Modeling the Cost-effectiveness of Esophageal Cancer Screening in China

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Abstract

Background: This study aimed to examine the cost-effectiveness of the standard endoscopic screening with Lugol’s iodine staining in EC screening in China. Methods: The Markov decision analysis model with eleven states was built. Separate cohorts were conducted consisting of those aged 40 to 69 years, classified as six age groups with five years interval. Three different strategies assumed for each cohort:(1) no screening; (2) endoscopic screening with Lugol’s iodine staining with annual follow-up for Low-grade
intraepithelial neoplasia; (3) endoscopic screening with Lugol’s iodine staining without follow-up. Quality-adjusted life-years (QALYs) served as effectiveness. The incremental cost-effectiveness ratio (ICER) was identified as the evaluating indicators. Sensitivity analysis was introduced to assess the robustness of the model. Results: For aged 40-49 years, the non-screening strategies were absolutely dominated with both more costs and less QALY, while for aged 50-69 years, the screening scenarios were absolutely dominated. Screening with follow-up was the preferred strategy. Compared to non-screening, screening with follow-up saved USD 10942.57 and USD 611.73 per QALY gained for aged 40-44 and 45-49 years separately. One-way sensitivity analysis addressed that the risk ratio of the EC incidence in population after screening compared to people without screening and the utility of precancerous lesion could affect the cost-effectiveness of the screening strategy. However, the probabilistic sensitivity analysis supported the results of the base case analysis. Conclusions: EC screening with follow-up targeting aged 40-49 years was the most cost-effective strategy.

Keywords: Esophageal cancer; Markov Model; Screening; Cost-effectiveness analysis

Background
Cancer still caused a serious disease burden. It ranked as the second leading cause of deaths worldwide. In 2016, there were 8.93 million cancer deaths, which accounted for 17.08% of the worldwide deaths. And esophageal cancer (EC) ranked as the ninth most common cancer and the sixth leading cause of cancer death worldwide [1, 2]. There were 806,300 total cases, 472,500 new cases, and 436,000 deaths in 2017 worldwide [3]. EC incidence varied considerably according to geographical distribution, with over half of the worldwide incidence occurred in China [4]. The morbidity and mortality were $22.16/10^5$ and was $16.64/10^5$ in 2013 in China [5]. Adenocarcinomas and squamous cell carcinomas were the major histological subtypes. And adenocarcinomas were more happened in developed countries with an increasing trend in the incidence, while squamous cell carcinomas were more popular in less-developed regions[4]. And the squamous cell carcinomas accounted for over 90% of all the EC cases in China[6].

Intraepithelial dysplasia is a precancerous lesion of EC, and the degree of dysplasia is highly correlated with the risk of EC[7]. Intraepithelial dysplasia can be classified into mild dysplasia, moderate dysplasia, and severe dysplasia[4]. A 13.5-year cohort study explained that about 25% of mild dysplasia, 50% of the moderate dysplasia, and 75% of the severe dysplasia
could progress to EC\[7\]. Compared to healthy people, the risk of developing EC was 2.2 to 2.9 times, 9.8 to 15.8 times, and 28.3 to 72.6 times higher for mild dysplasia, moderate dysplasia, and severe dysplasia, respectively [7-10]. Moreover, mild dysplasia and moderate dysplasia renamed as Low-grade intraepithelial neoplasia (LGIN). Noticeable was that the LGIN was an unstable disease, which could return to health through the intervention of life behavior. More than 90% of patients had progressed to the advanced stage at the time of diagnosis due to the asymptomatic characteristics in the early stage, with the 5-year survival rate was 15%-20\%[11]. About 40\% of patients had distant metastasis by diagnosis, and the 5-year survival rate was less than 5\%[12].

Several well-designed prospective preventive approaches have been developed to decrease the risk of EC; however, none of them has yet been proven effective[13, 14]. Screening is a rapid, simple, and safe method to detect the early stage of the disease. The main purpose of the screening is not only to find and treat the early patients, but also to find the precancerous lesions of the disease, and do follow-up intervention for them, finally to reduce the incidence and mortality of EC. Early in the 1980s, WHO have advocated the secondary prevention strategies for early detection, diagnosis, and treatment. Cancer screening, recommended by the WHO, is
the major strategy for primary and secondary prevention of disease[15].

