Age at Initiation and Frequency of Screening to Prevent Esophageal Squamous Cell Carcinoma in High-risk Regions: an Economic Evaluation

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ABSTRACT

The aim of this study was to identify the economic screening strategies for esophageal squamous cell carcinoma (ESCC) in high-risk regions. We used a validated ESCC health policy model for comparing different screening strategies for ESCC. Strategies varied in terms of age at initiation and frequency of screening. Model inputs were derived from parameter calibration and published literature. We estimated the effects of each strategy on the incidence of ESCC, costs, quality-adjusted life-year (QALY), and incremental cost-effectiveness ratios (ICERs). Compared with no screening, all competing screening strategies decreased the incidence of ESCC from 0.35% to 72.8%, and augmented the number of QALYs (0.002-0.086 QALYs per person) over a lifetime horizon. The screening strategies initiating at 40 years of age and repeated every 1–3 years, which gained over 70% of probabilities that was preferred in probabilistic sensitivity analysis at a $1,151/QALY willingness-to-pay threshold. Results were sensitive to the parameters related to the risks of developing basal cell hyperplasia/mild dysplasia. Endoscopy screening initiating at 40 years of age and repeated every 1–3 years could substantially reduce the disease burden and is cost-effective for the general population in high-risk regions.

Introduction

Esophageal cancer is ranked 11th worldwide and sixth China in all neoplasms (1). About 90% of the annual 456,000 incident cases were esophageal squamous cell carcinoma (ESCC). The risk factors of ESCC are multifactorial and strongly population-dependent, such as the smoking cigarettes and heavy alcohol consumption in the Western population, and the high-temperature foods, diet, and oral health and the microbiome in Eastern population (1). Because of the late stage at diagnosis for most patients and limited treatment options, the case fatality rate of ESCC is high and the prognosis is poor (2). Thus, identifying primary or secondary prevention strategies for reducing the disease burden of ESCC is a public health priority. In the context of high-risk regions of ESCC with more than 100 cases per 100,000 population annually, such as China, where about 40% of the world's disability-adjusted life-years (DALY) related to esophageal cancers occur (1). Implementation of ESCC screening program may provide a feasible option to reduce the disease burden, although there are no evidence-based guidelines for screening program. One recent study showed that lifetime once endoscopic screening and intervention significantly reduced the incidence (3.35% vs. 5.05%) and mortality (4.17% vs. 5.92%) of ESCC compared with the control group (3). However, this study did not consider the significant differences existed between the two groups at baseline for some risk factors.

One major weight for decision makers is the economic outcomes of this screening program. Several health economic analyses reported results of endoscopy screening from the Chinese perspective, which showed endoscopic screening might be cost-beneficial in high-risk areas of China (4–6). However, these reports included limited numbers of potential screening scenarios, furnishing a paucity of evidence related to the outcomes of screening intervention for policymakers, and may have had inadequate numbers of competing alternatives to generate correct information. Furthermore, the decision model in previous reports did not consider the impact of undetected cancer and the tumor-node-metastasis (TNM) stage of cancer (4–7). Screening programs would be helpful for diagnosing undetected cancer in its early stage, which might reduce the mortality caused by ESCC.

At the inception of our previous ESCC policy model, the goal of this analysis was to evaluate the health benefits (such as the reduction of ESCC incidence and life-years gained) and economic outcomes of many potential competing screening

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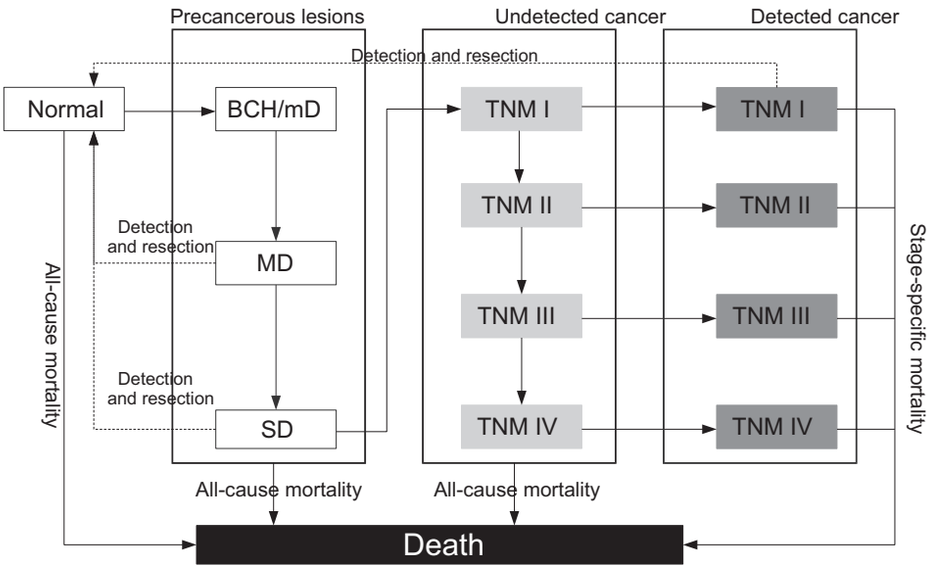

