

# SYSTEMATIC REVIEWS AND META-ANALYSIS

## Stage-Specific Survival From Esophageal Cancer in China and Implications for Control Strategies: A Systematic Review and Meta-Analyses



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**BACKGROUND AND AIMS:** Esophageal cancer claims more than 500,000 deaths worldwide, with half occurring in China. We aimed to synthesize existing evidence on stage-specific survival from this cancer in China to inform cancer control strategies. **METHODS:** English and Chinese literature databases were systematically searched to identify original research published up to May 31, 2019 that reported stage-specific survival from esophageal cancer in China. Two meta-analyses were performed using random-effects models to summarize stage-specific survival differences on relative and absolute scales. The number of esophageal cancer deaths that might have been prevented by early detection in China, in 2018, was estimated assuming 2 different downstaging scenarios. **RESULTS:** One hundred fifty eligible studies were identified, 97 had non-overlapping study populations (83,063 participants), 47 were included in the meta-analysis of hazard ratios, and 26 in the meta-analysis of survival probabilities. Late-stage (III–IV) was associated with 92% higher hazard of death compared with early-stage (0–II) (95% confidence interval 1.62–2.28), corresponding to an absolute 5-year survival difference of 31.2% (29.9%–32.4%). In all, 5.2% esophageal cancer deaths could have been prevented in China, in 2018, if the observed stage distribution at diagnosis (~50% early-stage) was shifted to the real-life conditions of a population-based endoscopic screening program (~60% early-stage) and 26.9% if shifted to that observed in the controlled setting of a randomized trial (~90% early-stage). **CONCLUSION:** Shifting downwards the stage distribution of esophageal cancer through screening would bring moderate reductions in mortality from the disease. Treatment improvements for early-stage patients are needed to reduce further mortality from this cancer.

**Keywords:** Esophageal cancer; Stage-specific survival; Systematic review; Meta-analysis; Avoidable deaths

Esophageal cancer (EC) claims 544,000 deaths worldwide, with half occurring in China.<sup>1</sup> Its incidence and mortality rank sixth and fourth, respectively, in the country.<sup>2</sup> Survival is universally poor with 5-year age-standardized relative survival for patients diagnosed in 2000–2014 being less than 30% in nearly all countries in the latest global cancer survival surveillance.<sup>3</sup> Primary prevention and early detection programs have been implemented in high-risk areas in China since the early 1970s,<sup>4</sup>

with successive national plans advocating early detection and the adoption of guidelines for early diagnosis and treatment of this cancer. Despite these efforts, 5-year age-standardized relative survival from EC in China has remained poor, although increased from 20.9% in patients diagnosed in 2003–2005 to a predicted estimate of 30.3% for those diagnosed in 2012–2015.<sup>5</sup>

The success of early detection programs for EC, either through screening of asymptomatic disease or downstaging of symptomatic disease, relies on the assumption that a shift toward early detection results in survival gains and, ultimately, mortality reductions. The American Joint Committee on Cancer (AJCC) has shown large variations in 5-year survival from ~50% to ~70% for stages 0 and I to less than 20% for stage IV based on “average” estimates from 33 centers across several countries.<sup>6</sup> Estimates of stage-specific survival from EC in China may differ from these because of differences in tumor biology (eg, predominance of squamous cell carcinoma [SCC]) and access to, and quality of, healthcare. Population-based cancer registries in mainland China do not report stage-specific survival. Hence, the only available information on stage-specific survival from EC in the country comes from hospital-based studies, which vary markedly in study design, patient source, sample size, follow-up approach, and analytical methodology.

In the absence of population-based studies on stage-specific survival in China, we conducted a systematic review aiming to (i) bring together all published estimates on stage-specific survival from EC in China and synthesize the evidence; (ii) quantify differences in stage-specific survival on both relative and absolute scales; (iii) investigate potential sources of heterogeneity; and (iv) estimate the

**Abbreviations used in this paper:** AC, adenocarcinoma; AJCC, American Joint Committee on Cancer; EC, esophageal cancer; HR, hazard ratio; IPD, individual patient data; KM, Kaplan-Meier; SCC, squamous cell carcinoma; UICC, Union for International Cancer Control.

Most current article

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number of deaths that could potentially be prevented through effective early detection interventions. The review will provide an up-to-date snapshot on stage differences in EC survival in China and a baseline against which to monitor the likely impact of future early detection interventions.

## Methods

The systematic review followed the principles highlighted in the Cochrane Handbook for systematic reviews (Text S1, Table S1).<sup>7</sup>

### Eligibility Criteria

Papers were eligible if they provided information on stage-specific survival of primary EC in China in the form of median survival time, Kaplan-Meier (KM) curves or hazard ratios (HRs) (Text S1). Papers were excluded if they (i) reported research conducted in non-humans; (ii) reported studies carried out outside China or in non-Chinese ethnic populations; (iii) were not original articles; (iv) did not enroll incident cases with primary EC; (v) did not report or provide data for deriving stage-specific survival estimates for EC; and/or (vi) included only rare histological types other than SCC or adenocarcinoma (AC). No restrictions were imposed on year of publication, language, study design, follow-up method, or outcome definition.

### Search Strategy

We systematically searched MEDLINE, Embase, Web of Science, and Wanfang (a major Chinese medical literature database) for original studies reporting stage-specific survival from EC in China (including Taiwan, Hong Kong, and Macao) published up to May 31, 2019, using appropriate search terms (Table S2). Annual reports of the National Central Cancer Registry of China (2010–2018), and of Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries, were also searched.

The titles and abstracts of papers identified were screened by one author (Y.H.) to assess potential eligibility, with a random sample of 200 independently screened by another author (Id.S.S.). The full texts of all papers deemed potentially eligible were then retrieved and screened, with the reasons for exclusion recorded (Figure 1).

### Data Extraction and Quality Assessment

A data extraction form was developed to extract relevant information from the eligible papers including author, publication year, study area, study design, participants' characteristics, tumor features, follow-up (eg, active/passive, losses), death ascertainment method, analytical method, and reported stage-specific survival estimates.

To assess study quality, we modified the Cochrane criteria<sup>7</sup> to assess 7 domains in methodology that are pertinent to time-to-event studies (Table S3): (i) study design; (ii) recruitment approach; (iii) follow-up method, (iv) losses to follow-up; (v) definition of survival time; (vi) analytical method; and (vii) availability of data on other key prognostic variables.

A 10% random sample of full-text papers in English was independently reviewed by another author (Id.S.S.) to check

eligibility, extract relevant data, and assess study quality. Only minor between-reviewer inconsistencies were identified and resolved among all authors.

