Journal of the National Cancer Center 4 (2024) 318–325

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Full Length Article

# Clinicopathological and therapeutic comparisons of esophageal cancer between China and the USA: a multicenter hospital-based study

Juan Zhu[1,2,†], Lingbin Du[2,†], Huizhang Li[1,†], Xianhui Ran[2], Hongmei Zeng[2,*], Wenqiang Wei[2,*]

[1] Department of Cancer Prevention, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, China
[2] Office of National Central Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ARTICLE INFO

*Keywords:*
Esophageal cancer
Squamous cell carcinoma
Adenocarcinoma
Hospital-based
SEER
China

ABSTRACT

*Background:* Esophageal cancer (EC) remains a global health challenge due to its poor prognosis. China and the United States of America (USA) represent two distinct epicenters of EC burden. Understanding the EC disparities in these two countries is vital for tailoring prevention strategies, optimizing treatment, and enhancing outcomes in both countries. Yet, there lacks a comprehensive comparison of EC characteristics between the two countries.

*Methods:* In this multicenter, retrospective hospital-based study, we enrolled primary EC patients who received their initial treatment at one of 23 hospitals in China during 2016–2017. Using electronic medical records and cancer registration records, information on demographics, lifestyle, and clinicopathological characteristics (including tumor site, pathology, stage, metastases, differentiation, and treatment) were collected. Additionally, we compared these data with the clinicopathological information of invasive EC patients diagnosed in 2016–2017 from the Surveillance, Epidemiology, and End Results (SEER) database in the USA.

*Results:* A total of 6,658 EC patients in China and 8,555 EC patients in the USA were included finally. 85.5% ($n$ = 5,694) of EC were esophageal squamous cell carcinoma (ESCC) in China, while esophageal adenocarcinoma (EAC) was prominent in the USA (58.9%, $n$ = 5,041). Among EC patients with known staging, the proportion of early stage was higher in China compared to the USA (48.3% vs. 30.5%). Among ESCC patients, early-stage cases were higher in China than in the USA (49.8% vs. 31.8%), while among EAC patients, late-stage cases were higher in China than in the USA (77.3% vs. 68.5%) (all $P < 0.001$). In China, EC mainly occurred in the middle third (60.2%) of the esophagus, whereas in the USA, it was more common in the lower third (59.9%) of the organ. Compared with EC patients with known metastatic status in the USA, China had fewer cases of lymph node metastases (51.4% vs. 57.7%) and distant metastases (7.9% vs. 33.8%). Regarding treatment, China had more surgical therapy (53.7% vs. 22.6%), less radiotherapy (35.6% vs. 53.3%), and less chemotherapy (46.7% vs. 59.7%) compared to the USA.

*Conclusions:* This study reveals notable disparities in EC between China and the USA, encompassing epidemiological, clinicopathological, and treatment dimensions. These findings provide insight for tailored strategies addressing regional variations in clinicopathological and therapeutic characteristics.

## 1. Introduction

Despite advances in cancer management, esophageal cancer (EC) continues to pose a significant challenge to global health, characterized by poor prognosis and substantial geographical variations in incidence and survival rates.[1-6] Notably, China accounts for approximately 50% of EC cases worldwide and bears the highest disease burden.[7] The incidence of EC in China has been decreasing in recent years, possibly benefiting from the promotion of screening programs.[8] Conversely, in the United States of America (USA), while the incidence is lower, EC, especially the adenocarcinoma (EAC) subtype, is on the rise. Steep incidence increases in EAC in highly developed countries are contrasted with incidence declines in esophageal squamous cell carcinoma (ESCC) in many parts of the world, which suggests an ongoing transition in epidemiological patterns.[9-12] EC tends to be diagnosed at advanced, often incurable stages, and the prognosis remains poor, leading to low 5-year age-standardized net survival rates of 10% to 30% in most countries (30% in China and 19.9% in the USA).[5,6,13,14]

* Corresponding authors.
*E-mail addresses:* hongmeizeng@cicams.ac.cn (H. Zeng), weiwq@cicams.ac.cn (W. Wei).
† These authors contribute equally to this work.

https://doi.org/10.1016/j.jncc.2024.04.001
Received 28 January 2024; Received in revised form 24 March 2024; Accepted 1 April 2024

China and the USA represent two distinct epicenters of EC burden, each with unique demographic and lifestyle profiles.[9-12] ESCC dominates the histological landscape in China, largely attributed to dietary habits, smoking, and consumption of hot beverages, while EAC, often arising from Barrett's esophagus, dominates the histological subtype in the USA, with risk factors including gastroesophageal reflux, obesity, and dietary habits. The differing pathological natures of ESCC and EAC influence their clinical management, with treatment plans diverging significantly, particularly in later stages.[15,16] Understanding these disparities is crucial for informing targeted prevention strategies, optimizing treatment approaches, and improving patient outcomes in both countries. However, a comprehensive comparison of EC characteristics between China and the USA remains limited, necessitating a large-scale, multicenter study to bridge this knowledge gap. By elucidating these features, clinicians and policymakers can tailor interventions to address the unique challenges posed by ESCC and EAC within their respective populations. Moreover, this comparative analysis could serve as a blueprint for other regions grappling with similar epidemiological patterns.

Therefore, this study aims to comprehensively compare the clinicopathological features of EC patients in China and the USA, utilizing multicenter retrospective data from Chinese hospitals and data from the Surveillance, Epidemiology, and End Results (SEER) program. Endeavoring to bridge the knowledge gap by meticulously analyzing the similarities and discrepancies in EC's clinical and pathological landscapes in China and the USA, it will contribute to a more nuanced understanding of EC and foster the development of more effective, socio-economic context-specific treatment, and management strategies.

