant. Risk prediction and assessment cannot continue to follow the risk factor study design that emphasizes the independent role of a variable. Instead, multiple concurrent factors for construction of an integrated risk prediction model should be taken into consideration to achieve a comprehensive evaluation of risk.

Based on this concept, we established a model to identify individuals at high risk for ESCC and precancerous lesions in the general population (27), and a model to predict the risk of progression of esophageal lesions (26) in a Chinese population based on the baseline endoscopic screening results for 15,000 subjects, and the longitudinal follow-up data for ESECC cohort. Statistical evaluation showed that the first model which had a sensitivity of 100%, could avoid up to 20% of endoscopic examinations in baseline screening. The application of progression prediction model could increase the accuracy of predicting the after-screening progression of precancerous lesions to malignant lesions from 70% using pathologic diagnosis alone to nearly 90%. We further evaluated the early-warning effect of endoscopic iodine staining abnormalities on the risk of progression of precancerous lesions identified in initial screening. This showed that the size of LULs plays a key role in predicting the risk of esophageal lesion progression. Specifically, a larger LUL (>10 mm) is a principal predictor of high risk for lesion progression to SDA lesions in esophagus, especially for non-dysplastic lesions. Based on these findings, we propose a modified surveillance strategy integrating findings of endoscopists and pathologists in risk stratification for esophageal lesion progression. With this strategy, patients with relatively large non-dysplastic lesions should undergo additional endoscopic surveillance. This surveillance strategy made up for the limitations associated with pathologic diagnosis alone. The percentage of missed ESCC cases during the follow-up period due to a lack of timely reexamination decreased by 65.3% (28).

These studies have increased the accuracy of identification of high-risk individuals before endoscopic screening, and allow for individualized endoscopic surveillance after screening. Our study revolutionizes the traditional models of whole-population screening and pathology-based surveillance which are currently in use in China. The new risk prediction model and endoscopic surveillance protocol are both easy to implement and scientifically reliable, and are the most complete and precise risk classification tools for ESCC screening in China to date. Based on the findings above, the theoretical framework and the chain of evidence which will result in precise screening strategies for ESCC that align with the actual situation in high-incidence areas in China have been preliminarily established.

A deeper understanding of value of opportunistic screening in prevention and control of ESCC in China is needed

According to decision-making, implementation and expense payment, cancer screening programs can be classified into community-based organized screening, which can be prompted by policy or project needs, and hospital-based opportunistic screening, which is determined jointly by doctors and patients in a clinical setting.

Organized screening is a voluntary screening program initiated by relevant government departments and medical service institutions that is independently or jointly funded by the government, medical institutions, and medical expense providers (such as the health insurance system). The target population, most of whom are asymptomatic individuals in the general community, together with the screening protocols, are clearly defined with uniform criteria, and the subjects bear little to no financial burden. However, community-based organized screening requires significant ongoing investment in human and material resources and is difficult to expand and sustain on a large scale.

With increasing quality and accessibility of medical services, hospital-based opportunistic screening has gradually attracted increased attention. Opportunistic screening refers to targeted screening for a given disease in high-risk patients. When seeking medical services for any reason, doctors and patients can initiate targeted screening based on the results of risk assessment and the socioeconomic situation and willingness of the patient to be

evaluated. Thus, subjects who undergo opportunistic screening are usually more proactive in screening decisions. Since the subjects are generally at high risk for the disease of interest, the detection rate of malignant lesions would be higher than that in the general population. In addition, the costs of opportunistic screening are mainly covered by the subjects and the medical insurance system. All of this suggests that opportunistic screening would be naturally more cost-effective than organized screening.

In the traditional epidemiologic concept, before the symptoms or signs of a given disease have appeared, active examination for early diagnosis of the disease is called a screening test. In contrast, when disease-related symptoms or signs are present, the examination that confirms the diagnosis and guides treatment is called a diagnostic test. Screening tests can usually alter or even prevent the natural progression of a disease through clinical intervention at an early stage. Classic diagnostic tests are mostly performed in clinical practice, and the identified disease stage reflects the distribution under natural circumstances. In the traditional definition, these two approaches have clear boundaries, that is to say, the presence or absence of symptoms. However, with continuous advancement of medical technology and screening practices, this boundary may become obscured.