## Outcomes

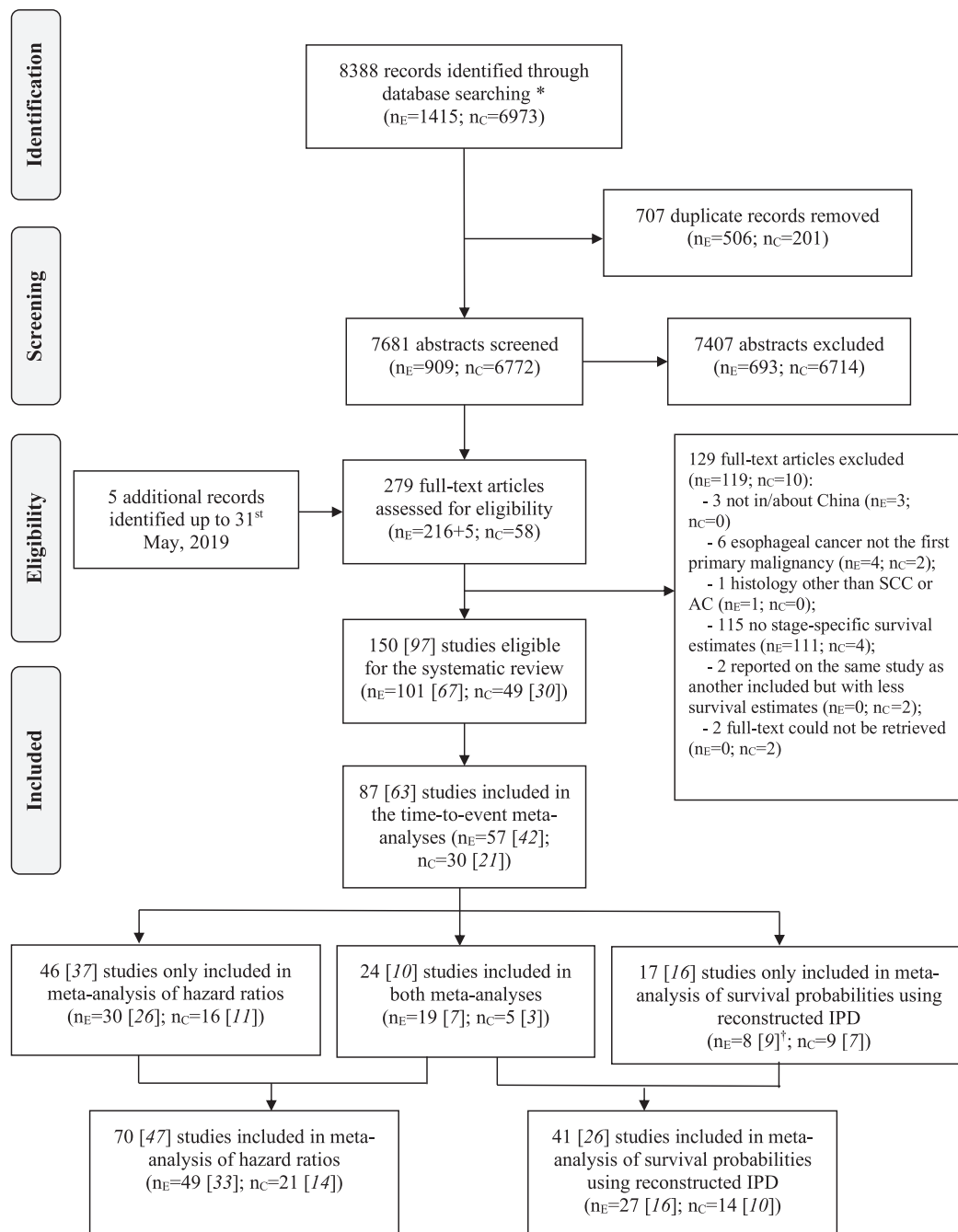
Stage-specific HRs and stage-specific survival probabilities were the primary outcomes of interest for quantification of summary differences in stage-specific survival on relative and absolute scales, respectively. The number of EC deaths that could potentially have been prevented in China, if the observed stage distribution was shifted downwards, was taken as a secondary outcome of interest.

### Non-overlapping Studies

Several studies had potentially overlapping populations as they recruited patients from the same hospital or used data from the same cancer registry, in overlapping time periods. Albeit the inclusion/exclusion criteria were often different, it was difficult to establish the degree to which their study populations might have overlapped; thus, only the single study with the broadest inclusion criteria, the longest study period, and/or the largest sample size were considered. Hereafter, this subset of studies is referred to as “non-overlapping studies”.

### Statistical Analysis

Two meta-analyses were performed to quantify the relative and absolute summary differences in stage-specific survival, respectively. For the first meta-analysis, aggregate HRs (or log HRs) and their variances were extracted, or derived, using the approach by Tierney et al.<sup>8</sup> We used random-effects models to estimate summary pooled HRs (pHRs) and forest plots to visualize study-specific HRs (R software version 3.6.2). Between-study heterogeneity was assessed using the  $I^2$  statistic.<sup>9</sup> Small-study effects and funnel plot asymmetry were examined using the Egger's test.<sup>10</sup> Meta-regression of study-specific HRs was performed to identify independent sources of between-study heterogeneity. Covariates with relative change (RC)  $\geq 1.2$  or  $P < .2$  in the univariable models were incorporated into a multiple meta-regression model and dropped one at a time. The final multiple meta-regression model was selected based on the adjusted R-squared value (Stata version 15.0). For the one-step meta-analysis on absolute differences in stage-specific survival, individual patient data (IPD) were reconstructed from the published KM survival curves by (i) extracting the coordinates for each survival curve using the Digitizeit software (version 2.5, from <https://www.digitizeit.de/>) and (ii) reconstructing individual-level time-to-event data from the extracted coordinates using the Guyot et al.<sup>11</sup> algorithm (R software version 3.6.2) and extracting their study-level covariates. Mixed-effects hazard regression models were then used to summarize stage-specific survival probabilities, accounting for study-level clustering.<sup>12</sup> Variables with a  $P < .05$  in the univariable hazard regression models were included in the multiple regression model. The final multiple hazard regression model was selected based on the Akaike Information Criteria.<sup>13</sup> Postestimation was used to calculate survival probabilities for each IPD record at 1, 3, and 5 years since diagnosis, which were then averaged over defined groupings of stage (0–II/III–IV, 0–I/II/III/IV) to obtain summary stage-specific survival probabilities and absolute



**Figure 1.** PRISMA flowchart of retrieved, excluded, and included studies in the systematic review and in the meta-analyses of relative and absolute stage-specific differences in survival from esophageal cancer in China (numbers in italics within square brackets refer to the number of non-overlapping studies—see Methods section).