## 2. Patients and methods

### 2.1. Study design and data source

#### 2.1.1. Hospital-based patient selection in China

A retrospective hospital-based study was carried out and included EC patients from 23 hospitals in 12 provinces (Anhui, Beijing, Guangxi, Hebei, Henan, Heilongjiang, Hubei, Jiangsu, Liaoning, Qinghai, Shandong, and Zhejiang) across 6 geographical regions (north, northeast, northwest, east, central, and south) in China (Supplementary Table 1). Using electronic medical records (EMR) at the individual level from the local hospitals and cancer registration records from population-based cancer registries, we identified all eligible cases diagnosed with EC between Jan 1, 2016, and Dec 31, 2017. For EC patients, the inclusion criteria included (1) primary EC patients confirmed using pathological examination; and (2) patients undergoing initial treatment at the investigative hospital without prior surgery, radiotherapy, or chemotherapy at other institutions; the exclusion criteria included: (1) multiple primary cancers, metastatic cancers, EC patients with *in situ* tumors or epithelial neoplasia; (2) pathological diagnoses outside the period of 2016–2017; and (3) EC patients who have received treatment (surgery/radiotherapy/chemotherapy) at other hospitals. The third edition of the International Classification of Diseases for Oncology topography was used for identifying EC (C15.0-C15.5, C15.8-C15.9).

The hospitals and areas were selected to ensure they were representative of the broader population in China. The rationale and criteria for area and hospital selection were as follows:

(1) Geographical stratification and representation: The selection of 12 provinces from six distinct geographical regions across Mainland China (2 in Northeast China, 2 in North China, 4 in East China, 2 in Central China, 1 in South China, 1 in Northwest China) was based on their geographic distribution and population density. This approach ensured broad national representation in our sample, reflecting the epidemiological characteristics of EC.
(2) Criteria for county/city selection within the 12 provinces: a) Each selected area had been conducting population-based cancer registration for over five years, ensuring adequate data accumulation. b) The quality of the population-based cancer registry data from these areas was certified by the International Agency for Research on Cancer (IARC) and the National Central Cancer Registry (NCCR), guaranteeing data reliability and validity. c) These areas had established death surveillance systems and cancer follow-up systems for more than five years, enabling continuous monitoring of cancer patients. d) The population-based cancer registries in these areas possessed both the capability and willingness to conduct hospital-based cancer registration, which facilitated comprehensive data collection.
(3) Hospital selection rationale: Given that most cancer patients typically seek treatment at specialized or large general hospitals, we invited the largest such hospital within each of the 23 chosen areas to participate. Selected hospitals were required to have Electronic Medical Records and Health Information Systems in place to ensure accurate, efficient, and complete information gathering. If the largest specialized cancer hospital/general hospital lacked either the capacity or willingness to carry out hospital-based cancer registration, the second-largest hospital was chosen instead.

#### 2.1.2. SEER database in the USA

For data from the USA, we obtained information on EC patients in the USA from 18 registries in the SEER database (2019 submission data) covering 27.8% of the USA population.[17] The SEER program is a comprehensive source of population-based information in the USA. To generate a case listing, SEER*Stat (version 8.3.8) was employed. For EC patients, the inclusion criteria included (1) primary site: esophagus, behavior code ICD-O-3: malignant; and (2) EC patients diagnosed between 2016 and 2017; the exclusion criteria included: (1) multiple primary cancers or metastatic cancers; (2) pathological diagnoses outside the period of 2016–2017; and (3) EC cases with *in situ* tumors.

### 2.2. Data extraction and synthesis

#### 2.2.1. Sociodemographic characteristics

Sociodemographic characteristics extracted in the hospital-based survey in China included area of residence, hospital type, hospital level, name, age at diagnosis, sex, height, weight, medical insurance coverage, smoking history, alcohol drinking history, family history of any cancer, and family history of EC. Demographic characteristics of age at diagnosis and sex of EC patients were extracted in the SEER database.

#### 2.2.2. Clinicopathological and treatment characteristics

To ensure compatibility and comparability between the SEER dataset and the Chinese hospital records, standardized extraction forms were used to collect essential clinicopathological and treatment variables both in hospital-based survey and SEER database. Clinicopathological characteristics were documented, such as tumor site, tumour-node-metastasis (TNM) stage: extent of primary tumor stage (T stage), regional lymph node spread (N stage), presence of distant metastases (M stage), disease stage (I-IV), pathological type [ESCC, EAC, or esophageal adenosquamous carcinoma (EASC)], and differentiation status/grade. Furthermore, therapeutic information, involving surgical treatment, radiotherapy, and chemotherapy was also collected.

It is worth noting that the SEER database staging variables I-IV were directly downloaded; nonetheless, because of the insufficient uniformity and consistency of staging information recorded in China, it was necessary to perform a transformation and reorganization of these data before they could be appropriately utilized or compared. The detailed staging process is shown in Supplementary Fig. 1. The abstraction took place at least one year after discharge to ensure the complete and accurate stage at the time of diagnosis and first-course treatment information in the hospital. The TNM staging system maintained by the American Joint Committee on Cancer (AJCC) was used for staging abstraction.[18] Stages I and II were defined as early-stage, and stages III and IV were defined as late-stage.

