Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Trial design and participants

To further determine the feasibility and efficacy of endoscopic screening for both EC and GC, in May 2015, the National Cancer Center (NCC) of China/Cancer Hospital, Chinese Academy of Medical Sciences (CICAMS) launched a multicenter community-based cluster RCT project in three high-risk areas (Linzhou County of Henan Province, Cixian County of Hebei Province, and Wuwei County of Gansu Province) and four non-high-risk areas (Sheyang County of Jiangsu Province, Luoshan County of Henan Province, Harbin City of Heilongjiang Province, and Changsha City of Hunan Province). The project was registered with the Protocol Registration System in the Chinese Clinical Trial Registry (identifier: ChiCTR-EOR-16008577) and approved by the independent Ethics Committee of the NCC/CICAMS (2015SQ00223). Details of the study design and initial results have been previously published.1,2

In total, 345 eligible villages/communities in seven screening centers constituted the randomization unit: 163 units from the three high-risk areas and 182 units from the four non-high-risk areas. Based on a stratified cluster sampling design, these units were randomly allocated to the screening arm or control arm at a ratio of 1:1 by each center for practical reasons and contamination prevention (eFigure 1–2). According to the study assignment, local village doctors or community public health workers at each site recruited and assigned participants to each group. The eligible participants were residents aged 40–69 years with no personal history of cancer and who did not undergo endoscopy in the past three years.

Screening, reexamination and treatment

The screening and re-examination procedures are shown in eFigure 3. The diagnoses were reported according to the American Joint Committee on Cancer Staging System (7th ed.). Stage I and II tumors were categorized as early cancer, and stage III and IV tumors were categorized as advanced cancer. The participants from the high-risk areas were automatically identified as high-risk individuals and were invited to undergo endoscopic screening. The participants from the non-high-risk areas were evaluated with a risk assessment questionnaire, and only subjects who were identified as high-risk individuals were invited to undergo endoscopic screening. The screened participants were given a local anesthetic, and the entire esophagus and stomach were visually examined. Lugols’ iodine staining in the esophagus and indigo carmine dye in the stomach were performed as necessary to aid in the diagnosis of suspicious lesions. Suspicious lesions were targeted for biopsy for further pathological diagnosis. Subjects without suspicious lesions did not undergo a biopsy.

Individuals with precancerous lesions were followed up by endoscopic re-examinations. A triennial endoscopic re-examination was required for mild esophageal dysplasia (mD), and an annual re-examination was required for moderate esophageal dysplasia (MD) or low-grade gastric intraepithelial neoplasia (LGIN).

The corresponding treatment was provided according to the diagnosis results. If the early lesions are histologically confirmed, the participants were recalled to the clinic, and intervention methods appropriate for the lesion severity were employed. For severe esophageal dysplasia/carcinoma in situ (SD/CIS), high-grade gastric intraepithelial neoplasia/carcinoma in situ (HGIN/CIS), early esophageal cancer (EC), or gastric cancer (GC), endoscopic mucosal resection or endoscopic submucosal dissection treatments were used as local therapies. For advanced EC or GC, the therapies included esophagectomy, radical operation, radiotherapy, and other conventional treatments.
eFigure 1. Flowchart of the overall participants in the multicenter randomized trial project.
Seven screening centers in China
Cixian, Changsha, Harbin, Linzhou, Luoshan, Sheyang, Wuwei

Eligibility for cluster enrollment:
1. No screening in the latest three years
2. Willingness to conduct the trial

31 towns, 345 villages
n=152,172

High-risk areas
163 villages, n=61,452
Non-high-risk areas
182 villages, n=90,720

Cluster randomization

Intervention group
81 villages, n=27,957
Exclusions:
Prevalent cancer cases 181
Age out of range 279
Having endoscopy already 377
Erroneous baseline data 9

Control group
82 villages, n=33,495
Exclusions:
Prevalent cancer cases 394
Age out of range 168
Having endoscopy already 31
Erroneous baseline data 9

Final inclusion in analysis
27,111
Final inclusion in analysis
32,893

Intervention group
92 villages, n=48,671
Exclusions:
Prevalent cancer cases 250
Age out of range 90
Duplicates 1
Erroneous baseline data 20

Control group
90 villages, n=42,049
Exclusions:
Prevalent cancer cases 232
Age out of range 46
Having endoscopy already 113
Duplicates 1
Erroneous baseline data 15

Final inclusion in analysis
48,310
Final inclusion in analysis
41,642

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eFigure 2. Flowchart of the participants in the high-risk areas.

