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ORIGINAL ARTICLE

Worldwide trends in esophageal cancer survival, by sub-site, morphology, and sex: an analysis of 696,974 adults diagnosed in 60 countries during 2000-2014 (CONCORD-3)

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Abstract

Background: Esophageal cancer survival is poor worldwide, though there is some variation. Differences in the distribution of anatomical sub-site and morphological sub-type may help explain international differences in survival for all esophageal cancers combined. We estimated survival by anatomic sub-site and morphological sub-type to understand further the impact of topography and morphology on international comparisons of esophageal cancer survival.

Methods: We estimated age-standardized one-year and five-year net survival among adults (15-99 years) diagnosed with esophageal cancer in each of 60 participating countries to monitor survival trends by calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014), sub-site, morphology, and sex.

Results: For adults diagnosed during 2010-2014, tumors in the lower third of the esophagus were the most common, followed by tumors of overlapping sub-site and sub-site not otherwise specified. The proportion of squamous cell carcinomas diagnosed during 2010-2014 was generally higher in Asian countries (50%-90%), while adenocarcinomas were more common in Europe, North

Abbreviations: CI, confidence interval; ICSS, International Cancer Survival Standard; ICD-O-3, International Classification of Diseases for Oncology; NOS, not otherwise specified.

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America and Oceania (50%-60%). From 2000-2004 to 2010-2014, the proportion of squamous cell carcinoma generally decreased, and the proportion of adenocarcinoma increased. Over time, there were few improvements in age-standardized five-year survival for each sub-site. Age-standardized one-year survival was highest in Japan for both squamous cell carcinoma (67.7%) and adenocarcinoma (69.0%), ranging between 20%-60% in most other countries. Age-standardized five-year survival from squamous cell carcinoma and adenocarcinoma was similar for most countries included, around 15%-20% for adults diagnosed during 2010-2014, though international variation was wider for squamous cell carcinoma. In most countries, survival for both squamous cell carcinoma and adenocarcinoma increased by less than 5% between 2000-2004 and 2010-2014.

Conclusions: Esophageal cancer survival remains poor in many countries. The distributions of sub-site and morphological sub-type vary between countries, but these differences do not fully explain international variation in esophageal cancer survival.

KEYWORDS

Cancer, esophagus, morphology, survival, topography, trends

1 | BACKGROUND

Esophageal cancer survival is relatively poor worldwide, with only limited improvement over the past few decades [1].

The second cycle of the CONCORD program established global surveillance of trends in cancer survival in 2015 [2]. CONCORD-3 updated global survival trends in 2018 by analyzing data on over 37.5 million cancer patients diagnosed with one of 18 common cancers during 2000-2014, contributed by 322 population-based cancer registries in 71 countries [1]. CONCORD-3 is the largest research program to date on population-based cancer survival, including information on anatomic sub-site and morphological subtype of the tumors included in analyses. Survival estimates are made as comparable as possible with centralized data quality control procedures and analysis and correction for background mortality in each region or country by age, sex, and calendar year.

CONCORD-3 reported wide international variation in five-year survival from esophageal cancer for all topographies and morphologies combined, ranging from 10% to 30% for adults diagnosed from 2010 to 2014[1]. Survival was highest in several East Asian countries. In addition, although survival increased in a few countries (e.g., China, Korea, and Japan), the improvements have been minimal.

Esophageal cancer is conventionally classified as upper third (cervical), middle third (thoracic) or lower third (abdominal). Squamous cell carcinoma and adenocarcinoma are the two most common morphological sub-types. Squamous cell carcinoma has historically been the most common sub-type, especially in low-income and middle-income countries in Asia where smoking, a known risk factor, is common[3, 4]. In North America and Western Europe, adenocarcinoma has more recently become the most common sub-type, possibly due to the link with Barrett's esophagus and the increasing prevalence of obesity [3, 4].

Previous studies of esophageal cancer survival by sub-site or morphology have been limited to one country or high-income countries in Europe, North America, and Oceania [5–11]. A more global picture of the distribution of and survival from esophageal cancer by sub-site and morphology is needed.

We have used data from CONCORD-3 for a more detailed study of whether international differences in the distribution of sub-site, morphology, and sex can help explain any of the international variation in esophageal cancer survival. We also provide estimates of time trends in esophageal cancer survival by sub-site, morphology, sex, and country, to identify groups for which survival is lowest, in order to help drive cancer control policies to improve esophageal cancer survival.

2 | METHODS

2.1 | Data

Data from 288 population-based cancer registries were available for 743,314 adults (15-99 years) diagnosed with esophageal cancer during 2000-2014 in 60 countries.

TABLE 1 Morphological sub-types.