**Table 1**
Demographic and clinical characteristics of EC patients in China and the USA.

| | China No. (%) | USA No. (%) | *P* value |
|---|---|---|---|
| All | 6,658 (100.0) | 8,555 (100.0) | |
| Age at diagnosis, years | | | < 0.001 |
| <55 | 865 (13.0) | 911 (10.6) | |
| 55–64 | 2,345 (35.2) | 2,307 (27.0) | |
| 65–74 | 2,555 (38.4) | 2,829 (33.1) | |
| ≥75 | 893 (13.4) | 2,508 (29.3) | |
| Sex | | | < 0.001 |
| Male | 4,954 (74.4) | 6,702 (78.3) | |
| Female | 1,704 (25.6) | 1,853 (21.7) | |
| AJCC TNM stage | | | < 0.001 |
| I | 864 (13.0) | 934 (10.9) | |
| II | 1,382 (20.8) | 1,129 (13.2) | |
| III | 1,920 (28.8) | 1,996 (23.3) | |
| IV | 484 (7.3) | 2,696 (31.5) | |
| Unknown | 2,008 (30.2) | 1,800 (21.0) | |
| T stage | | | < 0.001 |
| T1 | 805 (12.1) | 989 (11.6) | |
| T2 | 804 (12.1) | 787 (9.2) | |
| T3 | 2,174 (32.7) | 2,631 (30.8) | |
| T4 | 666 (10.0) | 660 (7.7) | |
| Unknown | 2,209 (33.2) | 3,488 (40.8) | |
| N stage | | | < 0.001 |
| N0 | 2,186 (32.8) | 2,961 (34.6) | |
| N1 | 1,550 (23.3) | 2,558 (29.9) | |
| N2 | 550 (8.3) | 1,048 (12.3) | |
| N3 | 214 (3.2) | 432 (5.0) | |
| Unknown | 2,158 (32.4) | 1,556 (18.2) | |
| M stage | | | < 0.001 |
| M0 | 4,904 (73.7) | 5,244 (61.3) | |
| M1 | 423 (6.4) | 2,682 (31.4) | |
| Unknown | 1,331 (20.0) | 629 (7.4) | |
| Pathological type | | | < 0.001 |
| ESCC | 5,694 (85.5) | 2,541 (29.7) | |
| EAC | 180 (2.7) | 5,041 (58.9) | |
| EASC | 53 (0.8) | 47 (0.5) | |
| Others | 142 (2.1) | 926 (10.8) | |
| Unknown | 589 (8.8) | 0 (0.0) | |
| Site | | | < 0.001 |
| Upper third of esophagus | 613 (9.2) | 620 (7.2) | |
| Middle third of esophagus | 4,005 (60.2) | 1,438 (16.8) | |
| Lower third of esophagus | 1,090 (16.4) | 5,124 (59.9) | |
| Overlapping lesion of esophagus | 337 (5.1) | 395 (4.6) | |
| Unknown | 613 (9.2) | 978 (11.4) | |
| Differentiation status | | | < 0.001 |
| Well differentiated | 255 (3.8) | 374 (4.4) | |
| Moderately differentiated | 1,600 (24.0) | 2,683 (31.4) | |
| Poorly/Undifferentiated | 1,343 (20.2) | 3,301 (38.6) | |
| Unknown | 3,460 (52.0) | 2,197 (25.7) | |
| Surgery | | | < 0.001 |
| No | 3,031 (45.5) | 6,277 (73.4) | |
| Yes | 3,574 (53.7) | 1,936 (22.6) | |
| Unknown | 53 (0.8) | 342 (4.0) | |

Abbreviations: AJCC, American Joint Committee on Cancer; EAC, esophageal adenocarcinoma; EASC, esophageal adenosquamous carcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; TNM, tumour-node-metastasis.

### *2.3. Quality control*

The rationale and criteria for province and hospital selection were formulated to ensure representativeness and consistency. A standardized study protocol was established to ensure integrity and accuracy, including data structure, data contents, abstracting methods, staging criteria, and file transmission procedures. The management team gathered on-site registrars and personnel from multiple centers for unified and comprehensive training (including the rationale of abstracting, coding, and staging), ensuring consistency in data collection across various investigation centers. To assess data quality, it was attempted to carry out a strict set of quality control measures, which involved adherence to the protocol and logical checks.

The EMR systems from which we extracted data are subject to regular quality control checks and audits within the participating hospitals. The data extraction process was performed under the supervision of experienced research personnel who are familiar with the structure and content of these EMRs. Furthermore, to assess inter-rater reliability, a subset of the data was independently reviewed by at least two researchers, with discrepancies resolved through discussions and consensus among the research team. In addition to this, we employed rigorous data validation procedures, including cross-checking key variables between multiple sources where possible, such as comparing questionnaire responses against corresponding medical records. We scrutinized the consistency of variable combinations for all submitted records. Any discrepancies or missing information were followed up with the respective hospitals or healthcare facilities to ensure data integrity. A detailed quality control report was provided to each registry, along with a request to correct any erroneous data. Subsequently, any resubmitted data were rechecked using the same rigorous procedures. Overall, these measures were im-