Currently, there are no global EC screening guidelines. However, EC national screening strategies have been in place for decades in China, which was carried out in rural and urban areas in 2005 and 2012, respectively[16]. Until 2013, 26 provinces and 110 cities had participated in the program[17]. The Screening was conducted by endoscopy accompanied with iodine iodine staining and indicative biopsy. EC screening resulted in markedly clinic benefits. First, the EC early diagnosis rates could reach 70.59% to 98.1% [18]. Also, One particular 10-year cohort study demonstrated decreasing cumulative mortality (3.35% vs. 5.05%) and cumulative incidence (4.17% vs. 5.92%) in the screening population compared to non-screening[19]. Moreover, the overall 5-year survival rate of early EC could reach to 97.4-100%, and the disease-specific 5-year survival rate can reach 100%[20-23]. However, the effectiveness of the EC screening cannot be demonstrated without consideration of the costs, due to the scarcity of medical resources and relative lower incidence. Moreover, the cost and effectiveness of EC screening were less well documented, especially for the areas with a lower incidence of EC. This study aimed to compare the costs and effectiveness of the EC screening, to identify the most cost-effective EC screening strategy and find the age limit at which screening should be
targeted in China.

**Methods**

*Screening methods*

EC Screening and early treatment was performed strictly following the National Guideline for Early Detection of Cancer[24]. The summarized screening procedures was that eligible residents aged 40 to 69 years can voluntarily participated the screening, after signed the informed consent, the participants were recommended to do the physical examination. Participants meeting the clinic screening criteria will then be examined by the standard endoscopy accompanied with Lugol’s iodine staining and indicative biopsy. All the histological diagnosis were conducted by the expert pathologists according to the AJCC cancer stage (Seventh Edition)[25]. Patients with clear histological diagnosis were recommended to undergo the following treatment. Individuals identified as LGIN were recommended to complete additional screening with endoscopy in 1-3 years. Patients diagnosed with intraductal carcinoma (IC) would undergo the standard treatment of the endoscopic submucosal dissection, while surgery was highly recommended for the cases with the submucosal cancer(SM) stage. For patients with moderate stage, surgery plus adjuvant chemoradiation was suggested, while cases with distant metastasis would
be treated with chemoradiation or symptomatic treatment.

**Model structure**

A decision analysis Markov model of EC with 11 health states was built in Treeage Pro (2019). The health states included: normal, LGIN, IC, SM, moderate cancer stage (Mod), advanced cancer stage (Adv), disease-free survival of IC (DFS_IC), disease-free survival of SM (DFS_SM), disease-free survival of Moderate stage (DFS_Mod), disease progress free of Advanced stage (PFS_Adv), and death. Here, IC included high-grade intraepithelial neoplasia, while moderate stage included stage IB, stage II and stage III. Stage IV was classified as an advanced cancer stage. Overall, IC and SM both constituted the early EC stage, while moderate and advanced stages were identified as the invasive EC stage. Fig.1 summarizes the state transition processes, with the arrows presenting the transition between states.

Individuals aged 40 to 69 years were assumed to be the participants. They were classified as six age groups, separated by five-year intervals (ages 40-44, 45-49, 50-54, 55-59, 60-64, and 65-69 years). Cohort simulation was performed until the cohort age reached 79 years or hypothetical death. A hypothetical cohort with 100,000 assigned for each age group. And three different strategies were assigned for each cohort: (1) non-screening, a
strategy that assuming all the individuals were not screened, patients were diagnosed by clinical symptoms; (2) screening with follow-up for LGIN, a strategy that assuming all the individuals undergo the one-time standard endoscopic screening, patients were identified by the screening. Meanwhile, assuming the LGIN undergo the annual endoscopic surveillance; (3) screening without follow-up, a strategy that assuming all the individuals undergo the one-time standard endoscopic screening, patients were identified by the screening. However, endoscopic surveillance of LGIN individuals was not required. Assuming all the patients identified by the three strategies had the correct diagnosis and adhered to the standardized treatment scenarios.