14 towns, 163 villages

Cixian
8 towns, 64 villages

Cluster randomization

Intervention group
32 villages, n=7390
Exclusions:
Prevalent cancer cases 17
Age out of range 69
Having endoscopy already 377
Final inclusion in analysis 6927

Control group
32 villages, n=10,023
Exclusions:
Prevalent cancer cases 65
Age out of range 33
Having endoscopy already 24
Erroneous baseline data 6
Final inclusion in analysis 9895

Lizhou
2 towns, 54 villages

Cluster randomization

Intervention group
27 villages, n=10,208
Exclusions:
Prevalent cancer cases 111
Age out of range 176
Erroneous baseline data 5
Final inclusion in analysis 9916

Control group
27 villages, n=11,136
Exclusions:
Prevalent cancer cases 212
Age out of range 102
Erroneous baseline data 2
Final inclusion in analysis 10,817

Wuwei
4 towns, 45 villages

Cluster randomization

Intervention group
22 villages, n=10,359
Exclusions:
Prevalent cancer cases 53
Age out of range 34
Erroneous baseline data 1
Final inclusion in analysis 10,268

Control group
23 villages, n=12,337
Exclusions:
Prevalent cancer cases 117
Age out of range 31
Having endoscopy already 7
Erroneous baseline data 1
Final inclusion in analysis 12,181

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eFigure 3. Flowchart of the screening and reexamination

Eligible participants*: All individuals aged 40–69 years from high-risk areas; high-risk individuals aged 40–69 years from non-high-risk areas.

Abbreviations: mD, mild dysplasia; MD, moderate dysplasia; SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; LGIN, low-grade intraepithelial neoplasia; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer.

2. Markov model

eFigure 4 shows our Markov model of the progression of UGIC, which includes both EC and GC. Circles represent health states, and solid lines with arrowheads represent transitions and their directions. Dotted lines represent persons with precancerous lesions or cancer identified by self-initiated examinations or screening without a time delay of state transition. A person in the detected mD, MD or LGIN state will return to an undetected state if the person fails to comply with the regular re-examination or a false-negative re-examination result is obtained. A person in the PT-SD/CIS or PT-HGIN/CIS state will return to the normal state if the person maintains the current state for more than 10 years. A person in the PT-early EC or GC state or in the PT-advanced EC or GC state will stay in the current state until death if the person maintains the current state for more than 10 years. The death state (not shown here) is the absorbing state of the model, a person in any other states will enter the death state due to age-specific natural background death, and a person in the detected advanced EC or GC state will face cause-specific mortality from EC or GC in addition to a natural background death rate.

Following the screening and re-examination procedures mentioned above, triennial endoscopic re-examination for detected mild esophageal dysplasia (mD) and annual endoscopic re-examination for detected moderate esophageal dysplasia (MD) and low-grade gastric intraepithelial neoplasia (LGIN) were considered in the model.

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eFigure 4. Markov model of upper gastrointestinal tract cancer (including esophageal cancer and gastric cancer) progression.

Abbreviations: mD, mild dysplasia; MD, moderate dysplasia; SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; LGIN, low-grade intraepithelial neoplasia; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer; PT, posttreatment.