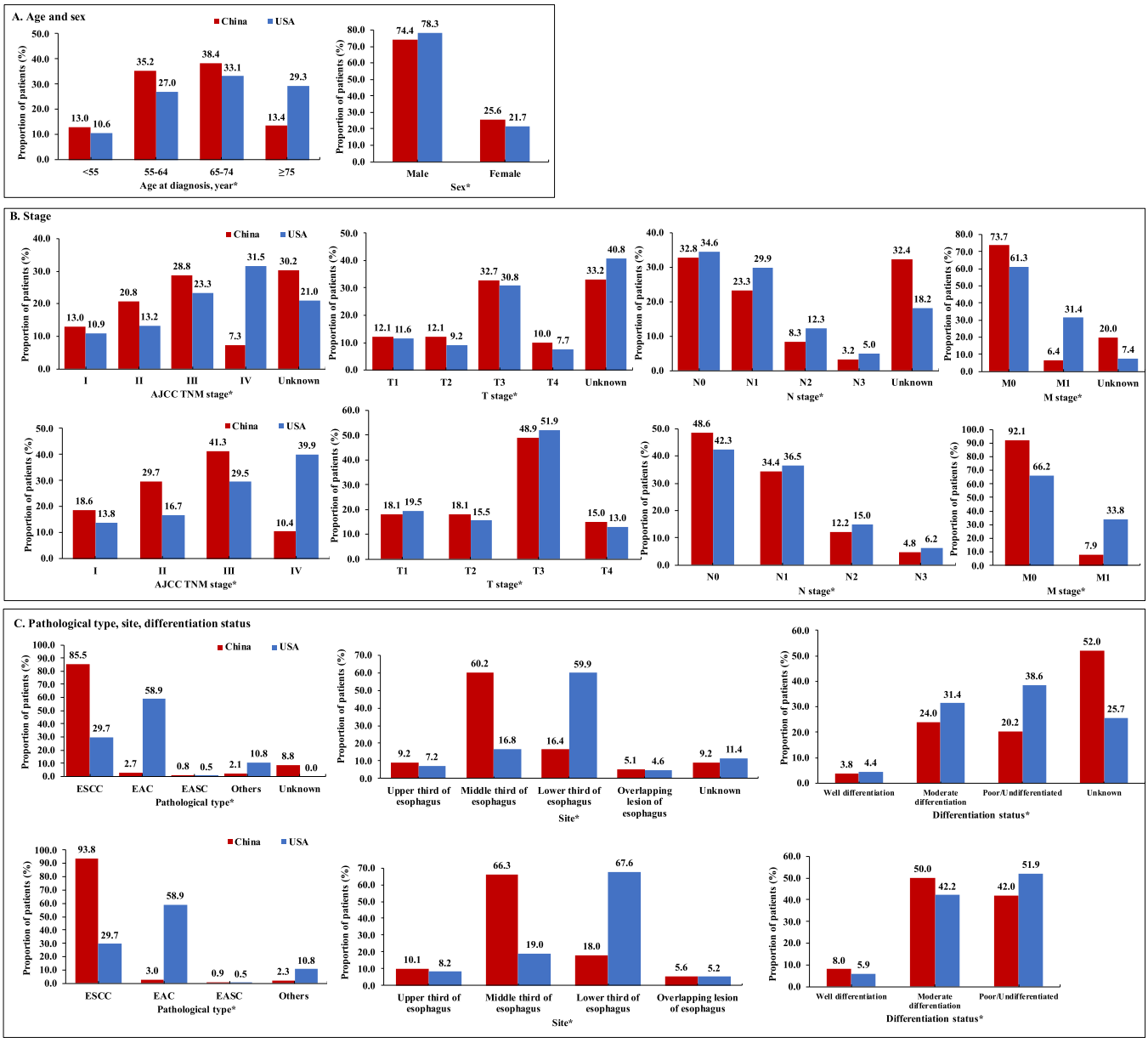


**Fig. 1.** Clinicopathological comparisons of esophageal cancer patients between China and the USA. (A) Age and sex. (B) Stage. (C) Pathological type, site and differentiation status. * indicates statistically significant differences between China and the USA in each clinicopathological feature. AJCC, American Joint Committee on Cancer; EAC, Esophageal adenocarcinoma; EASC, Esophageal adenosquamous carcinoma; ESCC, Esophageal squamous cell carcinoma; TNM, Tumour-Node-Metastasis.

plemented to enhance the accuracy and reliability of the collected data and to minimize potential sources of bias or error.

### 2.4. Statistical analysis

Absolute frequency and percentage were presented for categorical variables. We presented the internal composition of pathological characteristics and treatment modalities, while also reanalyzing the data after excluding the unknown categories. The chi-squared test or Fisher's exact test was applied to compare the clinicopathological characteristics and treatment between China and the USA. Data management, programming, and analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All tests of significance were two-tailed, and $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Sociodemographic characteristics of EC patients in China and the USA

The included 23 hospitals in China submitted a total of 6,693 patient records. We excluded patients diagnosed with *in situ* tumors ($n = 19$) and epithelial neoplasia ($n = 16$). A total of 6,658 EC patients were included finally in China, with a mean age of 64.84 years. 4,284 (64.3%) resided in urban areas, and 4,954 (74.4%) were males. 8,555 EC records were collected from SEER in the USA. The proportion of EC patients diagnosed at 65 to 74 years was highest in China and the USA. Younger (age at diagnosis <55 years) EC patients were diagnosed in China than in the USA (13.0% vs. 10.6%, $P < 0.001$). The proportion of EC in males was higher than that in females in both countries. The percentage of males was higher in the USA compared to that in China (78.3% vs. 74.4%) (Table 1).

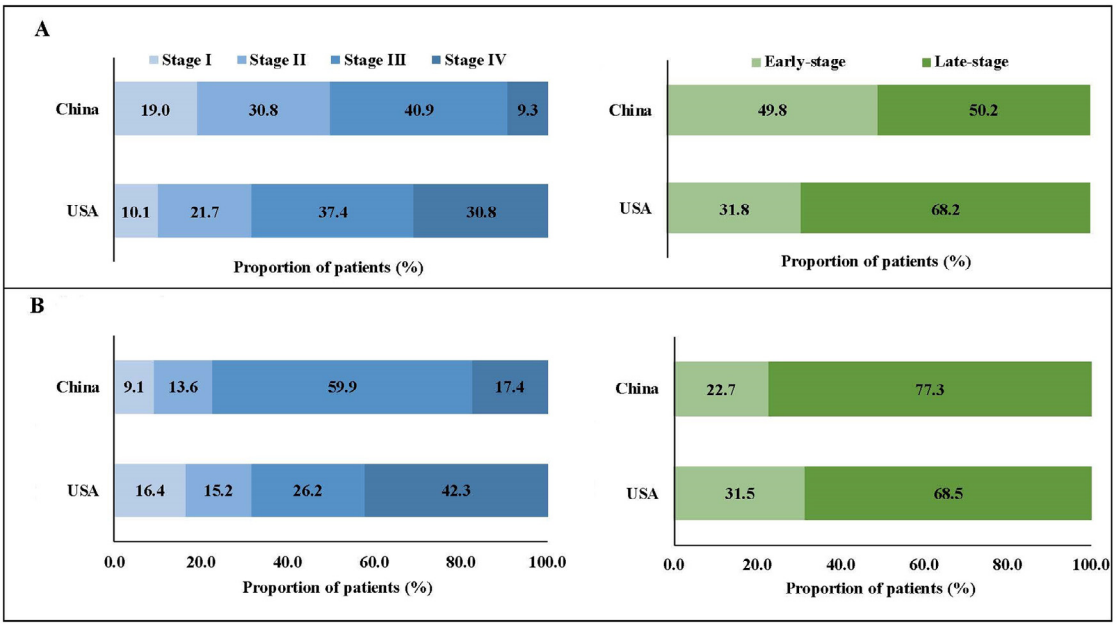


**Fig. 2.** Stage distribution at diagnosis of esophageal squamous cell carcinoma and adenocarcinoma between China and the USA. (A) Squamous cell carcinoma. (B) Adenocarcinoma. USA, United States of America.