Figure 1.
Schematic of the model structure. BCH, basal cell hyperplasia; mD, mild dysplasia; MD, moderate dysplasia; SD, severe dysplasia.

scenarios for the Chinese population in high-risk regions, overcoming some of the weakness of previous reports.

Materials and Methods

Analytic overview

Adopting our previous reported mathematical health policy model of ESCC natural history among Chinese population in high-risk region (8), we projected the health and economic outcomes related to the following secondly preventive strategies: (i) no screening, and (ii) endoscopic-based screening. For each competing alternative, we examined screening examination performance. The model structure were showed in **Fig. 1**. Costs were based on published estimates from the perspective of Chinese health care. Lifetime probabilities of precancerous lesions, ESCC, and cause-specific deaths, expected life years and quality-adjusted life year (QALY) and lifetime costs were model outputs. Incremental cost-effectiveness ratios (ICER) was used for assessing the relative performance of each strategy, which was expressed as the marginal cost per marginal QALY gained. Costs and QALY were annually discounted at 5%. All costs are reported in 2017 U.S. dollars.

Because of no consensus on the willingness-to-pay threshold for disease prevention, we present our health economic results in the Chinese context of the recently recommended threshold of $1,151 per QALY (9).

Natural history simulation model

The model tracks the development of ESCC through a sequence of precancerous lesions and eventually invasive cancer. The details about model's structure, underlying assumptions, and calibration are described in our recent published report (8). In brief, the model tracks the life histories of a birth cohort from 15-year-old to death. As each simulated person ages, precancerous lesions may incur. These precancerous lesions can progress from basal cell hyperplasia (BCH)/mild dysplasia (mD), to moderate dysplasia (MD), to severe dysplasia (SD). SD can progress into undetected cancer, which may transit through TNM stages I–IV, which may be diagnosed due to symptoms. Stage-specific mortality rates after disease diagnosis were predicted by the TNM stage at diagnosis. Those without diagnosed ESCC would incur all-cause mortality, which was derived from life-table (10). This parameterized mathematical model Model outcomes had sufficient calibration fit to the calibration targets, which defined a total of 34 targets (18 precancerous, 12 ESCC, and 4 proportions of ESCC TNM stage; ref. 8). In addition, the verification analyses showed reasonable external consistency between the model-predicted effectiveness of ESCC screening and the reported data from clinical trials (3, 11).

To protect the consistency of model outputs with the reported epidemiologic data, the ESCC health policy model was empirically calibrated to the age- and stage-specific incidence of ESCC and the age-specific prevalence and the multiplicity distribution of precancerous lesions as observed in the Chinese high-risk regions (Yanting, Cixian, and Yancheng County; refs. 5, 12–14). The calibrated model inputs were shown in **Table 1**.

Strategies

We simulated following 36 competing scenarios: no screening (reference strategy), and endoscopy screening with Lugol's iodine starting at 30, 35, 40, 45, 50, 55, and 60 years old with every 1, 2, 3, 5 and 10 year or lifetime once. The sensitivity and specificity of endoscopy screening were derived from the previous reports (4, 15). Adherence to endoscopy screening for ESCC in Chinese real-world practice was about 59.31% (4–6).

Table 1. Model inputs.