3. Model parameters and data sources

Initial probabilities

The initial probabilities of EC/GC-related health states were mainly obtained from screening baseline reports of our project in the high-risk areas. The base-case prevalence rates of EC/GC-related health states were calculated as the proportion of each pathologic stage of EC/GC among the subjects who underwent endoscopy at each initial screening age, which were used to determine the initial distributions of cohort members in health states of the model. Referring to previous reports from China, a wide range was set for each rate to cover the values reported in high-risk areas. Details are presented in eTable 1.

eTable 1. Prevalence rates (%) of EC/GC-related health states used in the model, by initial screening age

| Category      | Base-case value | Range                | Reference |
|---------------|-----------------|----------------------|-----------|
| mD            | 1.16            | 0.58–2.5             | 3–5       |
| MD            | 0.10            | 0.05–0.2             | 3–5       |
| SD/CIS        | 0.05            | 0.03–0.1             | 3–5       |
| Early EC      | 0.02            | 0.01–0.0             | 3–5       |
| Advanced EC   | 0.01            | 0.00–0.02            | 3–5       |

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Probabilities were specified as triangular distributions. Annual transition probabilities were specified as uniform distributions, with the upper and lower limits of range as the minimum and maximum values, respectively, and the base-case value as the most likely value.

Abbreviations: mD, mild dysplasia; MD, moderate dysplasia; SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; LGIN, low-grade intraepithelial neoplasia; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer.

**Annual transition probabilities**

The annual transition probabilities were derived from published observational studies concerning the natural history of EC/GC and economic evaluation studies of EC/GC; the probabilities are summarized in eTable 2. It is believed that patients with advanced EC/GC may mainly die from cancer and that patients with early EC/GC or precancerous lesions may not die from cancer. In the model, all posttreatment states were set as tunnel states to control their transition directions, which were associated with the duration of stay in their current states. All parameters were adjusted within a wide range in the sensitivity analyses to cover most of the reported data. In the probabilistic sensitivity analysis, the age-dependent annual transition probabilities were specified as uniform distributions, and the non-age-dependent annual transition probabilities were specified as triangular distributions.

**eTable 2. Annual transition probabilities used in the model**

| Parameter                | Base-case value | Range | Distribution | Reference |
|--------------------------|-----------------|-------|--------------|-----------|
| **Normal**               |                 |       |              |           |
| To mD                    | 0.012           | ±50%  | Triangular (0.006, 0.012, 0.018) | 7-9       |
| To LGIN                  | 0.007           | ±50%  | Triangular (0.0035, 0.007, 0.0105) | 7,10      |
| **mD**                   |                 |       |              |           |
| To normal                | 0.05            | ±50%  | Triangular (0.025, 0.05, 0.075) | 7-9       |
| To MD                    | 0.05            | ±50%  | Triangular (0.025, 0.05, 0.075) | 7-9       |
| **MD**                   |                 |       |              |           |
| To mD                    | 0.08            | ±50%  | Triangular (0.04, 0.08, 0.12) | 7-9       |
| To SD/CIS                | 0.12            | ±50%  | Triangular (0.06, 0.12, 0.18) | 7-9       |
| **SD/CIS**               |                 |       |              |           |
| To MD                    |                 |       | Uniform (0.085, 0.255) | 7-9       |
| 40–44 years              | 0.17            | ±50%  | Uniform (0.075, 0.225) | 7-9       |
| 45–49 years              | 0.15            | ±50%  | Uniform (0.07, 0.21) | 7-9       |
| 50–54 years              | 0.14            | ±50%  | Uniform (0.06, 0.18) | 7-9       |
| 55–59 years              | 0.12            | ±50%  | Uniform (0.055, 0.165) | 7-9       |
| ≥65 years                | 0.09            | ±50%  | Uniform (0.045, 0.135) | 7-9       |
| To early EC              |                 |       | Uniform (0.04, 0.12) | 7-9       |
| 40–44 years              | 0.08            | ±50%  | Uniform (0.05, 0.15) | 7-9       |
| 45–49 years              | 0.12            | ±50%  | Uniform (0.06, 0.21) | 7-9       |
| 50–54 years              | 0.14            | ±50%  | Uniform (0.07, 0.24) | 7-9       |
| 55–59 years              | 0.16            | ±50%  | Uniform (0.09, 0.27) | 7-9       |
| ≥65 years                | 0.18            | ±50%  | Uniform (0.25, 0.55) | 7-9       |