The onset of disease-related symptoms is usually continuous rather than simply being differentiated as positive or none. After symptom onset (even onset of very mild symptoms), the decision as to whether or not to undergo corresponding clinical examination depends both on personal factors, such as the patient's socioeconomic status and awareness of the need for medical care, and external factors, such as the accessibility and quality of medical service. With improvements in medicine and patient awareness of medical services, opportunistic screening has increasingly gained attention. In terms of disease stage at the time of diagnosis, a portion of outpatients may have had exhibited symptoms and the disease stage may be later than that of the subjects undergoing community-based screening noted above. However, early diagnosis can potentially be achieved if the clinical risk assessment and active referral for opportunistic screening under physician supervision lower the threshold for patients seeking treatment. The direct result of such early diagnosis is that the disease can be diagnosed at an earlier stage, also known as "downstaging". Therefore, opportunistic screening has the characteristics of both a screening test and a diagnostic test, particularly for endoscopic screening of EC, since the endoscopic

technology can also be used for the final diagnosis of ESCC and its precursor lesions. This type of screening also suggest that the definition of screening should not be limited by presence or absence of symptoms. If the screening population is strictly limited to individuals who are absolutely asymptomatic, the findings of relevant scientific research stand to lose their practical value to the real world.

In China, a large number of community-based organized screening programs have been implemented. Although this involves the investment of considerable human and material resources, these programs still cover only a small number of regions, and there is a large unfilled gap in the national need for screening. If the coverage for screening was expanded using the current strategy to achieve the primary outcome of reducing the rate of premature death from major chronic diseases in the Chinese population as proposed in the *Healthy China 2030 Planning Outline*, it is estimated that annual upper gastrointestinal endoscopy screening would have to be carried out nationwide in approximately 120 million people (12). Achieving this goal is almost impossible given the limitation of material and financial resources, and the number and capacity of existing professional and technical personnel in China. Clinical-based opportunistic screening provides a potential solution to this problem.

The majority of ESCC patients already have advanced stage disease at the time of diagnosis and have a poor prognosis. One of the main reasons why ESCC patients are diagnosed so late is that they do not receive timely diagnosis and treatment after symptom onset. In China, especially in rural high-incidence areas, many cancer patients do not seek medical attention until symptoms are quite obvious, as they are limited by their relatively low socioeconomic status and poor health awareness (29). Gastroenterologists, on the other hand, often fail to refer EC patients in a timely manner because symptoms of ESCC which include dysphagia and retrosternal pain are not always specific. Thus, promoting earlier medical evaluation and diagnosis for patients who are still asymptomatic or have mild symptoms to achieve downstaging is an important goal of opportunistic clinical screening for ESCC in China, especially for low-income and rural areas at high risk (30-33).

For opportunistic screening, the following key points must always be kept in mind: 1) Like population-based organized screening, opportunistic screening must also be based on a definite evidence of effectiveness to ensure that

early-stage patients will benefit from screening. 2) Accurate, reliable, and easy-to-perform risk assessment and stratification is an important prerequisite for the implementation of opportunistic screening in order to ensure appropriate referral and avoid overburdening medical facilities and wasting medical resources. 3) To promote opportunistic screening at the local level, experts must work together with primary medical institutions to form specific, stable cooperative alliances and screening networks, as well as provide opportunistic screening training and supervision of clinicians with relevant professional knowledge in each institution to improve their risk assessment capability and to achieve standardized recognition of screening results.

We established a multi-center cohort in two medical institutions in high- and low-incidence areas in northern and southern China, and collected data on risk factors for ESCC from more than 10,000 outpatients from department of endoscopy in these two institutions. Taking the pathologic diagnosis as the outcome variable, we constructed the first risk prediction model for esophageal malignancy that is suitable for opportunistic screening in China, and we have proposed criteria for corresponding risk classification. The prediction accuracy of this model for malignant esophageal lesions reached 87.1% in the training dataset from the high-risk population in northern China and 84.3% in a heterogeneous sample of a mixed population in a non-high-risk region in southern China (covering 30 Chinese provinces and autonomous regions). The model established in this study will facilitate the individualized risk assessments in the clinical settings, which are necessary for opportunistic screening and fulfill the prerequisite for the establishment and promotion of opportunistic screening program for ESCC in China (34).