Parameter	Expected value (SD)	Range	Source
Clinical data			
Normal → BCH/mD*	β0 = −8.96 (0.461)	−10.01 to −7.73	(8)
	β1 = 0.20481 (0.01815)	0.15 to 0.24	(8)
	β2 = 0.00002 (0.000004)	0.00001–0.00003	(8)
BCH/mD → MD*	α0 = −3.359 (0.171)	−3.34 to -2.49	(8)
	α1 = 0.03668 (0.0095)	0.03–0.08	(8)
MD → SD	15.38% (2.18%)	8.43%–18.25%	(8)
SD → Undetected ESCC (TNM I)	20.94% (2.96%)	10.1%–23.56%	(8)
Undetected ESCC (TNM I) → Undetected ESCC (TNM II)	46.65% (7.8%)	24.56%–58.35%	(8)
Undetected ESCC (TNM II) → Undetected ESCC (TNM III)	54.87% (10.27%)	28.22%–77.16%	(8)
Undetected ESCC (TNM III) → Undetected ESCC (TNM IV)	32.31% (4.72%)	11.76%–32.51%	(8)
Undetected ESCC (TNM I) → Detected ESCC (TNM I)	3.86% (0.9%)	1.89%–5.68%	(8)
Undetected ESCC (TNM II) → Detected ESCC (TNM II)	34.32% (6.65%)	16.37%–49.1%	(8)
Undetected ESCC (TNM III) → Detected ESCC (TNM III)	56.79% (12.15%)	27.3%–81.89%	(8)
Undetected ESCC (TNM IV) → Detected ESCC (TNM IV)	89.1% (11.84%)	44.62%–100%	(8)
Disease-specific mortality (ESCC TNM II)	15.15% (3.79%)	11.36%–18.93%	(12, 14)
Disease-specific mortality (ESCC TNM III)	35.97% (8.99%)	26.98%–44.96%	(12, 14)
Disease-specific mortality (ESCC TNM IV)	56.47% (14.12%)	42.35%–70.59%	(12, 14)
Risk ratio of ESCC	1 (0.14)	0.68–1.31	Estimated
Sensitivity of endoscopy screening with Lugol's iodine	96% (1.79%)	92%–99%	(4, 15)
Specificity of endoscopy screening with Lugol's iodine	90% (10.46%)	59%–100%	(4, 15)
Adherence to endoscopy screening	59.31% (5.46%)	48.62%–70%	(4–6)
Curative rate of mucosal resection	85.6% (12.76%)	50%–100%	(18)
Recurrence rate of ESCC after mucosal resection per year	4.4% (1.1%)	3.3%–5.5%	(19)
Cost data			
Screening per unit	19.77 (0.42)	18.9–20.55	(4–6)
Management of ESCC (TNM I) per patient	6,154 (245)	5,674–6,634	(13)
Management of ESCC (TNM II) per patient	7,381 (125)	7,136–7,627	(13)
Management of ESCC (TNM III) per patient	6,917 (106)	6,710–7,124	(13)
Management of ESCC (TNM IV) per patient	6,611 (174)	6,269–6,953	(13)
Mucosal resection per unit	621 (24)	575–668	(4–6)
Utility data			
Normal/No detected precancerous lesions or ESCC	1	NA	(21)
Detected precancerous lesions	0.99 (0.051)	0.8–1	(21)
Diagnosed ESCC (TNM I & II)	0.9 (0.051)	0.8–1	(21)
Diagnosed ESCC (TNM III & IV)	0.34 (0.172)	0–0.675	(21)
ESCC after ablative therapy or esophagectomy	0.97 (0.051)	0.8–1	(21)

*The detailed information showed in appendix text and our previous report.
Abbreviations: NA, not applicable.

ESCC secondly prevention with endoscopy screening will change some of the simulated disease course: some cancers will be averted by the detection and removal of precancerous lesions; other cancers will be diagnosed in an earlier stage with a more favorable prognosis. On the basis of the current evidences (2, 11, 16, 17), we assued all diagnosed high-raged dysplasia (MD and SD) would be removed by endoscopic mucosal resection, and those curative people were assumed to jump into the normal health state. The curative rate of mucosal resection was 85.6% (18). Asymptomatic undetected cancer received medical treatment. Because patients with ESCC tend to have a high incidence of metachronous ESCC, the model adopted a 4.4% annual incidence of newly diagnosed tumor after the mucosal resection for TNM stage I disease (19). By comparing all life course with screening with the corresponding life course without screening, the ESCC health policy model quantifies the health outcomes of screening, as well as the related costs.