**Model simulation**

QALY presented the effectiveness, and the incremental cost-effectiveness ratio (ICER) served as the economic evaluating indicator. ICER means the cost per unit of additional effectiveness. The calculation formula was: $\text{ICER} = \frac{\text{Cost}_A - \text{Cost}_B}{\text{QALY}_A - \text{QALY}_B}$. Cost-effectiveness analyses were used for the comparisons between the competing strategies, including “absolutely dominated strategy”, an option that had both more costs and less effectiveness, “extended dominated strategy”, an option that was less costs and less effectiveness than the alternative but had a higher ICER, and “undominated
strategy”, an option that had the cost-effectiveness under the criterion recommended by the WHO[26]. Other outcomes assessed included costs, EC cumulative incidence, and mortality. Moreover, the willingness-to-pay (WTP) was set as three times the gross domestic product per capita (GDP) (USD 77,000) in 2017 in Zhejiang Province in China.

**Parameters and Data Resources**

Cohort initial probabilities

Initial cohorts’ probabilities in non-screening cohorts were calculated by the 2012 age-specific incidence of EC in Zhejiang province, multiplied by the stage distribution by the time of diagnosis that was obtained from the hospital-based retrospective study[27]. Whereas, the screening cohorts were computed by the age-specific detection rate of EC, which was identified by screening from 2010 to 2017 in Zhejiang province, then multiplied by the stage distribution that was distinguished by screening. *Table 1* displays the age-specific incidence and detection rate of EC, while *table 2* addressed the stage distributions.

Transition probability between Markov states

Whereas EC annual incidence was used to distinguish the EC cases and normal people in the non-screening cohorts, the risk ratio (RR) of the EC incidence in population after screening compared to people without
screening was employed to adjust the EC incidence for the screening cohorts [19]. Also, stage distribution by the time at diagnosis was used to identify EC states in both scenarios. For screening scenario, the probabilities that transferred from LGIN to EC states were the EC annual incidence among the LGIN \((\text{table 1})\), multiplied by the stage distribution identified by screening. The calculation of EC incidence among the LGIN was the adjusted incidence according to the risk ratio of the EC incidence in LGIN compared to that of the true healthy population, combined with the detected proportion of LGIN during screening. The risk ratio was 3.66, which was summarized from published papers[8, 10, 28, 29]. No individuals would transfer between the LGIN and EC states under the non-screening scenario. Other transition probabilities between states were gained from various kinds of literature \((\text{table 3})\). The age-specific annual death probabilities for the normal population were defined as the difference between the population death probabilities and EC death probabilities. Population mortality was drawn from the sixth population service survey, while the EC mortality was obtained from the 2012 age-specific EC mortality in Zhejiang Province[27, 30]. The LGIN was considered as the precancerous lesion. The EC-specific 5-year survival was 100% for IC and DFS_IC; therefore, people with LGIN or IC were less likely
to die from EC. Consequently, the mortality for LGIN, IC, and DFS_IC was assumed to be the same as normal (table 1). Death probabilities of SM and invasive cancer were identified from published papers, while we adjusted the mortality risk according to the age (table 3).

Moreover, all the transition probabilities between states were presented as one-year probabilities. The transition between rate and probability was used to compute the transition probabilities from different follow-up periods. First, a one-year rate (r) was calculated by formula $r = \frac{-\ln(1-p)}{t}$; One-year probability (p) was then calculated by formula $p = 1 - \exp(-r)$, where t was the follow-up time[31].

Costs and utilities
Costs were estimated from a social perspective. And it consisted of screening costs, treatment costs, transportation and wage loss of patients and relatives due to the hospital visiting. Screening costs were calculated using the data of the screening program in Zhejiang Province, while treatment costs were extracted from the electronic medical record at Zhejiang Cancer Hospital and the price of medical services in provincial public hospitals in Zhejiang Province[32]. Every patient was assumed to have one accompanying relative. All costs were measured in the 2017 Chinese currency and were changed into US dollars using the purchasing
power parities with 3.506 in 2017[33]. State-specific utilities were extracted from published papers and the results of the screening. A discount rate of 5% was used for both costs and effectiveness [34, 35]. All the items of costs in the study will inflate at the same inflation rate of 4.7%[36]. The total state-specific costs and utilities were displayed in table 4 and table 5.