\*No eligible records were identified by the search of annual reports of the National Central Cancer Registry (2010–2018) and Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries.

†One study retrieved from the English databases contributed to both meta-analyses of hazard ratios and survival probabilities when these were based on all eligible studies but only to the meta-analysis of survival probability when they were based on non-overlapping studies. n<sub>E</sub> and n<sub>C</sub>, number of papers retrieved from the English and Chinese databases, respectively.

summary survival differences. A similar approach was used to estimate summary stage-specific survival probabilities and corresponding absolute differences by the study-level covariates included in the final multiple hazard regression model.

The number of deaths from EC that could have been potentially prevented in China in 2018, among patients diagnosed in the previous 5 years, was estimated assuming that although the country experienced the same stage-specific survival yielded by the present meta-analysis, the corresponding

stage distribution had been shifted downwards under 2 different scenarios. In scenario 1, we assumed early detection resulted in a tumor stage distribution similar to that reported by the nationwide cancer registry in South Korea (30.3%, 28.6%, 26.6%, and 14.5%, respectively, for stage 0–I, II, III, and IV)<sup>14</sup> where a population-based endoscopic screening program was implemented in 2002.<sup>15</sup> In scenario 2, we assumed that early detection led to a more marked tumor downstaging, resulting in a distribution similar to that observed in the screening arm of a cluster randomized trial of one-off endoscopic screening (70.97%, 19.35%, 6.45%, and 3.23%, respectively, for stages 0–I, II, III, and IV) in China<sup>16</sup> (Text S2 provides full estimation methods).

The primary statistical analyses were conducted within the subset of non-overlapping studies, whereas sensitivity analyses were conducted based on all eligible studies.

## Results

The search identified 8388 potentially eligible records (1415 and 6973, respectively, from the English and Chinese databases and none from the Cancer Registry reports). After removal of duplicate records, title/abstract screening, full-text screening, and 150 eligible studies were identified (Figure 1).

### Characteristics of the Studies

The 150 eligible studies ( $n = 127,042$ ) included 101 studies from the English database and 49 from the Chinese database (Figure 1). The summary characteristics of these studies are shown in Table 1. In all, 72.7% of the eligible studies had a retrospective design, 51.3% had a sample size  $< 300$ , 90% were conducted in urban areas, and 82% recruited patients from a cancer, tertiary, or other specialized hospital (Table 1). Relative to the studies from the English database, a higher proportion of those from the Chinese database had a retrospective design, recruited both SCC and AC patients, and used a national staging system<sup>17–24</sup> or its own staging system<sup>25</sup> (Table S4).

The individual characteristics of each eligible study, and their reported stage-specific survival estimates, are shown in Table S5. Patient eligibility was restricted to a particular tumor stage in 51 studies: 35 studies excluded patients with distant metastasis at diagnosis,<sup>17,26–59</sup> 8 included only patients at inoperable or medium/late stage,<sup>18,19,23,24,60–63</sup> 1 included only stage I patients,<sup>64</sup> 2 included only stage II patients,<sup>65,66</sup> 2 included only stage III patients,<sup>67,68</sup> and 3 included only stage IV patients.<sup>69–71</sup> (Table S5).

Ninety seven ( $n = 83,063$ ) of the 150 eligible studies were deemed nonoverlapping studies. The characteristics of the latter were similar to those described above for all eligible studies (Figure 1; Table 1 and Table S5).

### Study Quality Assessment

More than 95% of the eligible studies were at high risk of bias in one or more domains. In particular, a large

proportion of studies did not specify how participants were recruited (66%), the follow-up method used (35.3%), or losses to follow-up (57.3%). Yet appropriate survival analytical methods were adopted by 96% of the studies. Similar proportions were observed within the subset of non-overlapping studies (Table S6).

### Study-Specific Survival Estimates

The 150 eligible studies varied markedly in the survival estimates they reported both in terms of their metric (eg, median, overall survival, cancer-specific survival, HRs) and their time frame (eg, 1, 3, 5 years) (Table S5). Nevertheless, they all showed consistently that survival for early-stage disease was better than that for later-stage disease but with distinct between-study variability in the magnitude of the survival differences.

### Meta-Analysis and Meta-Regression of Hazard Ratios

Forty seven non-overlapping studies were included in the meta-analysis of HRs (Figure 1). Stage III–IV patients had a 92% higher hazard of death compared to stage 0–II patients, but with moderate between-study heterogeneity (17 studies [ $n = 4670$ ]; pHR 1.92, 95% confidence interval [CI] 1.62–2.28,  $I^2 = 49.4\%$ ; Figure 2A). Relative to stage 0–I, the hazard of death increased progressively for stage II (4 studies [ $n = 24,676$ ]; pHR 1.85, 1.40–2.45), III (5 studies [ $n = 15,553$ ]; 3.14, 2.19–4.49), and IV (2 studies [ $n = 720$ ]; 10.88, 0.35–334.7) (Figure 2C–E). The 17 studies ( $n = 11,555$ ) which treated stage as a continuous variable showed an 83% increase in the hazard of death for every category increment in stage (pHR 1.83, 1.43–2.35) but with substantial between-study heterogeneity ( $I^2 = 90.3\%$ ) (Figure 2F).

The meta-regression analysis identified sample size and recruitment ward as independent sources of between-study heterogeneity. Studies with a sample size  $\geq 300$  and those that included patients from radio/oncological wards reported higher hazards of death for late-stage disease vs early-stage than, respectively, those with smaller sample sizes (adjusted RC = 1.40, 95% CI 1.01–1.94) and those that only included surgical patients (adjusted RC = 1.26, 0.87–1.82) (Table S7).

Sensitivity analyses based on all 70 eligible studies for the meta-analysis of HRs (Figure 1) yielded similar pHRs (Figure S1) and identified the same independent sources of between-study heterogeneity (data not shown) as seen within the subset of non-overlapping studies.