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| Age Group         | Recurrence Probability | Distribution       |
|-------------------|------------------------|--------------------|
| 45–49 years       | 0.45                   | 0.30–0.60 Uniform (0.30, 0.60) |
| 50–54 years       | 0.50                   | 0.35–0.65 Uniform (0.35, 0.65) |
| 55–59 years       | 0.64                   | 0.49–0.79 Uniform (0.49, 0.79) |
| 60–64 years       | 0.71                   | 0.56–0.86 Uniform (0.56, 0.86) |
| ≥65 years         | 0.74                   | 0.59–0.89 Uniform (0.59, 0.89) |
| Advanced EC to death | 0.80                 | 0.58–0.90 Triangular (0.58, 0.80, 0.90) |

**LGIN**

| Age Group         | Recurrence Probability | Distribution       |
|-------------------|------------------------|--------------------|
| To normal         | 0.04 ±50%              | Triangular (0.02, 0.04, 0.06) |
| To HGIN/CIS       | 0.03 ±50%              | Triangular (0.015, 0.03, 0.045) |

**HGIN/CIS**

| Age Group         | Recurrence Probability | Distribution       |
|-------------------|------------------------|--------------------|
| To LGIN           |                        |                    |
| 40–44 years       | 0.17 ±50%              | Uniform (0.085, 0.255) |
| 45–49 years       | 0.15 ±50%              | Uniform (0.075, 0.225) |
| 50–54 years       | 0.14 ±50%              | Uniform (0.070, 0.210) |
| 55–59 years       | 0.12 ±50%              | Uniform (0.060, 0.180) |
| 60–64 years       | 0.11 ±50%              | Uniform (0.055, 0.165) |
| ≥65 years         | 0.09 ±50%              | Uniform (0.045, 0.135) |
| To early GCA      |                        |                    |
| 40–44 years       | 0.08 ±50%              | Uniform (0.04, 0.12) |
| 45–49 years       | 0.10 ±50%              | Uniform (0.05, 0.15) |
| 50–54 years       | 0.12 ±50%              | Uniform (0.06, 0.18) |
| 55–59 years       | 0.14 ±50%              | Uniform (0.07, 0.21) |
| 60–64 years       | 0.16 ±50%              | Uniform (0.08, 0.24) |
| ≥65 years         | 0.18 ±50%              | Uniform (0.09, 0.27) |
| Early GC to advanced GC |                   |                    |
| 40–44 years       | 0.40 ±50%              | Uniform (0.25, 0.55) |
| 45–49 years       | 0.45 ±50%              | Uniform (0.30, 0.60) |
| 50–54 years       | 0.50 ±50%              | Uniform (0.35, 0.65) |
| 55–59 years       | 0.64 ±50%              | Uniform (0.49, 0.79) |
| 60–64 years       | 0.71 ±50%              | Uniform (0.56, 0.86) |
| ≥65 years         | 0.74 ±50%              | Uniform (0.59, 0.89) |
| Advanced GC to death | 0.80                 | 0.58–0.90 Triangular (0.58, 0.80, 0.90) |

Abbreviations: mD, mild dysplasia; MD, moderate dysplasia; SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; LGIN, low-grade intraepithelial neoplasia; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer; PT, posttreatment.

**Compliance with treatment**

State-specific compliance with treatment was calculated as the proportion of screened patients who actually completed the whole treatment procedure in high-risk areas in our project as summarized in eTable 3. Compliance with treatment in advanced EC patients was assumed to be the same as that in advanced GC patients due to the small and unbalanced number of patients in this disease progression stage in the three study centers. The mean and 95% confidence intervals (CIs) of state-specific compliance with treatment were used as base-case values and ranges in the univariate sensitivity analysis. The beta distributions were calculated using an approximation of the mean and standard deviation (SD) of state-
specific compliance with treatment in the probabilistic sensitivity analysis, with an alpha of \((\text{mean}^2) \cdot (1 – \text{mean})/\left(\text{SD}^2\right)\) and a beta of \([\text{mean} \cdot (1 – \text{mean})/\left(\text{SD}^2\right) – (\text{mean})^2 \cdot (1 – \text{mean})/\left(\text{SD}^2\right)]\).