Sensitivity analysis

Sensitivity analyses for cost-effectiveness screening strategies were conducted. Probabilistic sensitivity analyses were performed to examine the influence of the multiple parameters that varied simultaneously on the outcome. Initial cohort probabilities and death probabilities assumed as Beta distribution, while the discount rate and inflation rate identified as Triangular distribution. Gamma distribution was set for costs. Moreover, Beta and Dirichlet were assigned to transition probabilities. One-way sensitivity analyses were simulated to access the effect of the single parameter changed on the outcome. The following assumption was made. Initial probabilities, state transition probabilities, risk ratios, and health utility were varied by±20% of the base case value, while costs changed by±30% of the base case value. Besides, 0-8% was simulated for the discount rate, and 3.2- 6.2% was used for the inflation rate.

Results
Simulated cumulative EC incidence and mortality

The simulated cumulative EC incidence, in the non-screening group, showed a decreasing trend with increasing age it decreased from 1010.62/10^5 in 40-44 years to 710.26/10^5 in 65-69 years, while in both screening scenarios, it increased first then decreased. In the screening strategy without follow-up, it increased from 711.21/10^5 in 40-44 years to 748.82/10^5 in 50-59 years and then decreased to 696.12/10^5 in 65-69 years. Whereas in the screening strategy with follow-up, it increased from 708.61/10^5 in 40-44 years to 708.81/10^5 in 45-49 years, and then decreased to 576.12/10^5 in 65-69 years. Meanwhile, compared to non-screening, for ages 40-54 years, screening scenarios led to decreasing of simulated cumulative EC mortality, while for ages 55-69 years, screening scenarios resulted in increasing values of simulated cumulative EC mortality. In particular, screening with follow-up more reduced simulated cumulative EC mortality compared to without follow-up. As age increased, the reductions in mortality lessened. For instance, in aged 40-44 years, screening reduced cumulative mortality by 29.00%, while for aged 50-54 years, screening with follow-up reduced cumulative EC mortality by 19.14%, and the non-follow-up strategy reduced mortality by 16.13%.

Incremental Cost-Effectiveness Ratios
The detail results of base-case analyses were displayed in table 6. For aged 40-49 years, the non-screening strategies were absolutely dominated, while for age 50-69 years, the screening scenarios were absolutely dominated. Compared to non-screening, screening with follow-up was the undominated strategy, while screening without follow-up was an extended dominated strategy. Screening with follow-up saved USD 10942.57 and USD 6611.73 per QALY gained for aged 40-44 and 45-49 years separately.

**Sensitivity Analyses**

The results of the probabilistic sensitivity analyses were addressed in figure 2. It explained that at a WTP of three times GDP per QALY, screening with follow-up was the preferred strategy. The outcome of the one-way sensitivity analysis was reported by using the “tornado diagram” (Fig 3), and only the parameters that could cause 99% of cumulative risk on the value of ICER were displayed. The calculated ICER in the tornado diagram compared the screening with follow-up to non-screening strategy. For aged 40-44 years, the changes in model parameters could not affect the cost-effectiveness of screening strategy with follow-up. However, for aged 45-49 years, raising the base cases value of RR to 0.84 and the u_LGIN to 1 could make the screening strategy gained more costs and less QALY.

**Discussion**
This study was the first attempt to examine the cost-effectiveness of the EC screening for the normal population. The data resources of EC incidence, detection rate, and cancer stage distributions alongside data of costs derived from Zhejiang Province were used to calibrate the model parameters. Based on the criterion for cost-effectiveness recommended by WHO[26], this study found that EC screening targeting aged 40-49 years showed the long-term cost-effectiveness. Moreover, this should be done with follow-up because this had shown to enhance the benefits of screening for relatively small additive costs. Additionally, probability sensitivity analysis had already approved that screening with follow-up was the preferred strategy.