Risk of ESCC

Because the majority of ESCC occurs in the "Asian Esophageal Cancer Belt" and geographic distribution varies greatly (1), we estimated the range of risk ratios of age-standardized incidence in three Chinese endemic regions (Yanting, Cixian, and Yancheng County) against their average incidence. Because the BCH/mD was the first step of developing ESCC from the normal esophagus and the prevalence of BCH/mD was positive related with the incidence of ESCC (11, 17, 1, 20), we assumed that the risk of ESCC could be crudely predicted by the risk of BCH/mD based on the expert opinion. On the basis of this approach, the predicted incidence might be well matched the corresponding observed values (Supplementary Fig. S1). So the estimated risk ratios of ESCC among different regions would be used for sensitivity analysis by applying them in adjusting the risk of BCH/mD (**Table 1**). The validated results could found in Supplementary Fig. S1.

Costs and utilities

Table 1 summarized the costs and utility estimates used in the analysis. Costs were calculated from a healthcare perspective and direct medical were considered. Costs related to screening were derived from the previous literatures (4–6), which included the endoscopic examination, histologic analysis, disposable supplies, equipment and facilities, etc. Costs related to ESCC management stratified by TNM stages were extracted from a hospital-based multicenter retrospective survey, which included 14,967 patients with esophageal cancer in 37 hospitals in 13 provinces/municipalities across China as a part of the Cancer Screening Program of Urban China (13). In the analysis, we assumed that a small (psychologic) loss in quality of life would be incurred for receiving a diagnosis of precancerous lesions, and larger losses in quality of life after a diagnosis of ESCC and treatment. The utility estimates were extracted from an internationally literature (21), which reported the utility scores related to esophageal adenocarcinoma that was assumed to be comparable with ESCC based on the expert opinion.

Sensitivity and uncertainty analysis

We carried out one-sensitivity analyses on all parameters to test how results changed across plausible ranges shown in **Table 1**. In addition, a probabilistic sensitivity analysis (PSA) was also conducted by using 1,000 second-order Monte Carlo iterations, in which model inputs, including cost, utilities, and natural history parameter sets, were simultaneously varied by sampling from their statistical distributions (i.e., gamma distribution for costs, normal distribution for log RRs and health resource utilization, and beta distribution for utilities, probabilities, and proportions). Cost-effectiveness acceptability curves based on the results of PSA was produced to present the probability of the cost-effective iterations at various willingness-to-pay thresholds.

Results

Clinical benefits

The health outcomes of 36 potential competing strategies illustrated in Supplementary Table S1 and Supplementary Figs. S2 and S3. For a hypothetical birth cohort of the 15-year old population in endemic regions, the projected lifetime risk of ESCC was 13.75% with 59.52 life years (Supplementary Table S1). When annual screening and every 5-year program were implemented, the greatest relative reduction in ESCC lifetime risk was 72.8% and 40.7% with the screening starting at 30 years old with 1.18 and 0.70 gain life years, where the proportion of detected TNM I ESCC changed from 1.14% in no screening to 0.88% and 1.33%, respectively. When every 3- and 10-year screening program were implemented, the greatest relative in ESCC lifetime risk was 54.5% and 27.3% with the screening starting at 35 years old with 0.89 and 0.46 gain life years, where the proportions of detected TNM I ESCC were 1.29% and 1.40%, respectively. When lifetime once screening program was implemented, the greatest relative reduction in ESCC lifetime risk was 12.08% with the screening at 60 years old with 0.16 life years, where the proportions of TNM I were 1.35%. The gain in life years in all lifetime once screening strategies was greatest for screening at 50 years (0.21 life years). The number of lesions needed to prevent a cancer is varid from 1.19 in lifetime once at 30 years strategy to 1.67 in 60 years initiation every 3 years strategy (Supplementary Fig. S4).

Cost and cost-effectiveness analysis

Discounted per-person costs were much higher in the annual screening strategies initiation at early age (30, 35, and 40 years old) and lifetime once screening strategies initiation at 30 and 35 years old than in the no screening strategy (Supplementary Table S1), mainly because the additional cost of the endoscopic examination were higher than the decrement of managing ESCC (Supplementary Table S2). Per-person costs for other screening strategies were lower than in the no screening strategy because the future additional medical costs related to the management of ESCC of the screening strategies against no screening strategy were lower than the additional cost of endoscopic examination.