Morphological sub-type	ICD-O-3 morphology code[a]
Squamous and transitional cell carcinomas	8051-8139
Adenocarcinomas	8140-8149, 8160-8169, 8180-8229, 8250-8509, 8520-8559, 8570-8579, 8940-8949
Other specified carcinomas	8030-8049, 8150-8159, 8170-8179, 8230-8239, 8240-8249, 8510-8519, 8560-8569, 8580-8679
Unspecified carcinomas	8010-8029, 8050
Sarcomas and other soft tissue tumors	8680-8719, 8800-8929, 8990-8999, 9040-9049, 9120-9349, 9370-9379, 9540-9589
Other specified tumors	8720-8799, 8930-8939, 8950-8989, 9000-9039, 9050-9119, 9360-9369, 9380-9539
Non-specific tumors	8000-8005

[a]Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL, editors. International Classification of Diseases for Oncology (ICD-O). First revision of 3rd ed. Geneva: World Health Organisation; 2013.

The CONCORD-3 protocol, the ethical approvals and the data quality control procedures have been described [1]. We included only primary, invasive malignant tumors (International Classification Diseases of Oncology, 3rd edition [12] (ICD-O-3) behavior code 3) in survival analyses. If a patient was diagnosed with two or more primary, invasive tumors of the esophagus, only the first record was included. Patients whose cancer registration was from a death certificate or autopsy only were excluded from analysis because their true survival time was unknown (Supplementary Table S1). Follow-up data on vital status (dead, alive, or lost to follow-up) until 31 December 2014 were available.

We categorized topography into four sub-sites based on the ICD-O-3 topographical code: cervical or upper third (C15.0 or C15.3), thoracic or middle third (C15.1 or C15.4) and abdominal or lower third (C15.2 or C15.5), with an additional category for cancers that overlapped sub-sites or for which the sub-site was not otherwise specified (NOS, C15.8 or C15.9).

We defined six morphological groups based on the literature and ICD-O-3 morphology codes [12]: squamous and transitional cell carcinomas, adenocarcinomas, other specified carcinomas, unspecified carcinomas, sarcomas and other soft tissue tumors, other specified cancers, and a separate category for tumors of non-specific morphology (Table 1).

2.2 | Statistical analyses

We estimated age-standardized one-year and five-year net survival by country, calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014), anatomic sub-site, morphological sub-type, and sex.

We used the cohort approach [13, 14] to estimate net survival for patients diagnosed during 2000-2004 and 2005-2009 because at least five years of follow-up data were available for all patients by the end of 2014. We used the period approach [15] to estimate survival for patients diagnosed during 2010-2014 because five years of follow-up data were not available for all patients by 31 December 2014. Period estimates were obtained by multiplying the conditional probabilities of survival in each successive year up to five years after diagnosis that had been observed during the most recent period for which adequate follow-up data were available.

We estimated net survival using the Pohar Perme estimator [16]. Net survival is the probability of a cancer patient surviving their cancer up to a given time since diagnosis, e.g., five years, after controlling for competing risks of death (background mortality), which are higher in the elderly. To account for the differences in background mortality between regions and over time, we constructed life tables of all-cause mortality specific to each country or region, single year of age, sex, calendar year, and, where possible, race or ethnic group. The Pohar Perme estimator was implemented using *stns* [17] in Stata version 15 (StataCorp, College Station, Texas, USA).

We produced survival estimates for five age groups at diagnosis (15-44, 45-54, 55-64, 65-74, and 75-99 years) and obtained age-standardized estimates for all ages combined, using the International Cancer Survival Standard (ICSS) weights [18]. We did not estimate survival if fewer than ten patients were available for analysis. If 10-49 patients were available in a given calendar period, we estimated survival for all ages combined. If 50 or more patients were available, we attempted survival estimation for each age group. If an age-specific estimate could not be produced, data for adjacent age groups were pooled, and the re-estimated survival was used for both age groups. If two or more age-specific estimates could not be produced, we reported only the unstandardized estimates for all ages combined. We did not merge data between consecutive calendar periods.

The pooled estimates for countries with more than one registry do not include data from registries for which the estimates were considered less reliable. Less reliable estimates for a given country are shown with a flag in figures and tables when they are the only available information from a given country or territory. A survival estimate is considered less reliable if 15% or more patients were either

lost to follow-up or excluded because they were registered only from a death certificate or autopsy or registered with unknown vital status or incomplete dates. Detailed quality control indicators can be found for each registry that participated in CONCORD-3 in the web appendix available online (https://doi.org/10.1016/S0140-6736(17)33326-3).

When examining trends in the distribution of sub-site or sub-type, we refer to increases or decreases in the proportion. Increases or decreases in the survival probabilities (%) are described in absolute terms.

We excluded 10,619 (1%) patients for whom the tumor morphology was unknown. Of the remaining 732,695 patients whose tumor morphology was known, we included all tumors reported by the registry as morphologically verified (684,821; 93%). Of the 40,465 (6%) tumors reported as not morphologically verified, we included 8,169 tumors with a specific ICD-O-3 morphology code (i.e., any code except 8000-8005) as a specific morphology code implied morphological verification had been completed. Of the 7,409 (1%) tumors coded as unknown whether morphological verification had been completed, we included 3,984 tumors for which a specific morphological code was available.