### *3.2. Clinicopathological comparisons of EC patients in China and the USA*

It was observed that ESCC accounted for the majority of EC cases in China (85.5%, $n = 5{,}694$), whereas EAC was more prevalent in the USA (58.9%, $n = 5{,}041$) ($P < 0.001$). Among Chinese EC patients, 33.8% were diagnosed at an early stage (stage I: 13.0%, stage II: 20.8%), 36.1% at a late stage (stage III: 28.8%, stage IV: 7.3%), and 30.2% had an unknown stage. A significantly higher proportion of older patients (over 65 years) was observed in the unstaged group compared to those with known stages. Furthermore, a substantial majority of patients with known stages (70.7%) received surgical treatment, contrasting with the much lower rate in the unstaged group (14.3%). Conversely, the unstaged group had a notably higher proportion of patients receiving radiation therapy (50.6%) compared to those with known stages (29.1%), all with statistically significant differences ($P < 0.001$) (Table 1, Supplementary Table 2). As illustrated in Fig. 1A, individuals in China were typically diagnosed with EC at a younger age than in the USA. As shown in Fig. 1B, earlier stages were more frequently identified among EC patients with known stages in China compared to the USA (48.3% vs. 30.5%, $P < 0.001$). Less presence of lymph node and distant metastases was detected among EC cases with known metastatic status in China than in the USA (51.4% vs. 57.7%, 7.9% vs. 33.8%, respectively; all $P < 0.001$). Moreover, the data revealed that EC occurrence tended to concentrate in the middle third of the esophagus in China (60.2%), whereas in the USA, it was predominantly located in the lower third of the esophagus (59.9%) ($P < 0.001$) (Fig. 1C).

The comparison of stages for ESCC patients exhibited a higher proportion of early-stage diagnoses in China relative to the USA (49.8% vs. 31.8%, $P < 0.001$). Additionally, the corresponding proportions of stages I, II, and III ESCC were consistently higher in China versus those in the USA ($P < 0.001$) (Fig. 2A). However, for EAC patients, the proportion of late-stage diagnoses was significantly higher in China versus that in the USA (77.3% vs. 68.5%, $P < 0.001$). Among EAC cases, the proportion of stage III was significantly higher in China versus that in the USA (59.9% vs. 26.2%), while the proportion of stage IV was lower in China versus that in the USA (17.4% vs. 42.3%) (Fig. 2B).

### *3.3. Comparisons of treatments for EC cases in China and the USA*

Fig. 3A illustrates that the proportion of EC cases receiving surgery in China was significantly higher versus that in the USA (53.7% vs. 22.6%, $P < 0.001$). Additionally, the proportion of surgical treatment for EC patients with early-stage diagnoses in China was significantly higher versus that in the USA (87.3% at stage I and 86.1% at stage II in China vs. 59.5% at stage I and 34.6% at stage II in the USA) ($P < 0.001$). The study also found that the proportions of surgical treatment for ESCC (56.9% vs. 13.1%), EAC (54.4% vs. 29.5%), and EASC (79.2% vs. 17.0%) patients in China were consistently higher versus those in the USA (all $P < 0.001$).

In contrast, the study revealed that the proportions of radiotherapy (35.6% vs. 53.3%, $P < 0.001$) and chemotherapy (46.7% vs. 59.7%, $P < 0.001$) in China were significantly lower versus those in the USA. These findings were consistent across ESCC, EAC, and EASC. Additionally, the proportions of radiation and chemotherapy for EC cases with early-stage diagnoses in China were significantly lower versus those in the USA ($P < 0.001$). In the USA, the proportions of radiation and chemotherapy were high in stages II (85.0% and 82.1%) and III (84.2% and 85.8%) (Fig. 3B-3C). Furthermore, we found targeted therapy was not commonly used in China (Fig. 3D).

## 4. Discussion

Our study for the first time provides the most updated and comprehensive information on the clinicopathological and therapeutic information of EC in China, which represents the latest and largest effort by the National Cancer Center of China regarding the diagnostic and therapeutic status of EC in China. Disparities in clinicopathological features between China (earlier stage, less lymph node metastasis and distant metastasis, moderate differentiation, frequent occurrence in the middle third of the esophagus, more surgical therapy, and less radiotherapy and chemotherapy) and the USA (poor differentiation/undifferentiation, more common occurrence in the lower third of the esophagus, less surgery, and more radiotherapy and chemotherapy) existed. This research stands as a pioneering and extensive multicenter endeavor, bridging the comparative knowledge gap in EC's clinical and pathological landscapes in China and the USA, promoting the development of more effective treatment and management strategies relevant to socioeconomic backgrounds. Our findings not only enriched the understanding of clinicopathological and therapeutic profiles of hospitalized EC patients in China and serve as a foundational informational resource for the Chinese government's cancer statistics, but also benefit numer-