**eTable 3. State-specific compliances with treatment estimated based on our project**

| No. of patients receiving treatment (total No. of patients) | Compliance with treatment |
|-----------------------------------------------------------|---------------------------|
| Wuwei City                                               | Linzhou County            |
| SD/CIS                                                   |                           | mean ± SD | 95%CI |
| 30 (35)                                                  | 58 (80)                   | 0.7458±0.0811 | 0.5625–0.9654 |
| Early EC                                                 |                            | 0.9405±0.0931 | 0.7149–1.0000 |
| Advanced EC\(^a\)                                        |                            | /           | /     |
| HGIN/CIS                                                 |                            | 0.5455±0.0467 | 0.4425–0.7746 |
| Early GC                                                 |                            | 0.9000±0.0951 | 0.6792–1.0000 |
| Advanced GC                                              |                            | 0.9643±0.0525 | 0.8393–1.0000 |

Abbreviations: SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer; CI, confidence interval; SD, standard deviation.

**Costs of screening and EC/GC-related treatment**

The cost of screening included screening mobilization and administration costs, endoscopic examination costs, and treatment costs for endoscopic complications, and these data were obtained from the seven study centers in both high-risk and non-high-risk areas in our project.\(^1,^2\) The results are shown in eTable 4.

This cost-effectiveness analysis was performed from the healthcare system perspective, and disease state costs in this study only included direct medical costs, including outpatient expenditure, inpatient expenditure, and expenditure for medicines self-purchased in retail pharmacies; however, direct nonmedical costs and indirect costs were not included. The cost of EC/GC-related treatment included the initial treatment cost in the detected states and the subsequent annual healthcare cost in the posttreatment states, which were determined based on the survey administered in our project to assess the economic burden of UGIC in China in 2017.\(^1,^1\) The survey was performed in seven hospitals from seven study centers in six provinces distributed in the eastern, central and western areas of China. In total, 20,105 outpatient records and 20,056 inpatient records were collected to obtain the per-capita outpatient and inpatient expenditures on a single visit/admission, respectively. In total, 2855 patients who were discharged from hospitals for more than one year were interviewed by telephone regarding their medical behaviors in the year of hospitalization and more than one year after discharge, including their outpatient visit rate, inpatient admission rate, self-medication expenditures, etc. Using these data, we calculated the disease stage-specific initial treatment costs and annual healthcare costs as shown in eTable 5.

The point estimates of the costs of screening and EC/GC-related treatment were used as base-case values and allowed ±50% variation in the cost parameters in the univariate sensitivity analysis. We used an approximation of the mean and SD to calculate the distribution in the probabilistic sensitivity analysis as follows: gamma distributions had an alpha of \((\text{mean}^2)/(\text{SD}^2)\) and a lambda of mean/(SD^2).
### eTable 4. Costs of screening estimated based on our project