2.3 | Patient and public involvement

The CONCORD Steering Committee has included cancer patients since 2000. However, patients were not involved directly in the study design of this manuscript.

3 | RESULTS

We analyzed survival with data for 696,974 adults from 288 population-based cancer registries in 60 countries.

3.1 | Distribution of anatomical sub-sites

Patients with tumors in the lower third of the esophagus comprised 38% (n = 265,159) of those diagnosed during 2000-2014, with the middle third accounting for 22% (n = 156,185) of the patients and the upper third for 8% (n = 52,927). For a further one-third of patients (n = 222,703; 32%), the tumors were in overlapping sub-sites or the sub-site was not specified (NOS).

The sub-site distribution varied between countries and by sex (Figure 1, Supplementary Table S2). For adults diagnosed during 2010-2014, overlapping sub-site and NOS tumors were the most frequent in 30 countries (Algeria, Mauritius, South Africa, 7 countries in Central and South America, 9 in Asia, and 11 in Europe). Tumors of the lower third were the most common in 21 countries (Puerto Rico, Canada and the US, Turkey, 15 countries in Europe, and Australia and New Zealand), while the middle third was the most common sub-site in Guadeloupe, Japan, Korea, Singapore, Taiwan, and Russia.

The proportion of patients diagnosed with a tumor assigned to overlapping sub-sites or NOS in 2010-2014 was lower than the proportion for 2000-2004. Correspondingly, the proportion of patients diagnosed with tumors in the middle or lower third of the esophagus increased over time (Figure 1, Supplementary Table S2). Given the high proportion of tumors assigned to an overlapping anatomic sub-site or NOS, we focused on survival by morphological sub-type.

3.2 | Distribution of morphological sub-type

Almost all esophageal tumors included in analyses (n = 680,709, 98%) had been coded to a specific morphology. Squamous cell carcinoma was the commonest morphological sub-type worldwide, representing 53% of all esophageal tumors. Adenocarcinoma was the second most common (38%), while unspecified carcinoma (5%), other specified carcinomas (2%) and non-specific tumors (2%) were rare. Other specified non-carcinomas (0.2%) and sarcomas/other soft tissue tumors (0.1%) were extremely rare (Supplementary Table S3).

The distribution of morphological sub-types differed between countries and by sex (Figure 2). In all participating countries in Africa, Central and South America and Asia, and in 20 European countries, squamous cell carcinoma was the commonest sub-type. Among these 48 countries, the proportion of squamous cell carcinomas increased over time in 14 countries, with the largest increase in China (11%; from 66.6% of all tumors in 2000-2004 to 77.3% in 2010-2014) (Supplementary Table S3). Adenocarcinoma was the commonest sub-type in Canada and the United States, eight European countries, Australia and New Zealand. In all of these 12 countries, the proportion of adenocarcinoma increased over time. Additionally, in 37 of 48 countries where squamous cell carcinoma was the most common subtype, the proportion of adenocarcinoma also increased over time, with the largest increase in Kuwait (17%; from 18.5% in 2000-2004 to 35.9% in 2010-2014).

In 39 of the 58 countries providing data for adults diagnosed during 2010-2014, squamous cell carcinoma was the commonest morphological sub-type for both men and women (Figure 2, Supplementary Table S4 [men], and Supplementary Table S5 [women]). In a further 18 countries, the distribution differed between men and women,