As compared with no screening in the base case, annually screening initiation at 30 years old was more expensive than other strategies but provided more health outcomes (Supplementary Table S1), which cost an additional $54.56 per person and provided an additional 0.09 QALYs per person; the corresponding ICERs were $638 per QALY gained. The analysis also presented a cost-effective frontier making up of following strategies: no screening, initiation at 60, 55, and 50 years old every 5 years, initiation at 50, 45, and 40 years old every 3 years, and initiation at 45, 40, 35, and 30 years old every 1 year (**Fig. 2**). The corresponding ICERs by comparing before and after strategies in the sequence of frontier line were $-472, −376, −305, −216, −112, 248, 1024, 1,379, 4,351, and 13,083/QALY, respectively. Screening strategies outside of the cost-effective frontier were dominated or extend dominated.

One-way sensitivity analysis demonstrates that the result was most sensitive to the several model inputs (screening initiation at 40 every 3 years vs. no screening), including the age-dependent (15–40 years old), baseline risk of developing BCH/mD from the normal esophagus, and the curative rate of mucosal resection (**Fig. 3**). Other parameters, such as the specificity of endoscopy screening have a moderate impact on the model outcomes. However, none of the adjustments of these parameters could push the ICERs to be higher than the threshold ($ 1,151/QALY).

As illustrated in **Fig. 4**, the probabilities of screening initiation at 40 every 1 and 3 years to be efficiently cost-effective were about 34% and 38%, respectively, according to the cost-effectiveness acceptability curve at a willingness-to-pay threshold of $1,151/QALY.

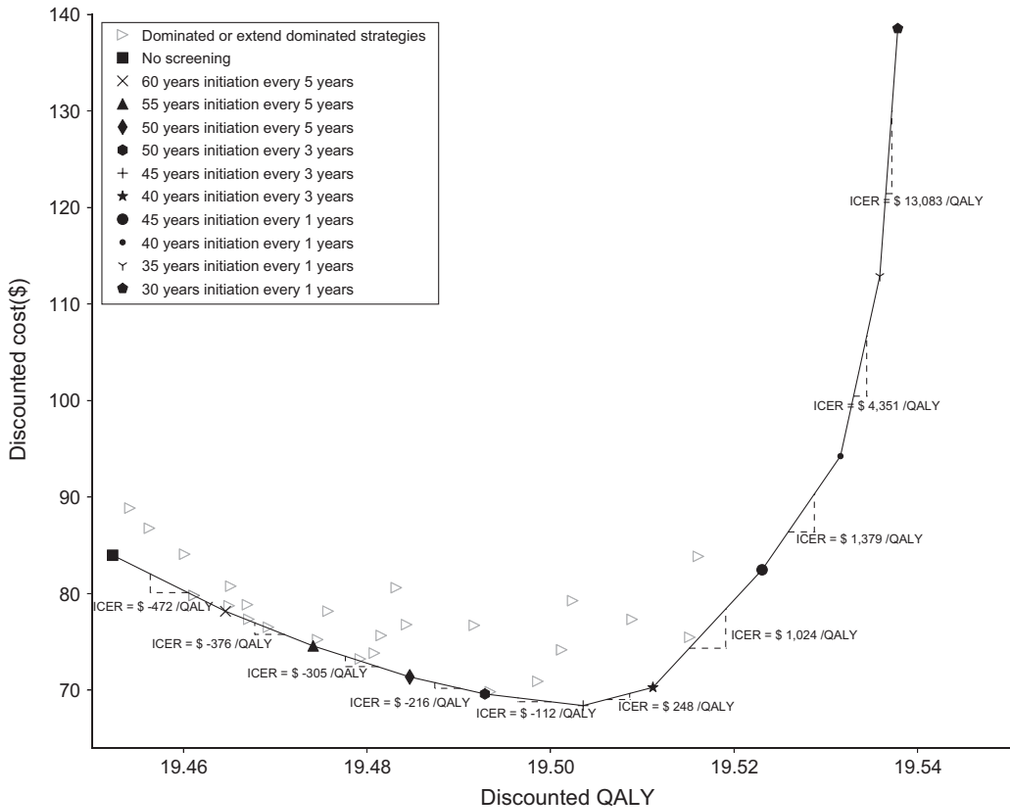

Figure 2.
Cost, QALY, and cost-effective frontier of the 35 potential screening strategies and no screening.