One-way sensitivity analyses found that RR value and u_LGIN had the strongest impact on the cost-effectiveness of EC screening. Changing the RR value from 0.70 to 0.84 could make the screening strategy non-cost-effectiveness, which meant that if screening could not cause a significant decreasing of the EC incidence, and then screening could be the dominated strategy or even an absolute dominated strategy, especially for the elderly population. In addition, the study strongly suggested that the endoscopic follow-up study should be conducted comprehensively, which plays a key role in reducing the EC mortality and morbidity. On the one
hand, it could promote the transition of LGIN to normal through lifestyle intervention due to its characteristic of non-stable lesions. On the other hand, it could detect early-stage cancer and treat them early through the follow-up observation. Similarly, the value of $u_{LGIN}$ had a negative association with the cost-effectiveness of screening, increasing the valued of $u_{LGIN}$ could increase the value of ICER, and then decrease the screening benefits. LGIN is the precancerous lesions of EC, which has a considerable higher risk of developing EC compared to normal people. And the mean of the screening detection rate of LGIN was 6.27%[37]. One of the main purposes of EC screening is to identify those population, finally to reduce the burden caused by EC through monitoring them. The study addressed that if increasing the value of $u_{LGIN}$ to 1 that could make the screening targeting 45-49 years becomes an absolutely dominated strategy. However, EC screening could result in an unequivocal psychological impact and mental stress on the true positive detected that cause a certain decrease in health status. Therefore, the value of the $U_{LGIN}$ is most unlikely to be equal to 1, which also proved the cost-effectiveness of screening targeting on 45-49 years. Compared to non-screening, two past studies had addressed that EC screening was cost-effectiveness in high-risk areas in China. Wei WQ found
that the ICER ranged from 11.5 USD/QALY to 34.0 USD/QALY for aged 40-50 years, while Hui C explained that screening costs USD 1027 and USD 14203.2 per QALY gained for higher-risk and average-risk population, respectively[38, 39]. However, our study found screening for 50 years and onward was less likely to get more QALYs. It was difficult to compare the results of this study with those of others, due to variations in experimental design factors, including Markov disease progress states, the targeted age ranges of interest, data resources, discount rate, and control groups. First, this study expands on previous models by additionally considering postoperative states for better align with the natural progression of EC by assessing disease-free survival and progress-free survival states for early, moderate, and late EC stage. Second, the past study had assessed the progression of EC from the starting point ages of 40, 45, and 50 years of age up to 70 years of age (WQ Wei), while Chin Hur had assessed individuals from 50 years up to 80 years. More importantly, only one non-screening cohort was applied for all age brackets in Wei WQ’s study. Nevertheless, in this study, each age bracket was compared to its non-screening group. The data resources in both of the past studies were collected from the Henan province, which was a high-risk province of EC with an incidence of 73.2/10^5 [40]. Distinctively, the data in our study were drawn from the Zhejiang
province, where was marked by the incidence of EC that was lower than the national level (ZJ: 12.93/10^5 vs. CH: 21.17/10^5) in 2012[27, 41]. Importantly, one-way sensitivity analysis approved that an increase in EC incidence was correlated with a decrease of ICER. Thus, the benefits reflected in the Zhejiang context suggested that EC screening with follow-up might have significant potential in a national context.

In addition, our study did not discuss the economic value of EC screening on elderly population aged more than 70 years, mainly because the study only simulated the population-based screening strategy targeting on aged 40-69 years that was conducted from 2010 to 2017 in Zhejiang Province which was advocated by the national screening guidelines. From 2016, the screening age was recommended to extend to 74 years in urban cancer screening program which was performed followed a distinctive screening procedure[37]. Whereas our study assumed all the individuals undergo an endoscopic screening, the urban endoscopic screening focused on the high-individual populations who were identified by the threshold of the risk function that was computed from the health risk appraisal questionnaire survey. Though our study projected population-based EC screening targeting on those 50 years and onward was not cost-effective, the EC screening targeting on those more elderly population based on the health
risk assessment maybe have the economic value. However, it was not argument very well until now. Further study should be done estimating the cost-effectiveness of EC screening strategy for high-risk individuals and the sensitivity and specificity of the health risk appraisal model.

Some limitations should be considered in the study when illustrating the outcomes. First, this study was conducted based on the Markov model; it could simulate the long-term costs and effectiveness of screening strategies. However, it could not provide accurate evaluation data like randomized clinical controlled trials. Then, the hidden costs were not included in the study, so it could underestimate the total expected costs. However, it could not affect the evaluation of the cost-effectiveness of EC screening, since the incremental cost-effectiveness ratio was the indicator. Besides, some model parameters were collected from Zhejiang province, like the costs, the EC incidence, and mortality. However, the sensitivity analyses approved that the robustness of the model. Moreover, the sensitivity and specificity of the screening test were not studied in the study, since the screening procedures used Lugol’s staining and biopsy are commonly regarded as the gold standard for EC diagnosis [42, 43].