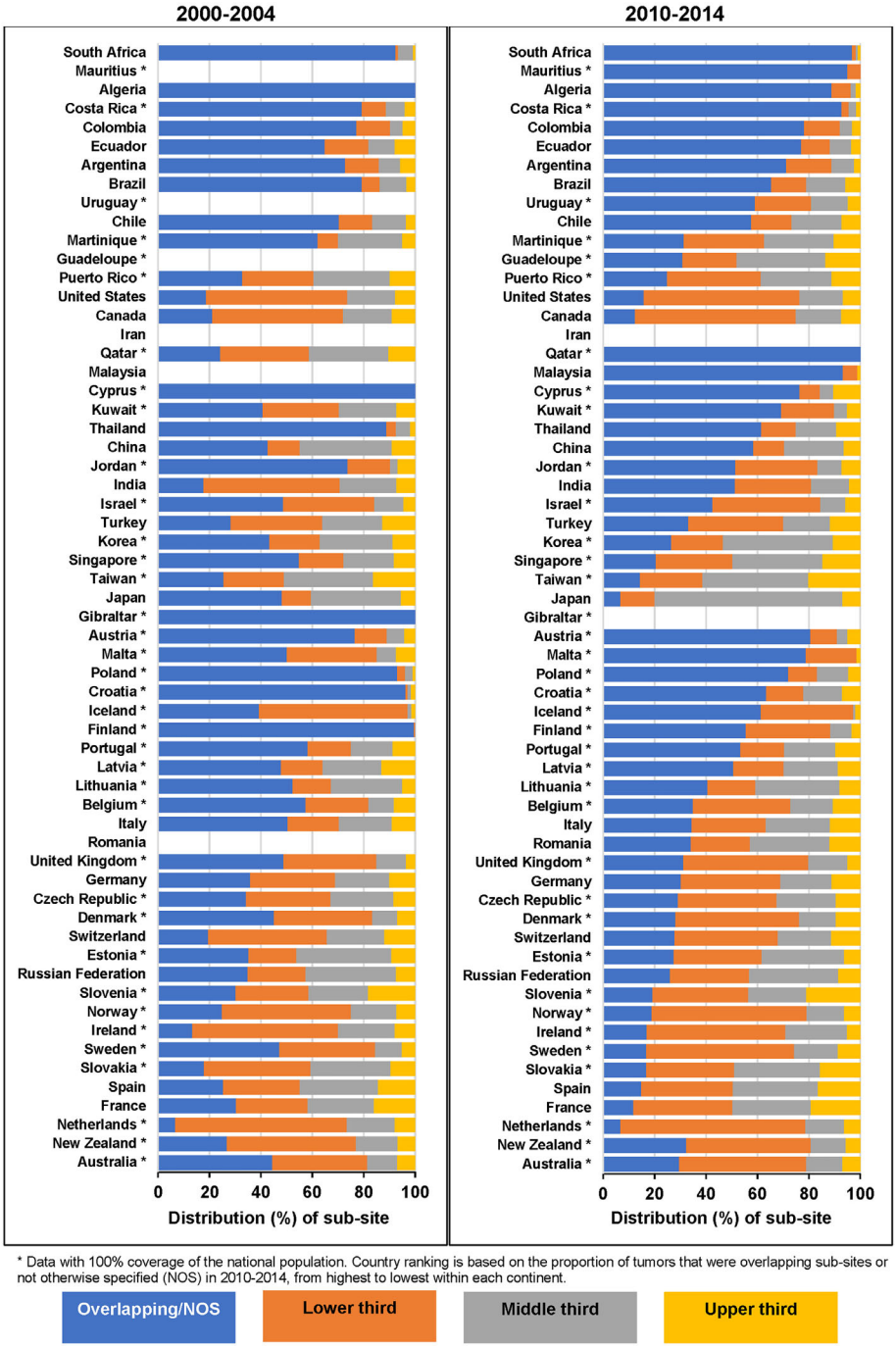


FIGURE 1 Distribution of anatomic sub-site by country and calendar period of diagnosis: adults (15-99 years) diagnosed with esophageal cancer.

* Data with 100% coverage of the national population. Country ranking is based on the proportion of tumors overlapping sub-sites or not otherwise specified (NOS) in 2010-2014, from highest to lowest within each continent.

with adenocarcinoma the most common sub-type for men and squamous cell carcinoma the most common sub-type for women. Malta was the only country where adenocarcinoma was the commonest sub-type for both men and women (Figure 2, Supplementary Table S4 [men], and Supplementary Table S5 [women]).

3.3 | Sex-specific survival

Age-standardized five-year survival from esophageal cancer for all tumors combined was around 5% higher in women than in men, though there was wide global variation in survival by sex (Supplementary Table S6). For