Among the non-overlapping studies there was little evidence of small-study effects on reported HRs among studies comparing stage III–IV vs 0–II ( $t = 0.18$ ,  $P = .597$ ), stage III vs 0–I ( $t = -0.23$ ,  $P = .820$ ), and stage II vs 0–I ( $t = -1.28$ ,  $P = .241$ ). In contrast, there was evidence of small-study effect among studies that analyzed stage as a continuous variable ( $t = 5.46$ ,  $P < .001$ ). Similar findings were observed

**Table 1.** Summary Characteristics of the 150 Eligible Studies and the 97 Non-overlapping Studies in the Systematic Review

|                                    | All eligible studies |      |          |      | Non-overlapping studies <sup>a</sup> |      |          |      |
|------------------------------------|----------------------|------|----------|------|--------------------------------------|------|----------|------|
|                                    | Studies              |      | Patients |      | Studies                              |      | Patients |      |
|                                    | N                    | %    | N        | %    | N                                    | %    | N        | %    |
| Study design                       |                      |      |          |      |                                      |      |          |      |
| PB+PC + RCT/PSM <sup>b</sup>       | 28                   | 18.7 | 39,947   | 31.4 | 14                                   | 14.4 | 9268     | 11.2 |
| Retrospective cohort               | 109                  | 72.7 | 84,227   | 66.3 | 72                                   | 74.2 | 71,282   | 85.8 |
| Other designs                      | 3                    | 2.0  | 640      | 0.5  | 2                                    | 2.1  | 385      | 0.5  |
| Not reported                       | 10                   | 6.7  | 2228     | 1.8  | 9                                    | 9.3  | 2128     | 2.6  |
| Study years                        |                      |      |          |      |                                      |      |          |      |
| Before 2005                        | 40                   | 26.7 | 20,634   | 16.2 | 28                                   | 28.9 | 17,072   | 20.6 |
| Spanning across 2005               | 44                   | 29.3 | 56,560   | 44.5 | 30                                   | 30.9 | 50,068   | 60.3 |
| After 2005                         | 64                   | 42.7 | 49,579   | 39.0 | 37                                   | 38.1 | 15,654   | 18.8 |
| Not reported                       | 2                    | 1.3  | 269      | 0.2  | 2                                    | 2.1  | 269      | 0.3  |
| Study size                         |                      |      |          |      |                                      |      |          |      |
| < 300                              | 77                   | 51.3 | 11,693   | 9.2  | 56                                   | 57.7 | 8085     | 9.7  |
| ≥ 300                              | 73                   | 48.7 | 115,349  | 90.8 | 41                                   | 42.3 | 74,978   | 90.3 |
| Median follow-up time              |                      |      |          |      |                                      |      |          |      |
| < 3 y                              | 34                   | 22.7 | 17,886   | 14.1 | 20                                   | 20.6 | 5222     | 6.3  |
| ≥ 3 y                              | 33                   | 22.0 | 15,419   | 12.1 | 20                                   | 20.6 | 8322     | 10.0 |
| Not reported                       | 83                   | 55.3 | 93,737   | 73.8 | 57                                   | 58.8 | 69,519   | 83.7 |
| High-risk EC area                  |                      |      |          |      |                                      |      |          |      |
| No                                 | 59                   | 39.3 | 52,630   | 41.4 | 37                                   | 38.1 | 21,548   | 25.9 |
| High-risk or mixed                 | 91                   | 60.7 | 74,412   | 58.6 | 60                                   | 61.9 | 61,515   | 74.1 |
| Study region                       |                      |      |          |      |                                      |      |          |      |
| East                               | 88                   | 58.7 | 38,941   | 30.7 | 55                                   | 56.7 | 25,187   | 30.3 |
| Central                            | 22                   | 14.7 | 45,085   | 35.5 | 15                                   | 15.5 | 43,413   | 52.3 |
| West                               | 12                   | 8.0  | 2939     | 2.3  | 12                                   | 12.4 | 2939     | 3.5  |
| Taiwan/Hong Kong/mix               | 24                   | 16.0 | 37,551   | 29.6 | 12                                   | 12.4 | 9154     | 11.0 |
| Not reported                       | 4                    | 2.7  | 2526     | 2.0  | 3                                    | 3.1  | 2370     | 2.9  |
| Study area                         |                      |      |          |      |                                      |      |          |      |
| Urban                              | 135                  | 90.0 | 123,621  | 97.3 | 84                                   | 86.6 | 79,937   | 96.2 |
| Rural                              | 12                   | 8.0  | 2953     | 2.3  | 10                                   | 10.3 | 2658     | 3.2  |
| Mixed                              | 3                    | 2.0  | 468      | 0.4  | 3                                    | 3.1  | 468      | 0.6  |
| Type of health facility            |                      |      |          |      |                                      |      |          |      |
| Cancer hospital                    | 67                   | 44.7 | 35,304   | 27.8 | 38                                   | 39.2 | 23,427   | 28.2 |
| Tertiary/other specialist hospital | 56                   | 37.3 | 53,628   | 42.2 | 46                                   | 47.4 | 50,218   | 60.5 |
| Secondary hospital                 | 7                    | 4.7  | 1479     | 1.2  | 5                                    | 5.2  | 1184     | 1.4  |
| Mixed                              | 20                   | 13.3 | 36,631   | 28.8 | 8                                    | 8.2  | 8234     | 9.9  |
| Recruitment ward                   |                      |      |          |      |                                      |      |          |      |
| Surgical only                      | 107                  | 71.3 | 93,951   | 74.0 | 69                                   | 71.1 | 71,059   | 85.5 |
| Radiological/oncological only      | 30                   | 20.0 | 11,504   | 9.1  | 19                                   | 19.6 | 3051     | 3.7  |
| Both                               | 10                   | 6.7  | 20,308   | 16.0 | 7                                    | 7.2  | 8176     | 9.8  |
| Not reported                       | 3                    | 2.0  | 1279     | 1.0  | 2                                    | 2.1  | 777      | 0.9  |
| Mean age at diagnosis              |                      |      |          |      |                                      |      |          |      |
| < 60 y                             | 70                   | 46.7 | 49,808   | 39.2 | 37                                   | 38.1 | 17,742   | 21.4 |
| ≥ 60 y                             | 53                   | 35.3 | 17,604   | 13.9 | 40                                   | 41.2 | 13,283   | 16.0 |
| Not reported                       | 27                   | 18.0 | 59,630   | 46.9 | 20                                   | 20.6 | 52,038   | 62.6 |
| Male-to-female ratio               |                      |      |          |      |                                      |      |          |      |
| ≤ 3.3                              | 76                   | 50.7 | 67,711   | 53.3 | 51                                   | 52.6 | 58,441   | 70.4 |
| > 3.3                              | 75                   | 50.0 | 58,667   | 46.2 | 47                                   | 48.5 | 23,958   | 28.8 |
| Not reported                       | 1                    | 0.7  | 664      | 0.5  | 1                                    | 1.0  | 664      | 0.8  |
| Staging classification             |                      |      |          |      |                                      |      |          |      |
| AJCC/UICC TNM (7 <sup>th</sup> )   | 52                   | 34.7 | 73,483   | 57.8 | 36                                   | 37.1 | 56,080   | 67.5 |
| Other staging systems              | 63                   | 42.0 | 39,643   | 31.2 | 35                                   | 36.1 | 17,526   | 21.1 |
| Not reported                       | 35                   | 23.3 | 13,916   | 11.0 | 26                                   | 26.8 | 9457     | 11.4 |
| Stage grouping categories          |                      |      |          |      |                                      |      |          |      |
| 0/I/II/III/IV                      | 61                   | 40.7 | 96,922   | 76.3 | 38                                   | 39.2 | 65,765   | 79.2 |
| Early/late                         | 23                   | 15.3 | 7920     | 6.2  | 18                                   | 18.6 | 4593     | 5.5  |
| Other categorisations <sup>c</sup> | 60                   | 40.0 | 20,251   | 15.9 | 38                                   | 39.2 | 11,921   | 14.4 |
| Not applicable <sup>d</sup>        | 6                    | 4.0  | 1949     | 1.5  | 3                                    | 3.1  | 784      | 0.9  |