Whether organized screening is conducted in a community population or is conducted as clinical-based opportunistic screening, the initiators and organizers are the government, the research teams, and medical institutions rather than the subjects undergoing screening. That is, high-risk individuals who should be screened but do not have enough awareness or motivation to participate the screening will still not be covered by the screening program. Therefore, application of these two screening strategies will result in coverage of only part or of only a small portion of the target population. The solution to this problem lies in motivating high-risk individuals who should be screened to proactively seek screening services. This is essential if a screening program is to achieve an ideal

protective effect on the population and for an overall reduction in the incidence of advanced-stage disease and associated mortality. Relying on mobile internet and social media platforms to build and promote easy-to-use online risk assessment tools will enable individuals to conveniently self-assess disease risk by providing interactive and user-friendly graphic assessment results and screening-related recommendations based on risk assessment results. In the era of big data and mobile internet, the emergence of such an App will inevitably bring new insight for precision screening for major chronic diseases such as ESCC.

Prospects

The implementation of a population-based cancer screening program will require investment of a substantial amount of resources, and the involved population will be large. The inherent invasiveness of the screening techniques, the heterogeneity in protection ability and the potential consequent negative effects will impact the safety and clinical effectiveness of the screening program, and even the physical and psychological health of the subjects. All screening can do harm, but some can do good, and screening may thus be viewed as double-edged sword. The key to planning a mass screening program is to find the balance between benefit and harm in specific circumstances. The absolute prevalence of precancerous lesions is low, most screening methods are invasive, and the psychological stress caused by positive diagnostic results is high. Moreover, medical resources are inevitably limited, and therefore “precision” and “individualization” should be the primary future directions for cancer screening. Risk prediction study covering a wide range of macro- and micro-predictors will be an effective research strategy for fighting diseases with “complex etiologies” and “strong heterogeneity”. Such research is the main focus of precision medicine in the prevention and control of significant disease, and will provide opportunity to take advantage of Chinese resources to achieve international standards and allow China to become a pioneer in the field of precision prevention and control of cancer.

ESCC screening in China has been the subject of decades of exploration and practice. Much front-line experience has been accumulated, and effective methods for this work and the associated organizational structure have been established. The establishment and application of risk prediction tools as well as risk stratification criteria have promoted precision screening for ESCC in China. At

present however, there are still several critical issues that need to be addressed:

1) Etiologic factors of ESCC with high population attributable risk in high-incidence areas of China need to be further investigated by jointly evaluating the environmental and genetic factors, especially the factors shared by men and women (35).

2) Further studies on the natural history from normal esophageal mucosa to malignant lesions, which are crucial for establishing an optimal screening strategy, based upon large-scale prospective cohort with repeated endoscopic reexamination are clearly warranted.

3) Early-warning biomarkers for the onset and progression of ESCC (e.g., oral microbiome, genetic susceptibility, tumor-associated antigen, circulating tumor DNA, etc.) warrant exploration in order to update existing risk prediction models.

4) Computer-aided diagnostic systems for endoscopic examination and biopsy based on technology such as artificial intelligence should be established to improve the diagnostic accuracy and standardization of biopsy in current screening practice.

5) Large real-world comparative studies should be conducted to evaluate the effectiveness of the latest endoscopic techniques (Narrow band imaging system with magnifying endoscopy, etc.) in screening practices.

6) Quantitative and qualitative studies assessing the long-term effects of early diagnosis and treatment on the psychological health and quality of life of the cancer patients who have been identified by screening are needed to establish more appropriate and efficient management strategies after screening.

7) Systematic health economics studies should be utilized to provide direct evidence of cost-effective screening strategy for varying populations under different resource conditions.

8) Large clinical RCTs are needed to provide definite evidence of the effectiveness of endoscopic treatment (endoscopic submucosal dissection, endoscopic mucosal resection, etc.) in patients with very early-stage malignant lesions in esophagus detected during screening.

These are the directions that urgently warrant breakthrough in the field of early diagnosis and treatment of ESCC in China at this time. Experience accumulated with esophageal adenocarcinoma in the West, which is the major subtype of EC there, is of limited reference value to ESCC in China. We therefore urge Chinese scientists in public health, clinical medicine, basic medicine, and all

related disciplines to work together to grasp and resolve this major China-specific health problem in the coming decades.

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Footnote

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