|                          | Screening mobilization & administration |       |       | Endoscopic examination |       |       | Treatment for endoscopic complications |       |       |
|--------------------------|-----------------------------------------|-------|-------|-------------------------|-------|-------|-----------------------------------------|-------|-------|
|                          | No. of persons in the screening intervention group | Total cost, US$ | Per-capita cost, US$ | No. of persons receiving endoscopy examination | Total cost, US$ | Per-capita cost, US$ | No. of persons with complications in endoscopic examination | Total cost, US$ | Per-capita cost, US$ |
| High-risk areas          |                                         |       |       |                         |       |       |                                         |       |       |
| Wuwei City               | 10,367                                  | 16,848 | 1.63  | 8506                    | 416,934 | 49.02 | 17                                      | 2265  | 133.24 |
| Cixian County            | 10,000                                  | 12,277 | 1.23  | 9189                    | 483,266 | 52.59 | 18                                      | 1983  | 110.17 |
| Linzhou County           | 10,061                                  | 11,093 | 1.10  | /                       | /       | /     | 20                                      | 1581  | 79.05  |
| Non-high-risk areas      |                                         |       |       |                         |       |       |                                         |       |       |
| Changsha City            | 10,478                                  | 9949  | 0.95  | 1430                    | 81,591  | 57.06 | 3                                       | 601   | 200.33 |
| Harbin City              | /                                       | /     | /     | /                       | 421     | 20,061 | 47.65 | 1                                      | 150   | 150    |
| Sheyang County           | 10,526                                  | 4592  | 0.44  | 3035                    | 98,415  | 32.43 | 8                                       | 1090  | 136.25 |
| Luoshan County           | 12,659                                  | 12,770 | 1.01  | 3100                    | 129,195 | 41.68 | 4                                       | 401   | 100.25 |
| Total                    | 64,091                                  | 67,529 | 1.05 ± 0.35c | 25,681 | 1,229,462 | 47.87 ± 7.93c | 71 | 8071 | 113.68 ± 36.39c |

*aLinzhou County used painless endoscopy for screening, which costs almost twice as much as ordinary endoscopy; thus, it was excluded when calculating this parameter.

*bHarbin City did not collect the costs of projects for screening mobilization and administration; thus, it was excluded when calculating this parameter.

*mean ± standard deviation (SD).

### eTable 5. Costs of EC/GC-related treatment in different disease progression stages based on the survey included in our project (US$)

|                          | Outpatient expenditure per visitb (a) | Inpatient expenditure per admission (b) | Inpatient visit rate in the year of hospitalization (c) | Inpatient admission rate in the year of hospitalization (d) | Annual outpatient visit rate at more than one year after discharge (e) | Annual self-medication expenditure (f) | Initial treatment cost (mean ± SD) = a × c + b × d | Annual healthcare cost (mean ± SD) = a × e + f |
|--------------------------|--------------------------------------|----------------------------------------|---------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| SD/CIS                   | 56                                   | 1151                                   | 2.13                                                    | 1.29                                                    | 1.46                                                                         | 134                                         | 1604 ± 879                                           | 216 ± 192                                           |
| Early EC                 | 112                                  | 3503                                   | 2.42                                                    | 2.13                                                    | 1.51                                                                         | 198                                         | 7732 ± 5068                                          | 367 ± 331                                           |

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|                |       |       |       |      |      |          |          |
|----------------|-------|-------|-------|------|------|----------|----------|
| Advanced EC    | 112   | 2979  | 2.58  | 2.36 | 1.04 | 226      | 7320 ± 4012 |
| HGIN/CIS       | 66    | 1165  | 1.61  | 1.13 | 1.44 | 148      | 1423 ± 1200  |
| Early GC       | 131   | 3152  | 2.52  | 2.29 | 1.59 | 200      | 7548 ± 3514  |
| Advanced GC    | 131   | 2567  | 2.76  | 2.62 | 1.46 | 244      | 7086 ± 2903  |
|                |       |       |       |      |      |          | 342 ± 239   |

*This parameter was assumed to be the same in patients with early and advanced cancers due to the lack of TNM staging information in outpatients.

Abbreviations: SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer; CI, confidence interval; SD, standard deviation.
Utility scores of EC/GC-related health states

Utility scores of EC/GC-related health states were obtained from the survey administered in our project to assess the quality of life of UGI C patients in China. The survey was conducted using a case-control design in seven hospitals from seven study centers in six provinces located across the eastern, central, and western regions of China. In total, 2855 UGIC patients and 2179 matched healthy controls completed the Chinese version of the three-level EQ-5D questionnaire by telephone. The EQ-5D was scored using a validated Chinese population-specific value set developed using the time trade-off technique to evaluate the disease stage-specific utility scores as shown in eTable 6. The utility scores ranged from 0 to 1, where 1 represents living without any EC/GC-related disease, and 0 represents death. The mean and 95% CIs of the EQ-5D utility scores were used as base-case values and ranges in the univariate sensitivity analysis.