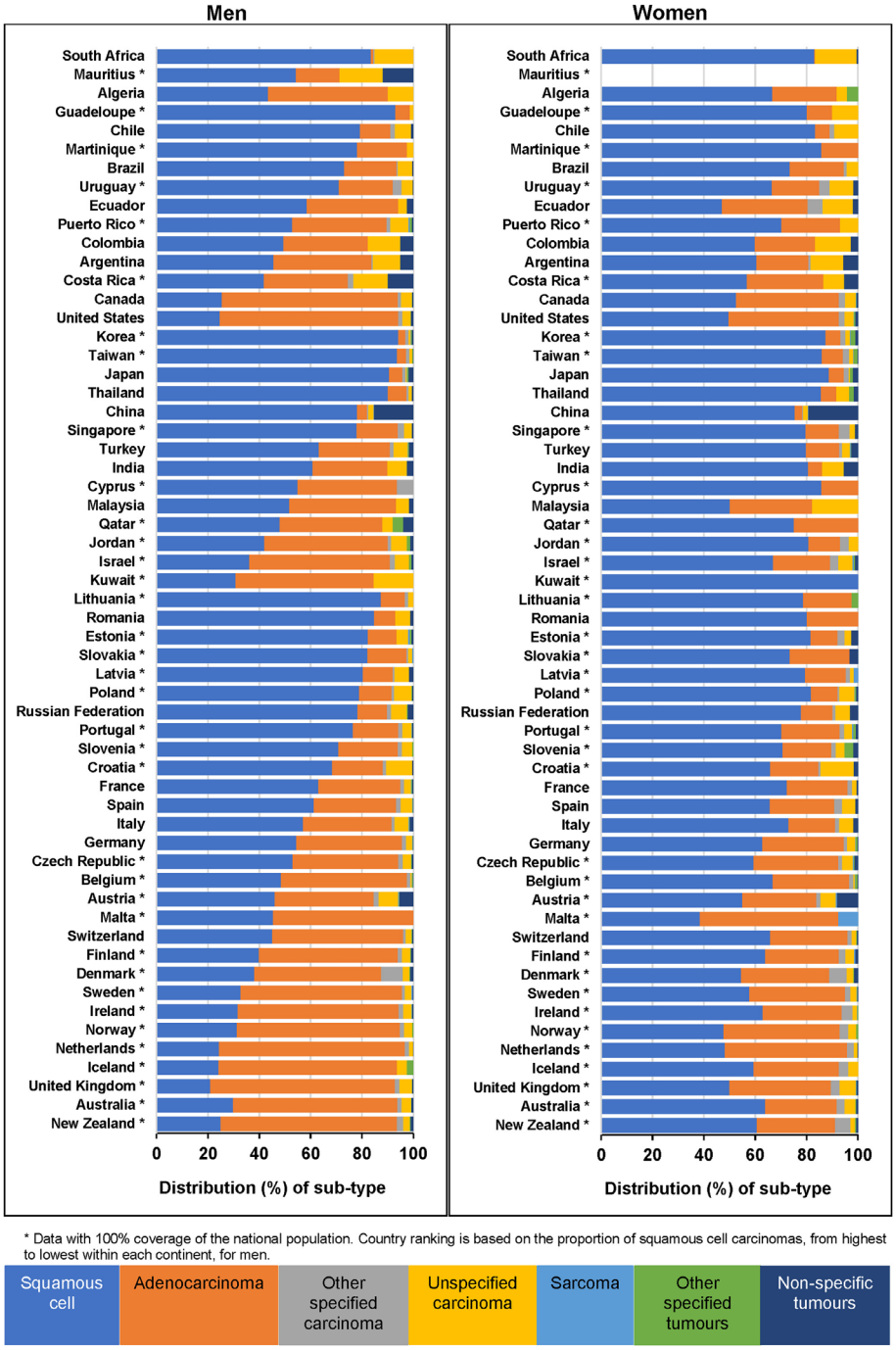


FIGURE 2 Distribution of morphological sub-types by sex and country: adults (15-99 years) diagnosed with esophageal cancer during 2010-2014.

* Data with 100% coverage of the national population. Country ranking is based on the proportion of squamous cell carcinomas, from highest to lowest within each continent, for men.

men diagnosed during 2010-2014, the five-year survival ranged from 3.5% (95% confidence interval (CI): 1.8%-5.2%) in Lithuania to 34.8% (95% CI: 33.4%-36.1%) in Japan. For women, the five-year survival ranged from 7.1% (95% CI: 2.4%-11.9%) in Latvia to 42.6% (95% CI: 39.7%-45.5%) in Japan.

Age-standardized five-year survival from all esophageal tumors combined generally increased over time for both women and men (Supplementary Table S6). For men, survival increased by less than 5% in most countries, although in South Korea the increase reached 13.3%. In Russia, survival decreased slightly over time, from

11.1% (95% CI: 8.0%-14.2%) in 2000-2004 to 7.5% (95% CI: 5.6%-9.3%) in 2010-2014. For women, survival increased slightly in most countries (around 5%), with the largest increase in Israel (20.2%). A slight decrease in survival was seen in Finland: five-year survival was 20.0% (95% CI: 15.3%-24.7%) in 2000-2004, which then decreased to 14.3% (95% CI: 10.6%-18.1%) in 2010-2014.

3.4 | Survival by anatomical sub-site

Five-year survival for adults diagnosed with a tumor of the lower third was highest in Japan (40.1%, 36.9%-43.3%) and lowest in Latvia (3.0%, 0.3%-5.8%) (Figure 3a, Supplementary Table S7). Survival from tumors in the middle third during 2010-2014 was highest in China (40.2%, 95% CI: 38.4%-42.1%) and lowest in Slovakia (2.8%, 0.6%-5.0%) (Figure 3b, Supplementary Table S6). For tumors of the upper third, the five-year survival was highest in China (34.8%, 31.3%-38.3%) and lowest in Slovenia (6.4%, 2.1%-10.7%) (Figure 3c, Supplementary Table S6), while for tumors in overlapping sub-sites or NOS, the five-year survival was highest in China (27.7%, 26.6%-28.8%), and lowest in Lithuania (2.9%, 0.9%-4.9%) (Figure 3d, Supplementary Table S7).