Table 1. Continued

|                          | All eligible studies |       |          |       | Non-overlapping studies <sup>a</sup> |       |          |       |
|--------------------------|----------------------|-------|----------|-------|--------------------------------------|-------|----------|-------|
|                          | Studies              |       | Patients |       | Studies                              |       | Patients |       |
|                          | N                    | %     | N        | %     | N                                    | %     | N        | %     |
| Histology                |                      |       |          |       |                                      |       |          |       |
| SCC only                 | 106                  | 70.7  | 109,014  | 85.8  | 68                                   | 70.1  | 72,064   | 86.8  |
| AC only                  | 2                    | 1.3   | 315      | 0.2   | 2                                    | 2.1   | 315      | 0.4   |
| Mixed                    | 35                   | 23.3  | 14,171   | 11.2  | 21                                   | 21.6  | 7393     | 8.9   |
| Not reported             | 7                    | 4.7   | 3542     | 2.8   | 6                                    | 6.2   | 3291     | 4.0   |
| High risk of bias        |                      |       |          |       |                                      |       |          |       |
| Study design             | 121                  | 80.7  | 86,690   | 68.2  | 82                                   | 84.5  | 73,390   | 88.4  |
| Participant accrual      | 99                   | 66.0  | 70,920   | 55.8  | 69                                   | 71.1  | 61,306   | 73.8  |
| Losses to follow-up      | 86                   | 57.3  | 78,097   | 61.5  | 58                                   | 59.8  | 66,957   | 80.6  |
| Follow-up method         | 53                   | 35.3  | 15,759   | 12.4  | 42                                   | 43.3  | 12,176   | 14.7  |
| Survival time scale      | 39                   | 26.0  | 17,635   | 13.9  | 33                                   | 34.0  | 15,139   | 18.2  |
| Survival analysis method | 6                    | 4.0   | 7650     | 6.0   | 6                                    | 6.2   | 7650     | 9.2   |
| Key prognostic variables | 49                   | 32.7  | 20,164   | 15.9  | 36                                   | 37.1  | 16,798   | 20.2  |
| Total                    | 150                  | 100.0 | 127,042  | 100.0 | 97                                   | 100.0 | 83,063   | 100.0 |

AC, adenocarcinoma; AJCC, American Joint Committee on Cancer; EC, esophageal cancer; NR, not reported; PB, population-based; PC, prospective cohort; PSM, propensity-score matched study; RCT, randomized controlled trial; SCC, squamous cell carcinoma; UICC, Union for International Cancer Control.

<sup>a</sup>Studies with nonoverlapping study populations (Methods section).

<sup>b</sup>All population-based studies were conducted using data from the cancer registry of Taiwan.

<sup>c</sup>Stage treated as a continuous variable or categorized in a way that do not allow regrouping as per the standard TNM stages (Table S5).

<sup>d</sup>Not applicable for studies which restricted recruitment of participants to those with a specific stage (eg, stage IV, only).

when all 70 eligible studies were considered (data not shown).

### Meta-Analysis Using Reconstructed Individual Patient Data

Twenty six non-overlapping studies ( $n = 15,415$ ) were included in the reconstructed IPD analysis (Figure 1), with 7915 early-stage and 7500 late-stage patients, followed up for a median of 63.1 (interquartile range 53.4–105.7) months. A total of 10,278 deaths occurred during follow-up (4469 and 5809, respectively, among early-stage and late-stage patients), corresponding to a median survival time of 27.8 (11.1–99.3) months.

The final multiple hazard regression model included tumor stage, study design, and sample size. Estimated summary stage-specific survival probabilities are shown in Table 2 and Figure S2. The probability of surviving EC declined gradually with more advanced stage, resulting in an absolute survival difference between stages 0–II and stages III–IV of 31.2% (95% CI 29.9%–32.4%) at 5 years after diagnosis [44.5% (43.4%–45.5%) vs 13.3% (12.6%–14.0%)] (Table 2).

Prospective studies reported lower survival estimates at all 3 time points for both early and late stage compared to retrospective studies. Studies with sample size  $< 300$  reported lower survival estimates compared to studies with sample size  $\geq 300$  for early stage but higher survival estimates for late stage (Table 2).