The utility scores were obtained from the survey administered in our project to assess the quality of life of UGI C patients in China. The survey was conducted using a case-control design in seven hospitals from seven study centers in six provinces located across the eastern, central, and western regions of China. In total, 2855 UGIC patients and 2179 matched healthy controls completed the Chinese version of the three-level EQ-5D questionnaire by telephone. The EQ-5D was scored using a validated Chinese population-specific value set developed using the time trade-off technique to evaluate the disease stage-specific utility scores as shown in eTable 6. The utility scores ranged from 0 to 1, where 1 represents living without any EC/GC-related disease, and 0 represents death. The mean and 95% CIs of the EQ-5D utility scores were used as base-case values and ranges in the univariate sensitivity analysis. The beta distributions were calculated using an approximation of the mean and SD of the utility scores in the probabilistic sensitivity analysis, with an alpha of \((\text{mean}^2 \cdot (1-\text{mean})/\text{SD}^2)\) and a beta of \([\text{mean} \cdot (1-\text{mean})/(\text{SD}^2) – (\text{mean}^2) \cdot (1-\text{mean})/\text{SD}^2]\).

### eTable 6. Utility scores of EC/GC-related health states based on the survey included in our project

| Health State | Sample Size | Utility Score (mean ± SD) | 95% CI |
|--------------|-------------|--------------------------|--------|
| Controls     | 2179        | 0.84 ± 0.16              | 0.79–0.89 |
| SD/CIS       | 257         | 0.70 ± 0.21              | 0.66–0.74 |
| Early EC     | 694         | 0.61 ± 0.29              | 0.56–0.66 |
| Advanced EC  | 492         | 0.92 ± 0.14              | 0.86–0.99 |
| HGIN/CIS     | 166         | 0.75 ± 0.19              | 0.71–0.78 |
| Early GC     | 655         | 0.57 ± 0.27              | 0.53–0.62 |
| Advanced GC  | 563         |                          |        |

*Excluding 13 EC patients and 15 GC patients with a clinical stage classified as “unknown”.

Abbreviations: SD/CIS, severe dysplasia/carcinoma in situ; EC, esophageal cancer; HGIN/CIS, high-grade intraepithelial neoplasia/carcinoma in situ; GC, gastric cancer; CI, confidence interval; SD, standard deviation.

4. Model validation

In internal validation, seven experts in different fields including clinical, epidemiology, and health economics were invited to confirm the face validity of the model. Two team members independently examined the model programming and calculation results, and gave a unanimous judgment. Model outputs about the tendency of each pathologic grade proportion were checked with the characteristics of natural history of EC/GC. For example, the proportions decreased with the severity of the disease in each age group (mD/LGIN ranked first), and the proportions of each EC/GC pathologic grade increased with age (a maximum in the 80–85 years). We also simulate each parameter change in a broad range to determine whether the direction and magnitude of model outputs behaved as expected.

In external validation, 2 folds of the observed national EC/GC incidence and mortality rates in 2015 were used as references, due to the lack of the reported age-specific data in high-risk areas and the disease characteristics in high-risk areas of China. A closed cohort of people aged 40–44 years were assumed to enter the model without screening intervention, and model projected outputs, i.e. projected age-specific EC/GC incidence and mortality rates were compared with the references. The results were shown in eFigure 5–6.

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eFigure 5. Model projected age-specific GC incidence and mortality rates compared to 2 folds of observed national GC incidence and mortality rates in 2015.

Abbreviations: EC, esophageal cancer.

A

![Projected vs. Observed EC Incidence](image)

B

![Projected vs. Observed EC Mortality](image)
eFigure 6. Model projected age-specific EC incidence and mortality rates compared to 2 folds of observed national EC incidence and mortality rates in 2015.

Abbreviations: GC, gastric cancer.

A

Projected GC incidence and Observed GC incidence

B

Projected GC mortality and Observed GC mortality
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