Discussion

Our analysis found that the lifetime risk of ESCC in high endemic regions was over than 13%, which is even higher than the lifetime risk of breast cancer (12%) in U.S. women (22). Therefore, the implementation of a screening program is umnet for reducing the disease burden related to ESCC. We reveal that a range of simulated screening strategies could decrease the rate of ESCC and deaths in high endemic regions compared with no screening. For example, if screening is initiated at 40 years of age and repeated every 3 years, nearly 8 ESCC per 100 people aged 40 years could be averted over 60 years. In the same instant, the strategy can be expected to yield additional 6.59 QALYs per 100 people. When lifetime once screening is initiated at 55 years of age, the risks of cumulative incidence of ESCC could be reduced about 22.3%, which is comparable with a recent population-based prevention study that reported the risk of ESCC could be reduced 29.6% in population aged 40–69 years living in a Chinese high endemic region (3). One recent study also found that screening six times between 40 and 70 years at a 5-year interval produced the greatest health benefit (0.15 life years) and leaded to the highest net present values (international dollar I$ 989) per patient with a benefit–cost ratio of 3.06 in comparison with no screening, which indicated endoscopic screening is cost-beneficial in high-risk areas of China (4). However, it should be noted the health outcomes reported by Yang and colleagues were lower than ours, which might be explained by the different study and model design. The model outcomes were also moderately sensitive to the the curative rate and the specificity of endoscopy screening. This finding indicates that new mucosal dissection and screening techniques should be developed.

The incidence of ESCC varies widely by region, even among the regions in the"Asian Esophageal Cancer Belt" (23). For example, Data from Cancer Incidence in Five Continents Vol. X showed the age-standardized incidence rates of esophageal cancer in three Chinese high-risk regions can considerably be varied from 100.6 in Yanting County to 192.7 in Cixian County per 100,000 (24). One-way sensitivity analysis showed the same screening strategy imitating at 30 years of age every 3 years could save more money in Cixian County than Yanting County. This finding indicated that screening with endoscopy was much more cost-effective among higher-risk regions than those with relatively lower risk. Therefore, the current health policy that implementing a screening program with endoscopy in Chinese endemic regions could be implied by our evidence.

Although the results are highly robust, our economic results were sensitive to several of model inputs. When the risks of developing BCH/mD from normal heath state were decreased,