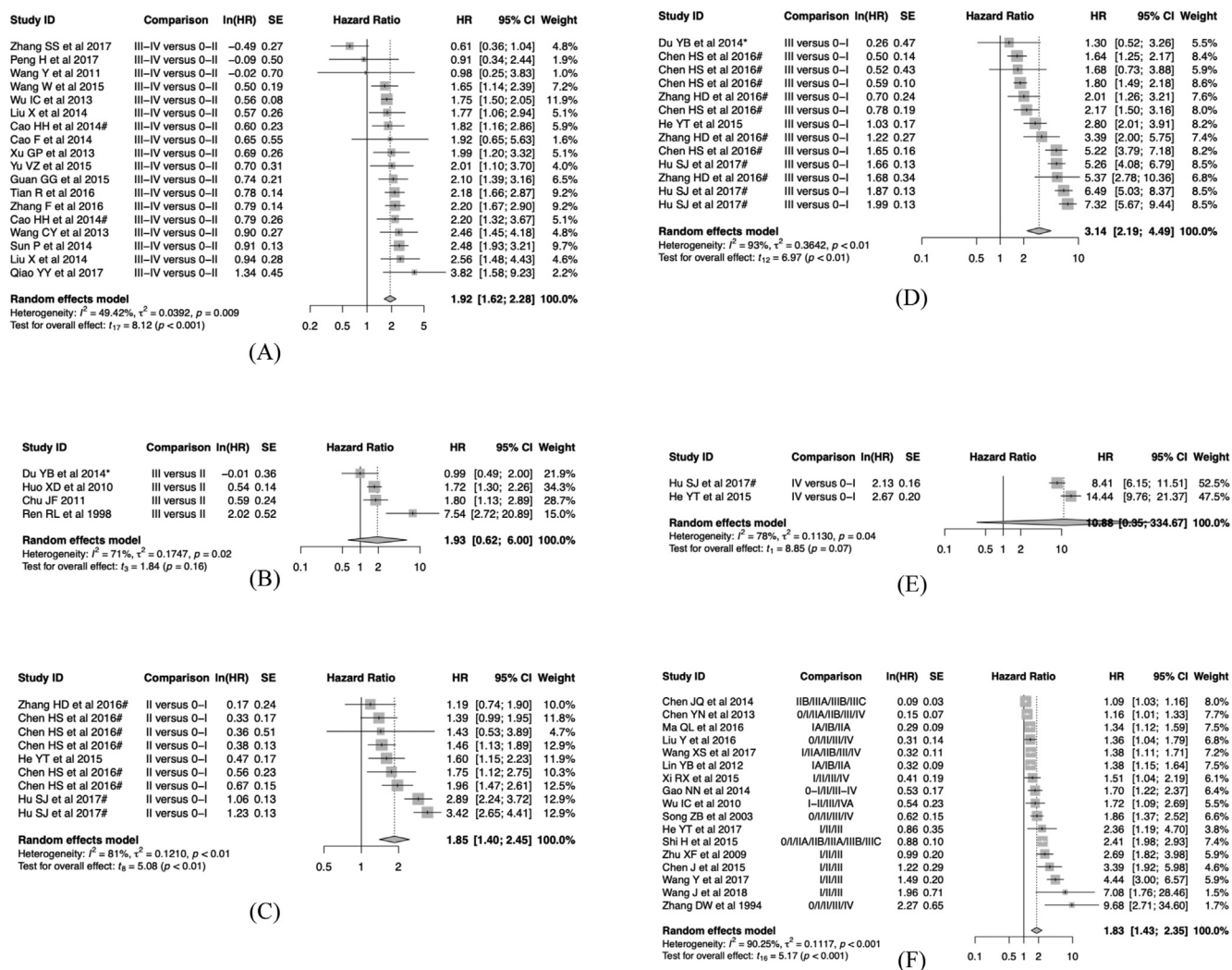
Sensitivity analyses of survival probabilities based on all 41 eligible studies ( $n = 34,934$ ; Figure 1) yielded similar summary survival probabilities (Table S8; Figure S3).

### Number of Deaths Potentially Prevented by Early Detection

Using the summary stage-specific survival estimates based on the subset of non-overlapping studies, we estimated that 5.2% and 26.9% of deaths from EC in China, in 2018, among cases diagnosed in the previous 5 years, could potentially have been prevented if the stage distribution at diagnosis observed in the current review (*status quo*: 10.8%, 40.0%, 46.5%, and 2.7%, respectively, for stages 0–I, II III, and IV) had been shifted, respectively, to the stage distribution reported in South Korea (scenario 1) or to the stage distribution observed in an endoscopic screening trial (scenario 2) (Figure 3). These estimates were robust to different assumptions (Text S2, Figure S4).

## Discussion

This systematic review, with meta-analyses, is the first to synthesize all the available evidence to yield stage-specific survival, on both absolute and relative scales, from EC in China. Using its survival figures, we estimated that between 5% (based on the real-life downstaging estimates observed in South Korea, where a population-based EC screening program was implemented) and 27% (based on the



**Figure 2.** Study-specific hazard ratios and summary pooled estimates of the effect of tumor stage on mortality after a diagnosis of esophageal cancer in China based on the subset of non-overlapping studies (Methods section): (A) stage III-IV vs stage 0-II; (B) stage III vs stage II; (C) stage II vs stage 0-I; (D) stage III vs stage 0-I; (E) stage IV vs stage 0-I; and (F) per one unit increment in stage category (stage taken as a continuous variable). Comparisons based on stage groupings with less than 5 studies are omitted.

\*The HRs reported in the original publication used late stage as the reference group; hence, HRs using early stage as the reference group were derived by inverting the reported HR values.

#Several study-specific HR estimates from a single study included in the meta-analyses as they corresponded to different (nonoverlapping) patient subgroups (eg, different treatment modalities).

downstaging estimates seen in the controlled setting of a randomized trial) of EC deaths in China, in 2018, among patients diagnosed in the previous 5 years, could have been potentially prevented by early detection efforts.

This systematic review has several strengths. Its inclusive search strategy, covering both English and Chinese bibliographic databases and annual cancer registry reports, ensured all relevant publications were included. Meta-analysis of study-level time-to-event data was used to synthesize HRs of late-stage vs early-stage disease. In addition, we applied a novel method to reconstruct individual-level time-to-event data from published KM curves, although this novel approach does not obtain individual-level data on covariates.

This review also has some limitations. First, only 150 studies were eligible for the qualitative synthesis. Second, it was very difficult to gauge the degree of overlap in study populations across studies. We used strict criteria to exclude all studies with potentially overlapping populations from the main analyses, which might have resulted in under-representation of certain subsets of patients. Reassuringly, sensitivity analyses based on all eligible studies yielded similar results. Third, the review was largely based, out of necessity, on hospital-based studies. But as appropriate staging work-up (eg, endoscopy with biopsy) can only be done in hospital settings, hospital-based estimates of stage-specific survival are unlikely to be less reliable than

**Table 2.** Summary Survival Probability Estimates for Early-Stage and Late-Stage Esophageal Cancer at 1, 3, and 5 Years After Diagnosis of Esophageal Cancer, and Corresponding Absolute Differences, From Reconstructed Individual Patient Data Based on 26 Non-overlapping Studies (15,415 Patients)