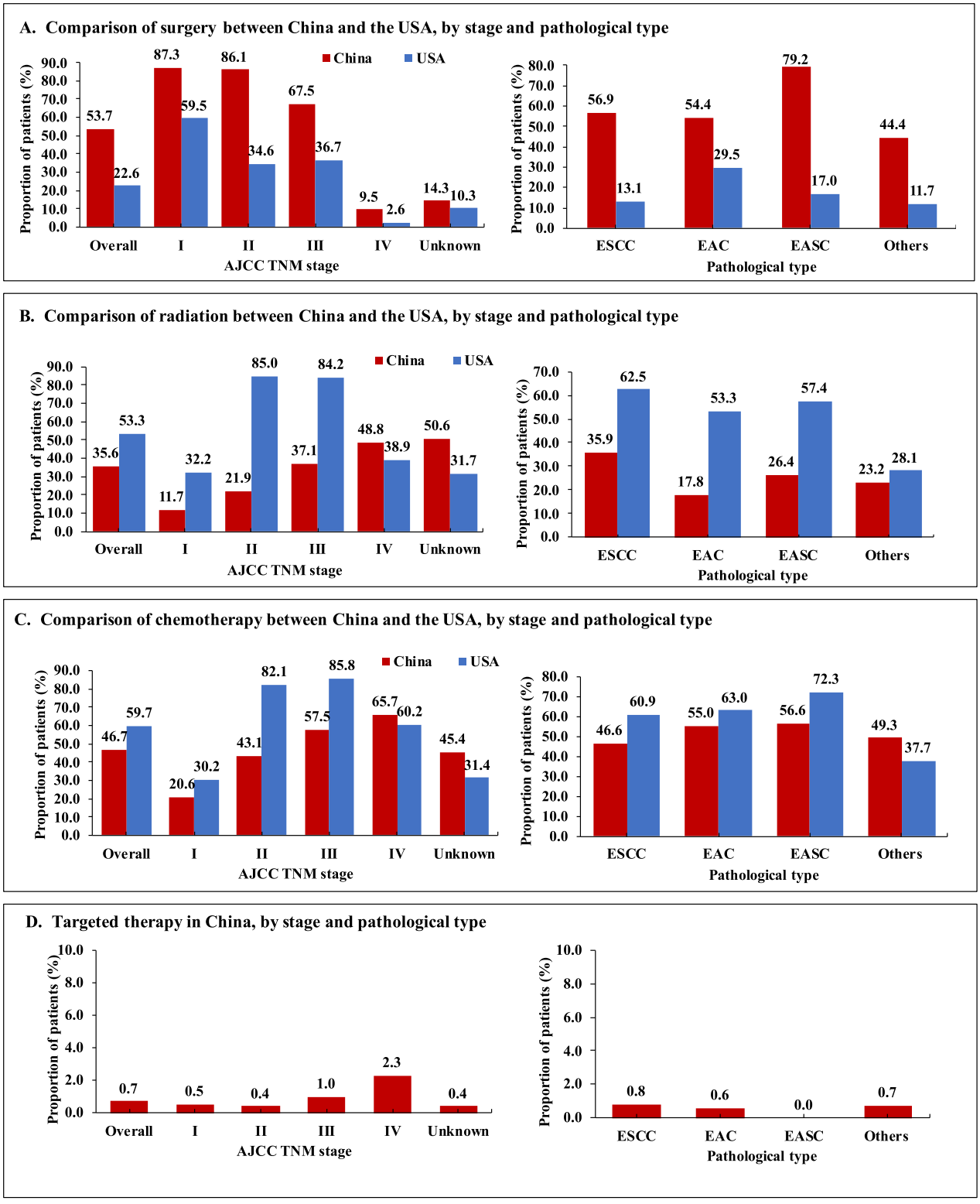


**Fig. 3.** Comparisons of treatment approaches between China and the USA, by stage and pathological type. (A) Comparison of surgery between China and the USA, by stage and pathological type. (B) Comparison of radiation between China and the USA, by stage and pathological type. (C) Comparison of chemotherapy between China and the USA, by stage and pathological type. (D) Targeted therapy in China, by stage and pathological type. AJCC, American Joint Committee on Cancer; EAC, esophageal adenocarcinoma; EASC, esophageal adenosquamous carcinoma; ESCC, esophageal squamous cell carcinoma; TNM, tumour-node-metastasis; USA, United States of America.

ous medical practitioners engaged in clinical practice and furnish critical insights for decision-making in EC prevention and control strategies.

### 4.1. Factors influencing the incidence, diagnosis, and treatment of EC

Disparities in the incidence, diagnosis, and treatment of EC may arise from multifaceted factors, such as lifestyle, environmental exposures, genetic predispositions, healthcare infrastructure, screening programs, and treatment guidelines. Understanding these variations is crucial for devising targeted interventions and improving patient outcomes.

Lifestyle, environmental and genetic factors: ESCC predominance in China may be linked to lifestyles such as tobacco smoking, heavy alcohol consumption, and the consumption of hot beverages and food at high temperatures, all of which are known risk factors for ESCC. Conversely, the prominence of EAC in the USA could be associated with factors like obesity and diets rich in processed foods and fats.[10-12] Environmental elements such as mineral or nutrition deficiencies (selenium/vitamin E/beta-carotene) in certain high-incidence areas of China may indirectly influence the occurrence of EC.[19] The potential effect of ethnicity and genetic differences between populations residing in the USA and China might lead to differences in the outcomes investigated and compared. A key factor contributing to the elevated risk of ESCC in Chinese and other Asian populations is the higher occurrence of germline mutations in the *NFE2L2* gene, which is three times higher compared to the Caucasian population in the USA.[20] Besides, distinct mutational patterns and driver genes in ESCC and EAC were identified at both genomic and epigenomic levels.[21] Several gene mutations and mutational signatures are correlated with the overall survival of patients. ESCC individuals positive for signature 16-like mutational profile had a significantly worse survival rate.[21] Uncovering genetic differences among various ethnicities lays the foundation for the personalized prevention, screening, and early diagnosis of EC. Additionally, targeted therapeutic drugs focusing on genes will offer more opportunities for curing EC patients.