Age-standardized five-year survival by sub-site generally followed the same patterns in men and women: highest for tumors of the lower and middle thirds and lowest for tumors of the upper third or for tumors of overlapping sub-site or NOS. The highest levels of survival in both men and women were generally seen in Asia (Supplementary Table S6 [all sub-sites combined, upper third, middle third] and Supplementary Table S7 [lower third and overlapping or esophagus, NOS]).

3.5 | Survival by morphological sub-type

Age-standardized one-year survival from squamous cell carcinoma varied widely worldwide. For adults diagnosed in 2010-2014, the one-year survival was highest in Japan (67.7%, 95% CI: 66.3%-69.1%) and lowest in Lithuania (21.8%, 17.0%-26.6%) (Figure 4, Supplementary Table S8). One-year survival from adenocarcinoma was similar, also with a wide international variation. For adults diagnosed in 2010-2014, the one-year survival was highest in Japan (69.0%, 64.7%-73.3%) and lowest in Slovakia (25.0%, 13.3%-36.7%). One-year survival estimates for the less common morphological sub-types can be found in Supplementary Table S9 and Supplementary Table S10.

Age-standardized five-year survival from squamous cell carcinoma was generally around 15%-20% (Supplementary Table S11). For adults diagnosed in 2010-2014, the five-year survival was highest in Japan (37.6%, 95% CI: 36.2%-38.9%) and lowest in India (2.0%, 95% CI: 0.0%-4.6%). For adenocarcinomas, age-standardized five-year survival was similar but with less worldwide variation (Figure 5, Supplementary Table S6). The highest survival for patients diagnosed during 2010-2014 was seen in Japan (37.5%, 95% CI: 32.7%-42.3%) and the lowest in Russia (9.0%, 95% CI: 5.1%-12.9%). Five-year survival estimates for the other morphological sub-types can be found in Supplementary Table S12 and Supplementary Table S13.

One- and five-year survival from both squamous cell carcinoma and adenocarcinoma were generally higher for women than men (Supplementary Table S8 [one-year survival] and Supplementary Table S11 [five-year survival]). During 2010-2014, one-year survival from squamous cell carcinoma reached 67.1% (95%CI: 65.5%-68.8%) for men and 70.0% (95% CI: 67.1%-72.9%) for women in Japan. There was a wider gap in the five-year survival from squamous cell carcinoma: 36.2% (95% CI: 34.7%-37.7%) for men in Japan and 46.4% (95% CI: 37.7-55.0%) for women in Israel. Survival was lowest for men in Lithuania (one-year: 20.6%, 95% CI: 15.7%-25.5%; five-year: 4.0%, 95% CI: 1.8%-6.2%) and for women in Thailand (one-year: 18.0%, 95% CI: 11.3%-24.7%; five-year: 6.1%, 95% CI: 2.4%-9.8%).

For adenocarcinoma, one-year and five-year survival estimates were highest for men in Japan (one-year: 70.5%, 95% CI: 65.8%-75.1%; five-year: 37.0%, 95% CI: 31.8%-42.3%) (Supplementary Table S8 [one-year survival] and Supplementary Table S11 [five-year survival]). For women, one- and five-year survival were highest in Belgium (one-year: 58.2%, 95% CI: 52.6%-63.8%; five-year: 28.6%, 95% CI: 23.1%-34.0%). Survival was lowest for men in Russia (one-year: 23.5%, 95% CI: 17.0%-30.0%; five-year: 7.1%, 95% CI: 4.0%-10.1%). For women with an adenocarcinoma, one-year survival was lowest in the Czech Republic (30.2%, 95% CI: 23.3%-37.1%), and five-year survival was lowest in France (7.3%, 95% CI: 0.0%-15.3%).

One-year survival increased by around 5%-10% for both squamous cell carcinoma and adenocarcinoma, while five-year survival increased by less than 5% (Supplementary Table S8 [one-year survival] and Supplementary Table S11 [five-year survival]). For squamous cell carcinoma, the greatest improvement in one-year survival was in Slovenia (15.4% increase), while for five-year survival, the largest improvement was in Israel (13.8%). One- and five-year survival improved the most in Puerto Rico (one-year: 23.0%; five-year: 17.7%) for adenocarcinoma.

One-year survival from squamous cell carcinoma improved the most for men in Slovenia (18.3%), while, for women, improvements were greatest in Norway (17.2%).

There were large increases in five-year survival from squamous cell carcinoma in Korea (12.9%) for men and in Israel (25.7%) for women. For adenocarcinoma, one-year survival improved the most for men in Puerto Rico (21.2%) and for women in Norway (13.6%), while five-year survival improved the most for men in Switzerland (16.1%) and women in Italy (11.5%).