|                                | Summary survival (S) and absolute differences (AD) <sup>a</sup> |       |       |              |       |       |              |       |       |
|--------------------------------|-----------------------------------------------------------------|-------|-------|--------------|-------|-------|--------------|-------|-------|
|                                | 1 y (95% CI)                                                    |       |       | 3 y (95% CI) |       |       | 5 y (95% CI) |       |       |
| All                            |                                                                 |       |       |              |       |       |              |       |       |
| Early-stage (0-II) (S)         | 83.17                                                           | 82.58 | 83.74 | 56.60        | 55.62 | 57.56 | 44.48        | 43.43 | 45.53 |
| Late-stage (III-IV) (S)        | 61.98                                                           | 61.08 | 62.86 | 23.60        | 22.76 | 24.45 | 13.31        | 12.62 | 14.01 |
| Early-stage vs late-stage (AD) | 21.19                                                           | 20.13 | 22.25 | 32.99        | 31.71 | 34.28 | 31.17        | 29.91 | 32.44 |
| 0-I (S)                        | 88.85                                                           | 87.93 | 89.70 | 69.38        | 67.32 | 71.34 | 59.32        | 56.86 | 61.69 |
| II (S)                         | 81.76                                                           | 81.09 | 82.42 | 53.96        | 52.84 | 55.06 | 41.62        | 40.44 | 42.79 |
| III (S)                        | 61.92                                                           | 61.01 | 62.82 | 23.86        | 22.99 | 24.73 | 13.58        | 12.86 | 14.31 |
| IV (S)                         | 57.03                                                           | 53.61 | 60.29 | 18.73        | 15.71 | 21.97 | 9.68         | 7.51  | 12.16 |
| 0-I vs II (AD)                 | 7.09                                                            | 5.98  | 8.19  | 15.42        | 13.13 | 17.72 | 17.70        | 15.02 | 20.39 |
| 0-I vs III (AD)                | 26.93                                                           | 25.66 | 28.19 | 45.52        | 43.33 | 47.72 | 45.74        | 43.22 | 48.26 |
| 0-I vs IV (AD)                 | 31.82                                                           | 28.36 | 35.28 | 50.65        | 46.92 | 54.37 | 49.64        | 46.29 | 52.99 |
| By study design:               |                                                                 |       |       |              |       |       |              |       |       |
| PB/PC/RCT studies              |                                                                 |       |       |              |       |       |              |       |       |
| Early-stage (S)                | 76.57                                                           | 75.56 | 77.54 | 42.95        | 41.31 | 44.57 | 29.47        | 27.83 | 31.13 |
| Late-stage (S)                 | 55.77                                                           | 54.63 | 56.88 | 15.75        | 14.81 | 16.71 | 6.91         | 6.28  | 7.59  |
| Early-stage vs late-stage (AD) | 20.80                                                           | 19.30 | 22.30 | 27.20        | 25.31 | 29.08 | 22.56        | 20.78 | 24.34 |
| Retrospective studies          |                                                                 |       |       |              |       |       |              |       |       |
| Early-stage (S)                | 85.76                                                           | 85.20 | 86.29 | 61.95        | 60.94 | 62.94 | 50.37        | 49.25 | 51.47 |
| Late-stage (S)                 | 71.29                                                           | 70.29 | 72.27 | 35.38        | 34.09 | 36.68 | 22.90        | 21.71 | 24.11 |
| Early-stage vs late-stage (AD) | 14.47                                                           | 13.34 | 15.59 | 26.56        | 24.93 | 28.20 | 27.47        | 25.83 | 29.10 |
| By sample size:                |                                                                 |       |       |              |       |       |              |       |       |
| < 300                          |                                                                 |       |       |              |       |       |              |       |       |
| Early-stage (S)                | 80.23                                                           | 78.95 | 81.45 | 50.57        | 48.39 | 52.71 | 37.85        | 35.63 | 40.07 |
| Late-stage (S)                 | 66.86                                                           | 65.12 | 68.54 | 28.96        | 26.85 | 31.10 | 17.20        | 15.41 | 19.08 |
| Early-stage vs late-stage (AD) | 13.37                                                           | 11.25 | 15.48 | 21.62        | 18.58 | 24.65 | 20.65        | 17.76 | 23.53 |
| ≥ 300                          |                                                                 |       |       |              |       |       |              |       |       |
| Early-stage (S)                | 83.54                                                           | 82.94 | 84.11 | 57.35        | 56.33 | 58.35 | 45.31        | 44.21 | 46.41 |
| Late-stage (S)                 | 61.25                                                           | 60.31 | 62.18 | 22.81        | 21.93 | 23.70 | 12.73        | 12.03 | 13.45 |
| Early-stage vs late-stage (AD) | 22.28                                                           | 20.80 | 23.77 | 34.54        | 32.33 | 36.75 | 32.58        | 30.53 | 34.64 |

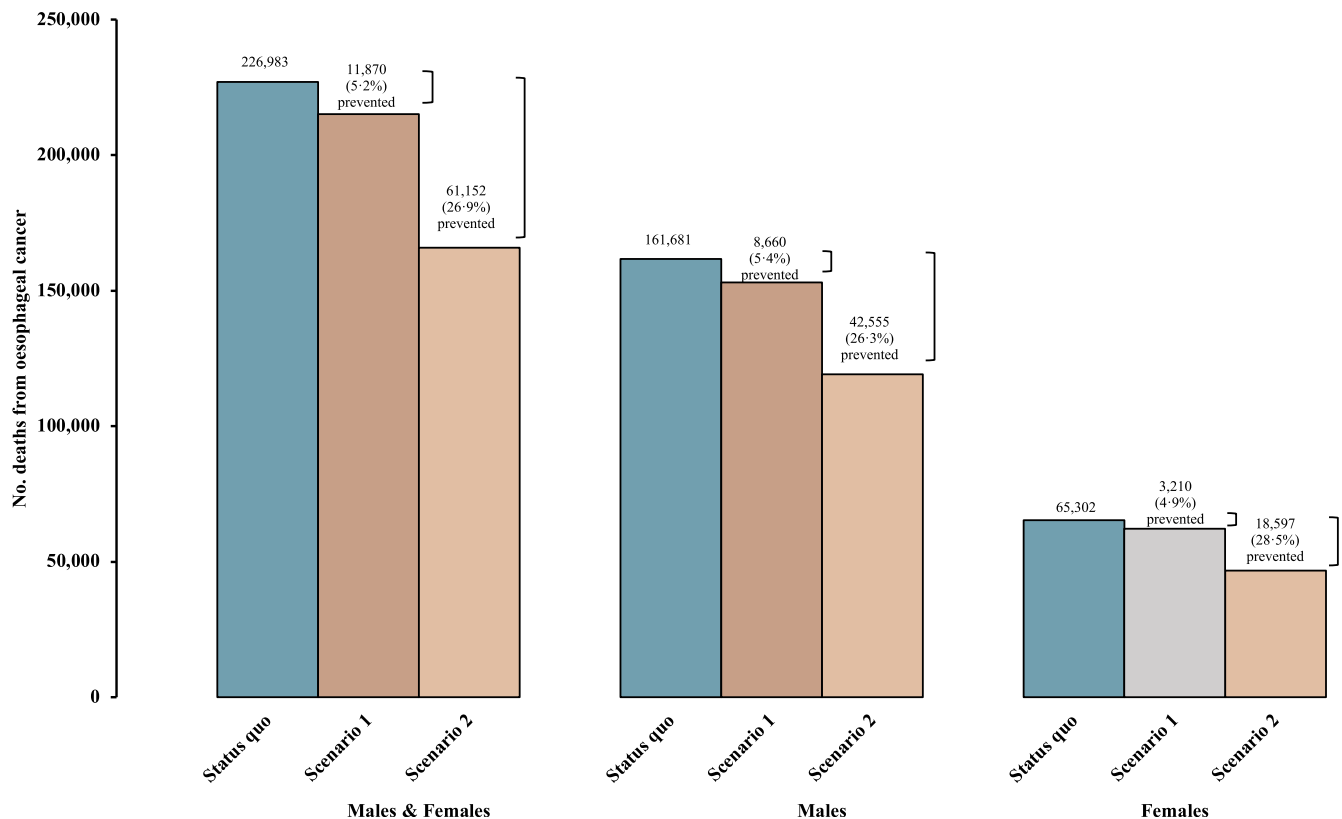
PB, population-based; PC, prospective cohort; RCT, randomized controlled trial.