Differences in screening programs: China's higher proportion of early-stage cases might reflect the effectiveness of screening initiatives or extensive primary healthcare networks, which could be bolstered by government-sponsored screening campaigns.[22] In high-incidence regions of EC in China, such as Linzhou city, Cixian county, and Linqu county, large-scale endoscopic screening programs have been implemented. These included the Cancer Screening Program in Rural Areas (since 2005), the Cancer Screening Program in the Huai River Areas (since 2009), the Cancer Screening Program in Urban Areas (since 2012), and the National Cohort of Esophageal Cancer (since 2016).[22] These screening efforts have led to significant reductions in EC incidence (decreased by 19%) and mortality (decreased by 18%), improvements in 5-year survival (increased from 20.9% in 2003–2005 to 30.3% in 2012–2015),[13] and confirmed cost-effectiveness.[8,23-25] Japan and South Korea have also established nationwide endoscopic screening programs that have proven effective in reducing mortality rates for EC and gastric cancer.[26] In contrast, screening for EC in the USA has not been widely adopted due to the lower incidence of the disease, making it less feasible. The USA primarily focuses on endoscopic surveillance for high-risk populations, such as those with Barrett's esophagus, resulting in potentially lower early detection rates. This disparity in screening practices between the USA and Asian countries like China, Japan, and Korea—where stage distribution for EC is more favorable—may partially explain the observed differences in survival outcomes.[27]

Difference in treatment guidelines, medical practices and patients' choice: Variations in treatment protocols between China and the USA may stem from differences in healthcare systems, availability of resources, and cultural factors. One possible explanation for the higher utilization of surgery in China is the prevalence of endoscopic procedures that may include simultaneous surgical intervention. Endoscopic techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), allow for the minimally invasive removal of early-stage esophageal cancers without the need for invasive surgery.[15] In comparison, a higher prevalence of late-stage cases in the USA may favor non-surgical approaches such as chemotherapy, radiation therapy, and neoadjuvant treatments.[16] Moreover, patients' preferences play a pivotal role in treatment decision-making. Cultural attitudes towards healthcare, trust in medical professionals, and individual beliefs in treatment efficacy and side effects, and socioeconomic factors may shape patients' decisions regarding therapy. In China, where there might be a stronger deference to medical authority, patients may be more inclined to follow physicians' recommendations, including surgical interventions. In the USA, patients might prioritize shared decision-making, weighing treatment options against their perceived impact on their lifestyle and well-being.

### 4.2. Reasons for a high proportion of unknown stage in China

Compared with the USA, patients in China had a higher proportion of unknown-stage in this study. The missing TNM classifications can be attributed to several underlying factors.[28,29] First, despite more than half of these patients undergoing surgery, historical data collection methods might not have consistently recorded TNM stages due to variations in documentation practices across different institutions or over time. Additionally, while China has made strides towards aligning with international standards in cancer treatment, differences in the implementation of standardized diagnoses and treatments, and potential differences in physician training and clinical practice standards could impact standardized diagnoses and tumor staging. While surgical intervention was performed, the pathological staging could have been inconclusive due to incomplete resection specimens or insufficient lymph node sampling, which are essential for accurate TNM categorization. Third, the establishment and improvement of comprehensive and accurate tumor registration and reporting systems take time. The maturity and completeness of such systems would impact the thorough collection and analysis of tumor staging information. This analysis vividly points to the current status quo in China regarding the collection and analysis of tumor staging information, as well as highlighting the need for us to make greater efforts.

Our study has some limitations. First, being hospital-based research, the findings might not be fully generalizable to the entire EC population in China, even though we covered various geographic and socioeconomic population groups in the country. Second, this study was observational and retrospective in nature, and the historical data collection methods might not have consistently recorded TNM stages. Third, the high proportion of unknown stage cases in the analysis may introduce bias in our results. Despite implementing a standardized study protocol for stage abstracting and conducting various training programs to ensure data quality, non-differential misclassification might still exist, introducing measurement error into the results. More efforts are required in China to gather population-based data regarding the stage at diagnosis.[30] Fourth, we lacked access to detailed screening information at the individual level, thereby limiting our ability to assess the screening's impact on stage migration. Therefore, it is essential to keep these limitations in mind when interpreting the findings of this study.

## 5. Conclusion

In conclusion, this study uncovers striking disparities in EC between China and the USA, encompassing epidemiological, clinicopathological, and treatment dimensions. These findings offer valuable insights into regional variations in EC characteristics, informing the need for tailored, context-specific prevention, diagnosis, and treatment strategies in both countries. Future research should capitalize on these findings, delving into the root causes of these disparities and developing targeted interventions aimed at reducing the global burden of EC and improving patient outcomes. By fostering international collaboration and knowledge exchange, we can accelerate progress in EC research and ultimately en-

hance the lives of millions affected by this devastating disease worldwide.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Ethics statement

Ethical approval for the study was received in China from the Ethics Committee Review Board (IRB) of the Cancer Institute and Hospital, Chinese Academy of Medical Science (approval number: NCC2018-016/1645). Due to the retrospective nature of the study, obtaining written consent was not possible; however, we adhered to a stringent protocol approved by the IRB. Data handling strictly complied with patient confidentiality and privacy laws. In respecting participant rights and privacy, we employed an opt-out or waiver of individual informed consent—common in retrospective studies using anonymized and de-identified data. The IRB granted approval after thorough consideration of the minimal risk involved with such anonymized patient data usage.

## Acknowledgments

We thank members of Hospital-based Cancer Registration (HBCR) including Huizhang Li, Yutong He, Shuzheng Liu, Renqiang Han, Zhenqiu Zha, Ning Wang, Qiulin Li, Jiyu Tuo, Yunyong Liu, Bingbing Song, Yanyan Li, Jian Zhu, Bianyun Li, Shuguang Dai, Guohui Song, Junjun Zhu, Mumu Shi, Gang Wu, Yan Wang, Xin Zhou, Yunyan Yan, Liwen Zhu, Jinhua Yang, Kun Jiang, Xiaopeng Zhang, Kuangrong Wei, Yunfeng Zhu for their contributions of data collection and quality control. This work was supported by the National Key R&D Program of China (grant number: 2022YFC3600805, 2016YFC1302502).

## Data availability

The corresponding author had full access to all the data in the study and was responsible for the decision to submit it for publication.

## Author contributions

J.Z., L.D., H.Z., and W.W. contributed to the conception and design of the study. J.Z., H.L. and X.R. did the data curation; J.Z. and X.R. performed formal data analysis. H.Z. and W.W. did the funding acquisition and project administration; J.Z., L.D. drafted the paper; and H.L., X.R., H.Z., and W.W. interpreted the results. All authors contributed to data interpretation and rewriting of the paper. All authors reviewed and approved the final version. All authors had full access to all the data and were responsible for the decision to submit the manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.04.001.