**Conclusion**

Compared to non-screening, the EC screening with follow-up targeting aged
40-49 years showed long-term cost-effectiveness in China, while the screening for ages 50 years and onward were absolutely dominated strategy. The EC incidence and mortality in Zhejiang province were comparable with the national level. Meanwhile, probability sensitivity analysis had demonstrated the robust of the model. Consequently, the results of the study could present the cost-effectiveness of national EC screening. More importantly, the government and policymaker should take comprehensive measures to improve the opportunity EC screening, to manage the behavioral risk exposure and promote healthy lifestyles. In addition, EC still poses a huge threat on worldwide population; building a solid global EC screening guideline and cost-effectiveness analysis are more crucial in nowadays. Hopefully, much work on the topic of global EC screening could be well argument in the future.

**List of abbreviations**

EC: esophageal cancer; LGIN: Low-grade intraepithelial neoplasia; IC: intraductal carcinoma

SM: submucosal cancer; Mod: moderate cancer stage; Adv: advanced cancer stage; IC_DFS: disease-free survival state of IC; SM_DFS: disease-free survival state of SM; Mod_DFS: disease-free survival state of Moderate stage; Adv_PFS: disease progress free state of Advanced stage; QALY:
Quality-adjusted life-years; ICER: incremental cost-effectiveness ratio.

**Declarations**

**Ethics approval and consent to participate**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Consent for publication**

The informed consent was not performed, because the study does not contain human participants.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests

**Author Contributions:** Yuanyuan LI analyzed the data and wrote the manuscript. Lingbin Du interpreted and analyzed the data. Youqing Wang collected the data and funding acquisition. Yuxuan Gu drafted the work. Xiaoqian Hu performed software analysis. Xuemei Zhen visualized the draft. Xueshan Sun revised the draft. Hengjin Dong designed the work and reviewed the draft. All authors read and approved the final manuscript.

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Table 1 Age-specific EC incidence and detection rate, and mortality for normal people

| Age     | EC annual incidence | EC annual incidence among LGIN | EC detection rate | Mortality for normal people |
|---------|---------------------|--------------------------------|-------------------|-----------------------------|
| 40-44   | 1.36                | 4.96                           | 16.92             | 122.41                      |
| 45-49   | 4.90                | 17.68                          | 70.65             | 184.60                      |
| 50-54   | 9.93                | 34.95                          | 193.45            | 343.55                      |
| 55-59   | 25.41               | 84.00                          | 518.59            | 475.18                      |
| 60-64   | 35.48               | 108.02                         | 976.17            | 738.42                      |
| 65-69   | 46.25               | 118.02                         | 2072.48           | 1262.28                     |
| 70-74   | 63.97               | 163.22                         | -                 | 2380.26                     |
| 75-79   | 64.45               | 164.36                         | -                 | 4094.67                     |

Note: One-way sensitivity analysis values±20%; Beta distribution assumed for probability sensitivity analysis.
Table 2 Stages distributions of EC under the screening and non-screening scenarios

| Stage | Non-screening [%] | screening [%] | Distribution |
|-------|-------------------|--------------|--------------|
|       | Proportion        | SA range     | Proportion   | SA range     |               |
| IC    | 3.65              | 2.92 ~ 4.38  | 88.24        | 70.59 ~ 100  | Dirichlet     |
| SM    | 4.93              | 3.94 ~ 5.92  | 2.52         | 2.02 ~ 3.02  |               |
| Mod   | 66.06             | 52.85 ~      | 6.72         | 5.38 ~ 8.06  |               |
| Adv   | 25.36             | 20.29 ~      | 2.52         | 2.02 ~ 3.02  |               |

Note: SA: One-way sensitivity analysis.