<sup>a</sup>Survival probability estimated from a mixed-effects hazard regression model which included stage, study design, and sample size (section entitled “Meta-analysis using reconstructed individual patient data”) and expressed as a percentage (0–100).

population-based estimates from cancer registry data. Fourth, tumor-staging methodology might have varied across health facilities. However, only type of recruitment ward was identified as a source of between-study heterogeneity with studies including radio/oncological patients reporting higher HRs for late vs early stage than studies recruiting surgical patients only (Table S7). This might reflect genuine differences in disease stage, with nonsurgical late-stage patients being diagnosed at a more advanced stage than surgical late-stage patients and/or differences in the staging approach (eg, pathological staging for surgical patients vs clinical staging for nonsurgical patients). Fifth, the low quality of many of the included studies might have biased the pooled survival estimates. Reassuringly, however, the pooled 5-year all-stage survival estimates from IPD of 19 studies ( $n = 7349$ ) that did not restrict recruitment to any particular stage (41.1%, 95% CI 40.1%–42.1%) were similar to that reported in a recent systematic review and meta-analysis of hospital-based studies in China (40.1%, 33.7%–46.4%),<sup>72</sup> albeit higher

than the estimates reported by the National Cancer Registry for 2003–2005 (18.4%)<sup>73</sup> and most regional cancer registries (Table S9).

The areas with the highest EC risk worldwide stretch from north-eastern Iran to China, where SCC represents more than 90% of cases. In contrast to high-income countries, where tobacco smoking and alcohol consumption are the most important risk factors for EC,<sup>74</sup> other risk factors have been reported in high-risk areas, such as consumption of hot tea, nitroso compounds in food, lack of access to piped water, and poor oral health.<sup>75</sup> Primary prevention aimed at reducing exposure to these risk factors has had a little impact and thus early detection, based on endoscopic screening, has been recommended in high-risk areas. Our estimation of the number of potentially preventable deaths through endoscopic screening under 2 contrasting scenarios showed that screening would lead to only modest-to-moderate reductions in mortality. These estimations rely on the assumption that downstaging is feasible with tumors diagnosed at a late stage having a similar natural history to



**Figure 3.** Number (%) of deaths from esophageal cancer that could potentially have been prevented in China, in 2018, among patients diagnosed in the previous 5 years, if the current stage distribution (*status quo*) were shifted downwards to: (i) *scenario 1*, the nationwide stage distribution in South Korea (30.3%, 28.6%, 26.6%, and 14.5% tumor diagnosed, respectively, at stages 0–I, II, III, and IV) and (ii) *scenario 2*, the stage distribution reported in the intervention arm of an intensive endoscopic screening trial in China (71.0%, 19.4%, 6.4%, and 3.2%, respectively, at stages 0–I, II, III, and IV) (estimations based on the stage distribution and stage-specific survival estimates yielded by the meta-analyses of non-overlapping studies; Text S2 provides full discussion of estimation methods and underlying assumptions).

those diagnosed at an earlier stage as opposed to being intrinsically more biologically aggressive. The estimations also rely on the assumption that gains in survival through early diagnosis will ultimately translate into mortality reductions rather than simply reflecting lead-time bias<sup>76</sup>—an issue that can only be answered by randomized controlled trials with the primary outcome being mortality.<sup>77</sup>

Even if proven to be effective, implementation of population-based endoscopic screening in China would be a huge challenge. In a randomized controlled trial aiming to assess the cost-effectiveness of endoscopic screening in high-risk areas (Endoscopic Screening for Esophageal Cancer in China, ESECC, NCT01688908),<sup>77</sup> the cost of a single screening procedure was found to be much higher than what was previously reported in other countries (eg, the United States, Japan, etc.) relative to local per capita gross domestic product (US \$4246 in 2016 in Hua County, Henan Province, a well-recognized high-risk area of EC in China).<sup>78</sup> A simulation study concluded that endoscopic screening every 2 years was cost-effective in areas with high incidence of gastric cancer and EC but it relies on the national level of per capita gross domestic product (US \$10,276 in China) as the threshold for willingness to pay,<sup>79</sup> which was much

higher than that for Hua County. Although the cost-effectiveness of endoscopic screening may be enhanced by adoption of risk prediction models,<sup>80</sup> and development of less invasive techniques, implementation of a population-based screening program would still impose a heavy financial and administrative burden on local governments.<sup>78</sup> The findings from the present study are also a reminder that for early detection to significantly reduce mortality, it needs to be coupled with effective treatment for early-stage disease. As EC is one of the commonest cancers in China, survival improvements for this cancer will be critical to achieving the Healthy China 2030 goal of a 15% increase in 5-year all-cancer survival by 2030.

## Supplementary Materials

Material associated with this article can be found in the online version at <https://doi.org/10.1016/j.gastha.2022.10.012>.

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#### Authors' Contributions:

All authors contributed to the design and methodology of the study. Yu He led the data extraction and curation, conducted all the statistical analyses, and produced the original draft of the manuscript. Manuela Quaresma supported the data curation and the statistical analyses and contributed to the reviewing and final editing of the manuscript. Isabel dos-Santos-Silva supervised the conduct of the study, contributed to data extraction, and to the writing and final editing of the manuscript.

#### Conflict of Interest:

The authors disclose no conflicts.

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#### Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

#### Data Transparency Statement:

Data collected in this study and the analytic methods may be made available to bona fide researchers 1 year after publication upon reasonable request to the corresponding author (Isabel dos-Santos-Silva; [isabel.silva@lshtm.ac.uk](mailto:isabel.silva@lshtm.ac.uk)).

#### Reporting Guidelines:

PRISMA, SAGER.