## References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024 Published online Aprial 4, 2024. doi:10.3322/caac.21834.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. doi:10.3322/caac.21763.
3. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology*. 2018;154(2):360–373. doi:10.1053/j.gastro.2017.08.023.
4. Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology*. 2020;159(1):335–349 e15. doi:10.1053/j.gastro.2020.02.068.
5. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health*. 2018;6:e555–e567. doi:10.1016/S2214-109X(18)30127-X.
6. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023–1075. doi:10.1016/S0140-6736(17)33326-3.
7. Han BF, Zheng RS, Zeng HM, et al. Cancer incidence and mortality in China, 2022. *J Natl Cancer Cent*. 2024;4(1):47–53. doi:10.1016/j.jncc.2024.01.006.
8. Chen R, Liu Y, Song G, et al. Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. *Gut*. 2021;70(2):251–260. doi:10.1136/gutjnl-2019-320200.
9. Arnold M, Ferlay J, van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*. 2020;69(9):1564–1571. doi:10.1136/gutjnl-2020-321600.
10. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J*. 2022;135(5):584–590. doi:10.1097/CM9.0000000000002108.
11. Ho ALK, Smyth EC. A global perspective on oesophageal cancer: two diseases in one. *Lancet Gastroenterol Hepatol*. 2020;5(6):521–522. doi:10.1016/S2468-1253(20)30047-9.
12. Thrumurthy SG, Chaudry MA, Thrumurthy SSD, Mughal M. Oesophageal cancer: risks, prevention, and diagnosis. *BMJ*. 2019;366:l4373. doi:10.1136/bmj.l4373.
13. An L, Zheng R, Zeng H, et al. The survival of esophageal cancer by subtype in China with comparison to the United States. *Int J Cancer*. 2023;152(2):151–161. doi:10.1002/ijc.34232.
14. Morgan E, Soerjomataram I, Gavin AT, et al. International trends in oesophageal cancer survival by histological subtype between 1995 and 2014. *Gut*. 2021;70(2):234–242. doi:10.1136/gutjnl-2020-321089.
15. Health Commission of the People's Republic of ChinaNational guidelines for diagnosis and treatment of esophageal carcinoma 2022 in China (English version). *Chin J Cancer Res*. 2022;34(4):309–334. doi:10.21147/j.issn.1000-9604.2022.04.01.
16. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, version 2.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2023;21(4):393–422. doi:10.6004/jnccn.20230.0019.
17. National Cancer Institute. Surveillance, Epidemiology, and End Results Program SEER ∗ _Stat Databases: November 2019 Submission. Accessed December 20, 2021. https://seer.cancer.gov/data-software/documentation/seerstat/nov2019/.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.*. 2010;176:1471–1474. doi:10.1245/s10434-010-0985-4.
19. Wang SM, Taylor PR, Fan JH, et al. Effects of nutrition intervention on total and cancer mortality: 25-year post-trial follow-up of the 5.25-year Linxian Nutrition Intervention Trial. *J Natl Cancer Inst*. 2018;110(11):1229–1238. doi:10.1093/jnci/djy043.
20. Deng J, Chen H, Zhou D, et al. Comparative genomic analysis of esophageal squamous cell carcinoma between Asian and Caucasian patient populations. *Nat Commun*. 2017;8(1):1533. doi:10.1038/s41467-017-01730-x.
21. Lin DC, Dinh HQ, Xie JJ, et al. Identification of distinct mutational patterns and new driver genes in oesophageal squamous cell carcinomas and adenocarcinomas. *Gut*. 2018;67(10):1769–1779. doi:10.1136/gutjnl-2017-314607.
22. Xia C, Basu P, Kramer BS, et al. Cancer screening in China: a steep road from evidence to implementation. *Lancet Public Health*. 2023;8(12):e996–e1005. doi:10.1016/S2468-2667(23)00186-X.
23. He ZH, Liu Z, Liu MF, et al. Efficacy of endoscopic screening for esophageal cancer in China (ESECC): design and preliminary results of a population-based randomised Controlled trial. *Gut*. 2019;68:198–206. doi:10.1136/gutjnl-2017-315520.
24. Liu MF, Yang WL, Guo CH, et al. Effectiveness of endoscopic screening on esophageal cancer incidence and mortality: a 9-year report of the Endoscopic Screening for Esophageal Cancer in China (ESECC) Randomized Trial. *J Clin Oncol*. 2024;8 Published online March. doi:10.1200/JCO.23.01284.
25. Xia R, Zeng H, Liu W, et al. Estimated cost-effectiveness of endoscopic screening for upper gastrointestinal tract cancer in high-risk areas in China. *JAMA Netw Open*. 2021;4(8):e2121403. doi:10.1001/jamanetworkopen.2021.21403.
26. Kim JH, Han KD, Lee JK, et al. Big Data Research Group (BDRG) of the Korean Society of Gastroenterology (KSG). Association between the National Cancer Screening Programme (NSCP) for gastric cancer and oesophageal cancer mortality. *Br J Cancer*. 2020;123(3):480–486. doi:10.1038/s41416-020-0883-x.
27. He YT, Liang D, Du L, et al. Clinical characteristics and survival of 5283 esophageal cancer patients: a multicenter study from eighteen hospitals across six regions in China. *Cancer Commun*. 2020;40(10):531–544. doi:10.1002/cac2.12087.
28. Zeng H, Ran X, An L, et al. Disparities in stage at diagnosis for five common cancers in China: a multicentre, hospital-based, observational study. *Lancet Public Health*. 2021;12:e877–e887. doi:10.1016/S2468-2667(21)00157-2.
29. Shan TH, Ran XH, Li HZ, et al. Disparities in stage at diagnosis for liver cancer in China. *J Natl Cancer Center*. 2023;3(1):7–13. doi:10.1016/j.jncc.2022.12.002.
30. Wei W, Zeng H, Zheng R, et al. Cancer registration in China and its role in cancer prevention and control. *Lancet Oncol*. 2020;217:e342–e349. doi:10.1016/S1470-2045(20)30073-5.