Table 3 Other parameters in the Model

| Parameters          | Inputs | SA Range       | Distribution | Reference |
|---------------------|--------|----------------|--------------|-----------|
| Transition probability |        |                |              |           |
| Normal to LGIN      | 0.0000 | —              | —            | —         |
| LGIN to normal      | 0.1427 | 0.1142 ~ 0.1712| Beta         | [44-50]   |
| IC to DFS_IC        | 0.9363 | 0.7490 ~ 0.9363| Beta         | [21]      |
| IC progress         | 0.0534 | 0.0427 ~ 0.0641| Beta         | [21, 51-53]|
| SM proportion       | 0.2143 | 0.1714 ~ 0.2572| Dirichlet    | Screening |
| Mod proportion      | 0.5714 | 0.4571 ~ 0.6857| Dirichlet    |           |
| Adv proportion      | 0.2143 | 0.1714 ~ 0.2572| Dirichlet    |           |
DFS_IC to IC 0.0069 0.0055 ~ 0.0083 Beta [54]
DFS_IC progress 0.0268 0.0214 ~ 0.0322 Beta [55]
SM proportion 0.5556 0.4445 ~ 0.6667 Dirichlet [55]
Mod proportion 0.4444 0.3555 ~ 0.5333 Dirichlet [55]
Adv proportion 0.0000 0.0000 ~ 0.0000 Dirichlet [55]
SM to DFS_SM 0.9051-d_nor 0.7241 ~ 1.0000 Beta [56]
SM progress 0.7386 0.1109 ~ 0.1663 Beta [57, 58]
Mod proportion 0.7562 0.6050 ~ 0.9074 Beta [52, 55]
Adv proportion 0.2438 0.1950 ~ 0.2926 Beta [52, 55]
DFS_SM to SM 0.0393 0.0314 ~ 0.0472 Beta [56]
DFS_SM progress 0.0883 0.0706 ~ 0.1060 Beta [57]
Mod proportion 0.7562 0.6050 ~ 0.9074 Beta [52, 55]
Adv proportion 0.2438 0.1950 ~ 0.2926 Beta [52, 55]
Mod to DFS_Mod 0.5930-d_nor 0.4744 ~ 0.7116 Beta [67]
Mod to Adv 0.6031 0.0254 ~ 0.0380 Beta [68]
DFS_Mod to Mod 0.8452 0.0340 ~ 0.0510 Dirichlet [68]
DFS_Mod to Adv 0.0097 0.0078 ~ 0.0116 Dirichlet [68]
Adv to PFS 0.0750 0.1574 ~ 0.2360 Dirichlet [69]
PFS progress 0.7002 0.5602 ~ 0.8402 Dirichlet [70]

EC state-specific death probability (age≤65)
SM 0.0994 0.0795 ~ 0.1193 Beta [71]
DFS_SM 0.0633 0.0506 ~ 0.0760 Beta [71]
Mod 0.2988 0.2390 ~ 0.3586 Beta [58]
DFS_Mod 0.1902 0.1522 ~ 0.2282 Beta [58]
Adv 0.4613 0.3690 ~ 0.5536 Beta [70, 72]
PFS 0.4303 0.3442 ~ 0.5164 Beta [70, 72]

Risk ratios of EC death probability among patients aged more than 65 years compared to aged less than 65 years
RR_SM / ±30% Lognormal [73]
RR_DFS_SM / 1.30 1.20 ~ 1.50 Lognormal [73]
RR_Mod / 1.20 1.10 ~ 1.30 Lognormal [73]
RR_DFS_Mod / 1.16 1.10 ~ 1.20 Lognormal [73]
RR_Adv / 1.16 1.10 ~ 1.20 Lognormal [73]

Note: SA was one-way sensitivity analysis; d_nor: Mortality for normal people, see table 1.

Table 4 State-specific costs estimates for esophageal cancer (USD)

| State    | Screening costs | Treatment-related costs | SA range | Distribution |
|----------|-----------------|-------------------------|----------|--------------|
| Normal   | 61.8            | 0.0                     |          |              |
| LGIN     | 61.8            | 149.5                   |          |              |
| IC       | 61.8            | 17561.9                 |          |              |
| SM       | 61.8            | 20781.6                 | ±30%     | Gamma        |
| Mod      | 61.8            | 25217.4                 |          |              |
| Adv      | 61.8            | 23702.5                 |          |              |
| DFS_IC   | 0.0             | 837.5                   |          |              |
| DFS_SM   | 0.0             | 1580.0                  |          |              |
### DFS_Mod