4 | DISCUSSION

This study included high-quality individual records for 696,974 patients diagnosed with esophageal cancer from 288 population-based cancer registries in 60 countries. It is the largest study to date of trends in esophageal cancer survival by sub-site, morphology, and sex. We used the same

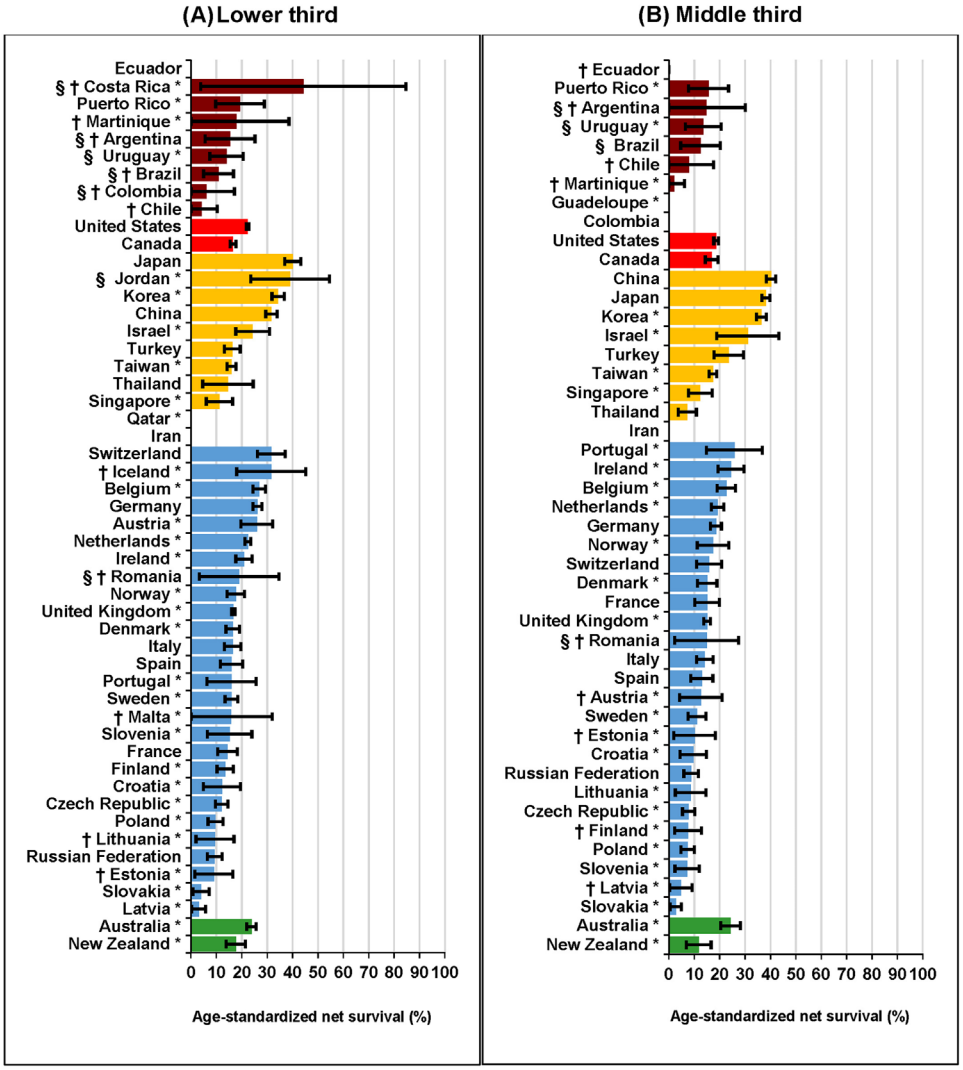
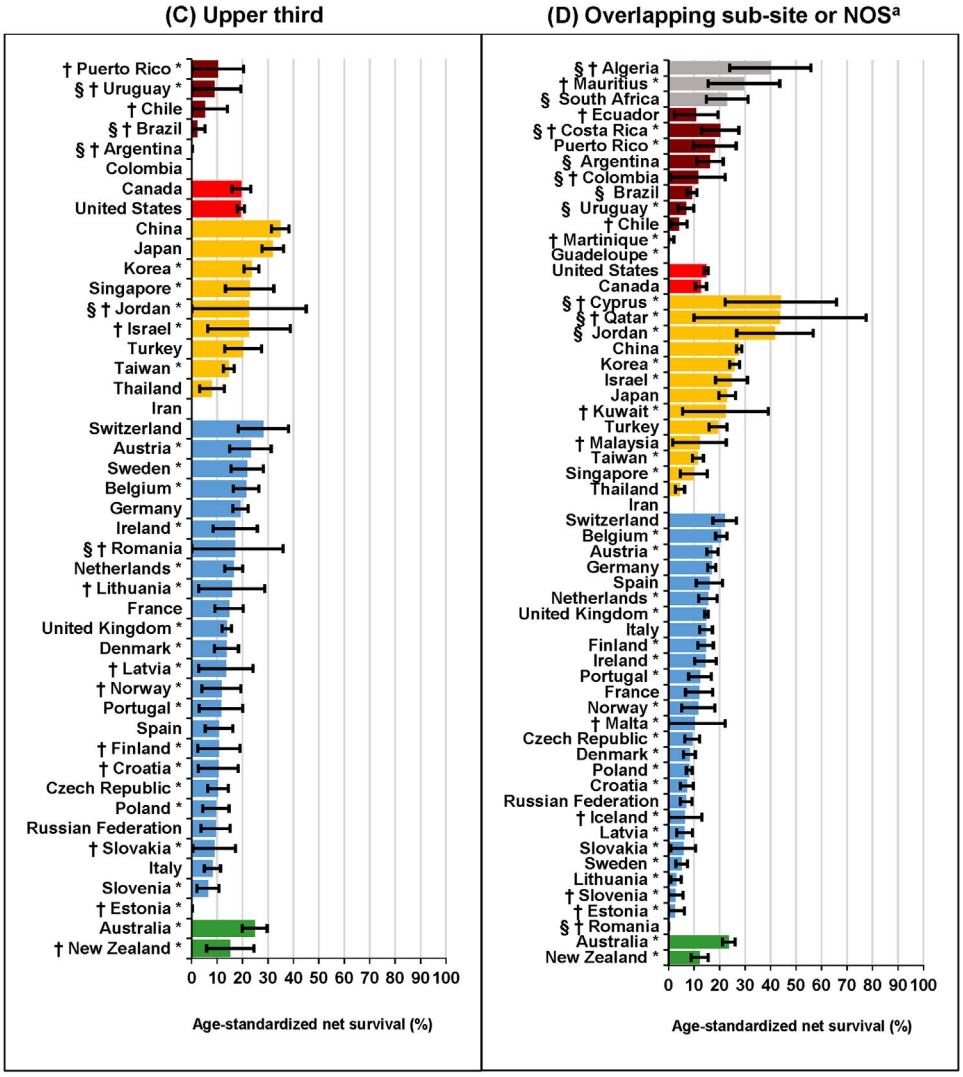