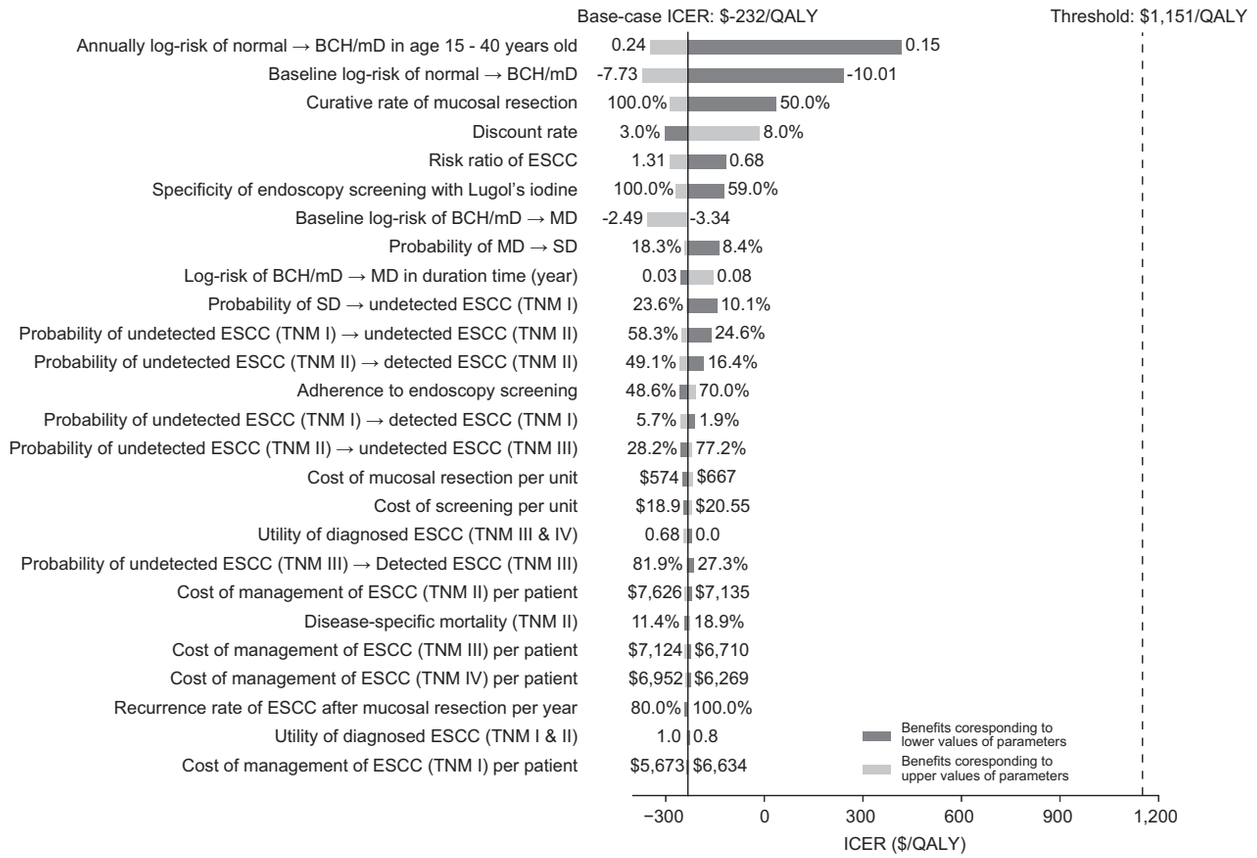

Figure 3.
One-way analyses of screening initiation at 40 every 3 years compared with no screening.

including the age-dependent (15–40 years old) and baseline risks, the ICERs of screening initiation at 40 every 3 years compared with no screening rose considerably. This results strengthened the above finding that the endoscopy screening program needs to be tailored based on the local or individual's risk. One recent study developed a Chinese population-based model to identify individuals at high risk for ESCC, which included several risk factors, such as age, cigarette smoking, use of coal or wood, body mass index, irregular eating habits, and intake of high-temperature foods. The receiver operating characteristic curve value was 0.795 in younger than 60 years and 0.681 in older than 60 years. As reported by the author, about 16.6% endoscopies could be avoided if the risk was implemented in the screening program (25). It could be expected that such a model would be helpful for tailoring the screening the program, although further validation study is needed.

Strengths of this study are worth highlighting. To our knowledge, it is the first study that evaluated the economic outcomes of different screening strategies for ESCC in high-risk regions through the validated economic modeling with the synthesized latest evidence. Compared with previously published reports (4, 5, 5), the current study not only reported the cost-effectiveness of a lifetime once screening strategy also extensively evaluated the screening intensity of screening programs, including the screening initiation age from 30 to 60 years and intervals from 1 year to lifetime once, which might provide more potentially competing strategies for policy-makers. Second, because the incidence of ESCC is negatively correlated with Human Development Index (26), the affordability of implementing a screening program is a challenge in a health resource-limited setting. Thus, the screening program needs to balance the health outcomes and limited financial budget. To achieve this task, this study identified the cost-saving screening strategies with the greatest health outcomes, such as the strategy initiated at 40 years of age and repeated every 3 years, which was also robust in the sensitivity analysis. This study also used the relatively lower willingness-to-pay threshold (the US $1,151) instead of local GDP per capita (I $6542) as previous research done (4). Therefore, the findings of this study might be easily transferred to other low-income regions with a high disease burden of ESCC.

There are several weaknesses. First, as with most economic studies about cancer screening, our findings are weakened by available data. The natural history of precancerous lesions and their regression to normal and progression to ESCC is not clearly elucidated. If the lesions can be regressive, the number