| Death | 0.0 | 0.0 |

**Note SA: One-way sensitivity analysis values.**

### Table 5 State-specific utilities for esophageal cancer

| State    | Mean  | SD    | SA range         | Distribution | Reference |
|----------|-------|-------|------------------|--------------|-----------|
| Normal   | 1.000 | 0.000 | 0.000 ~ 0.000    | Beta         | -         |
| LGIN     | 0.941 | 0.089 | 0.753 ~ 1.000    | Beta         | 79        |
| IC       | 0.852 | 0.029 | 0.682 ~ 1.000    | Beta         | *         |
| DFS_IC   | 0.940 | 0.100 | 0.752 ~ 1.000    | Beta         | 80        |
| SM       | 0.693 | 0.310 | 0.554 ~ 0.832    | Beta         | *         |
| DFS_SM   | 0.870 | 0.150 | 0.696 ~ 1.000    | Beta         | 80        |
| Mod      | 0.780 | 0.140 | 0.624 ~ 0.936    | Beta         | 80        |
| DFS_Mod  | 0.810 | 0.170 | 0.648 ~ 0.972    | Beta         | 80        |
| Adv      | 0.720 | 0.180 | 0.576 ~ 0.864    | Beta         | 80        |
| PFS_Adv  | 0.740 | 0.190 | 0.592 ~ 0.888    | Beta         | 80        |
| Death    | 0.000 | 0.000 | 0.000 ~ 0.000    | Beta         | -         |

**Note: *results of quality-related life survey by screening; SA One-way sensitivity analysis values;**

### Table 6 Summary of Cost-effectiveness analyses among different screening strategies for EC

| Age | Strategy | Costs (USD: million) | QALY (Thousa nd years) | ICER (USD/QALY) | Cumulative Incidence (1/10⁵) | Cumulative Mortality (1/10⁵) |
|-----|----------|-----------------------|------------------------|-----------------|-----------------------------|-----------------------------|
| 40-44 | Non_scr | 40.02 | 1655.24 | _ | absolutely dominated | 1010.62 | 776.76 |
| | Scr_nfol | 35.14 | 1655.59 | -14007.6 | extended dominated | 711.21 | 555.45 |
| | Scr_fol | 35.17 | 1655.69 | -10942.5 | undominated | 708.61 | 553.32 |
| 45-49 | Non_scr | 40.63 | 1557.40 | _ | absolutely dominated | 1010.04 | 778.32 |
| | Scr_nfol | 38.65 | 1557.31 | 21808.7 | extended dominated | 719.08 | 587.97 |
| | Scr_fol | 38.78 | 1557.68 | -6611.73 | undominated | 708.81 | 579.22 |
| 50-54 | Non_scr | 40.52 | 1437.30 | _ | absolutely dominated | 994.97 | 766.49 |
| | Scr_nfol | 44.85 | 1436.15 | -3753.98 | absolutely dominated | 726.70 | 642.84 |
| | Scr_fol | 45.29 | 1437.07 | -20461.8 | absolutely dominated | 701.17 | 619.77 |
| 55-59 | Non_scr | 39.83 | 1295.22 | _ | absolutely dominated | 962.42 | 746.15 |
| | Scr_nfol | 58.84 | 1291.50 | -5111.10 | absolutely dominated | 748.82 | 767.25 |
| | Scr_fol | 60.30 | 1293.66 | -13111.8 | absolutely dominated | 691.03 | 709.45 |
| 60-64 | Non_scr | 35.20 | 1120.73 | _ | absolutely dominated | 857.94 | 649.89 |
| | Scr_nfol | 70.82 | 1114.21 | -5458.94 | absolutely dominated | 720.35 | 829.78 |
| | Scr_fol | 74.17 | 1117.47 | -11949.7 | absolutely dominated | 637.03 | 738.52 |
| 65-69 | Non_scr | 28.49 | 908.42 | _ | absolutely dominated | 710.26 | 512.38 |
| | Scr_nfol | 95.20 | 896.88 | -5780.43 | absolutely dominated | 696.12 | 952.77 |
| | Scr_fol | 103.19 | 901.82 | -11311.1 | absolutely dominated | 576.12 | 806.34 |

**Note: Scr_fol: screening with follow-up; Scr_nfol: screening without follow-up; Non_scr**