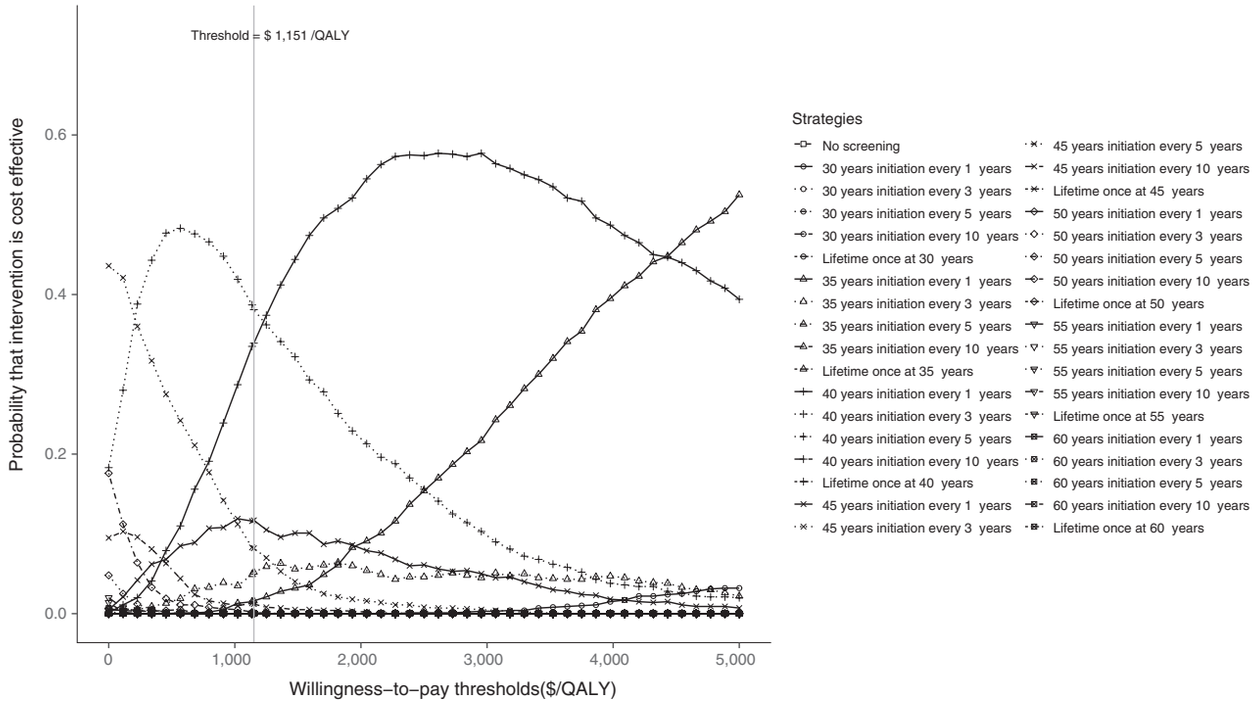

Figure 4.

Cost-effectiveness acceptability curves indicating the probabilities of 36 competing strategies to be cost-effective at different willingness-to-pay levels.

need to treat will increase and the ratio between harm and benefits will be lower. In particular, the length of the screening interval would not be necessarily better when shorter. However, our model was synthesized with the currently best available epidemiologic data including precancerous lesions prevalence rates and ESCC incidence rates and modeled precancerous lesions progression over time to closely match the reported clinical datasets. Because the policymakers often pay attention to the whole population rather than the individual, the findings also might be an useful evidence for policymakers. Second, we did not model esophagus adenocarcinoma. However, screening with endoscopy is believed to early detect upper gastrointestinal cancers (esophageal adenocarcinoma with its premalignant precursor Barrett's esophagus, esophageal squamous cell cancer, gastric adenocarcinoma). Thus, the current analysis might underestimate the health benefits of the screening programs because they can identify additional upper gastrointestinal cancers. It should be noted that this potentially important issue needs to be solved by combining all upper gastrointestinal cancers in one screening policy model. Third, the current analysis evaluates the economic outcomes of different screening programs in high-risk regions. Because of the notably different incidence of ESCC in different regions, the findings of the current analysis could not be generalized to average- or low-risk regions, which should be addressed in a future study. Finally, although this analysis did model the most widely recommended screening techniques, other potential technologies are being developed and may become viable in the future, such as capsule endoscopy that can improve the adherence to screening, was not evaluated. However, because the findings of this evaluation reflected the general health conditions of preventing ESCC in high endemic regions, it might be a valuable reference for decision-makers.

In summary, the endoscopy screening with Lugol's iodine starting at 35–40 years old and repeated every 1–3 years for ESCC will be cost-effective in high endemic regions and the finding are robust. Future studies should address the issue that which optimized screening programs should be implemented in average- or low-risk regions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Q. Zhang
Development of methodology: B. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Wu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Wu, Z.-H. Wang, Q. Zhang
Writing, review, and/or revision of the manuscript: Z.-H. Wang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z.-H. Wang
Study supervision: Q. Zhang

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