FIGURE 3 Age-standardized five-year net survival (%) by anatomic sub-site and country: adults (15-99 years) diagnosed with esophageal cancer during 2010-2014. (A) Age-standardized five-year net survival (%) by country: adults (15-99 years) diagnosed with tumors of the lower third of the esophagus during 2010-2014. (B) Age-standardized five-year net survival (%) by country: adults (15-99 years) diagnosed with tumors of the middle third of the esophagus during 2010-2014. (C) Age-standardized five-year net survival (%) by country: adults (15-99 years) diagnosed with tumors of the upper third of the esophagus during 2010-2014. (D) Age-standardized five-year net survival (%) by country: adults (15-99 years) diagnosed with tumors overlapping sub-sites or not otherwise specified (NOS) during 2010-2014.
* Data with 100% coverage of the national population. § National estimate flagged as less reliable. † National estimate not age-standardized.
[a] Not otherwise specified. The different colors represent the types of countries in terms of continental/geographical location, e.g., Africa, South America, North America, Asia, Middle East, Europe, etc.



* Data with 100% coverage of the national population. § National estimate flagged as less reliable. † National estimate not age-standardized. [a] Not otherwise specified.

FIGURE 3 Continued

standardized data quality controls and the same robust methods to produce net survival estimates for all countries included in the analyses.

Survival from esophageal cancer remains poor in many countries, regardless of the anatomic sub-site or morphological sub-type, despite some improvements during the 15-year period from 2000 to 2014. The distribution of anatomic sub-site has changed slightly, with an increase in the proportion of tumors arising in the lower and middle thirds of the esophagus and a decline in the proportion assigned to overlapping sub-sites or sub-sites not otherwise specified (NOS). Esophageal cancer is generally diagnosed at endoscopy, with biopsies taken for pathological confirmation [3]. As diagnostic techniques improve, fewer patients should be diagnosed with a non-specific sub-site. However, 37 of the 58 countries providing data for 2010-2014 still coded 30% or more of tumors to overlapping or unspecified sub-sites. This indicates that adequate diagnostic techniques are either not routinely available or are not routinely used in pathological reports of the anatomic sub-site.

The distribution of morphological sub-types has also changed. The proportion of squamous cell carcinomas has fallen in most countries, but there were increases in some African, Asian, and Eastern European countries, with the largest increases in China (11%) and South Africa (10%). Conversely, the proportion of adenocarcinomas has increased in most countries, with the largest increases in Kuwait (17%) and Finland (14%). These results confirm that while squamous cell carcinoma has historically been the most common morphological sub-type worldwide, especially in low- and middle-income countries, adenocarcinoma is becoming more common in most high-income countries [3, 8].

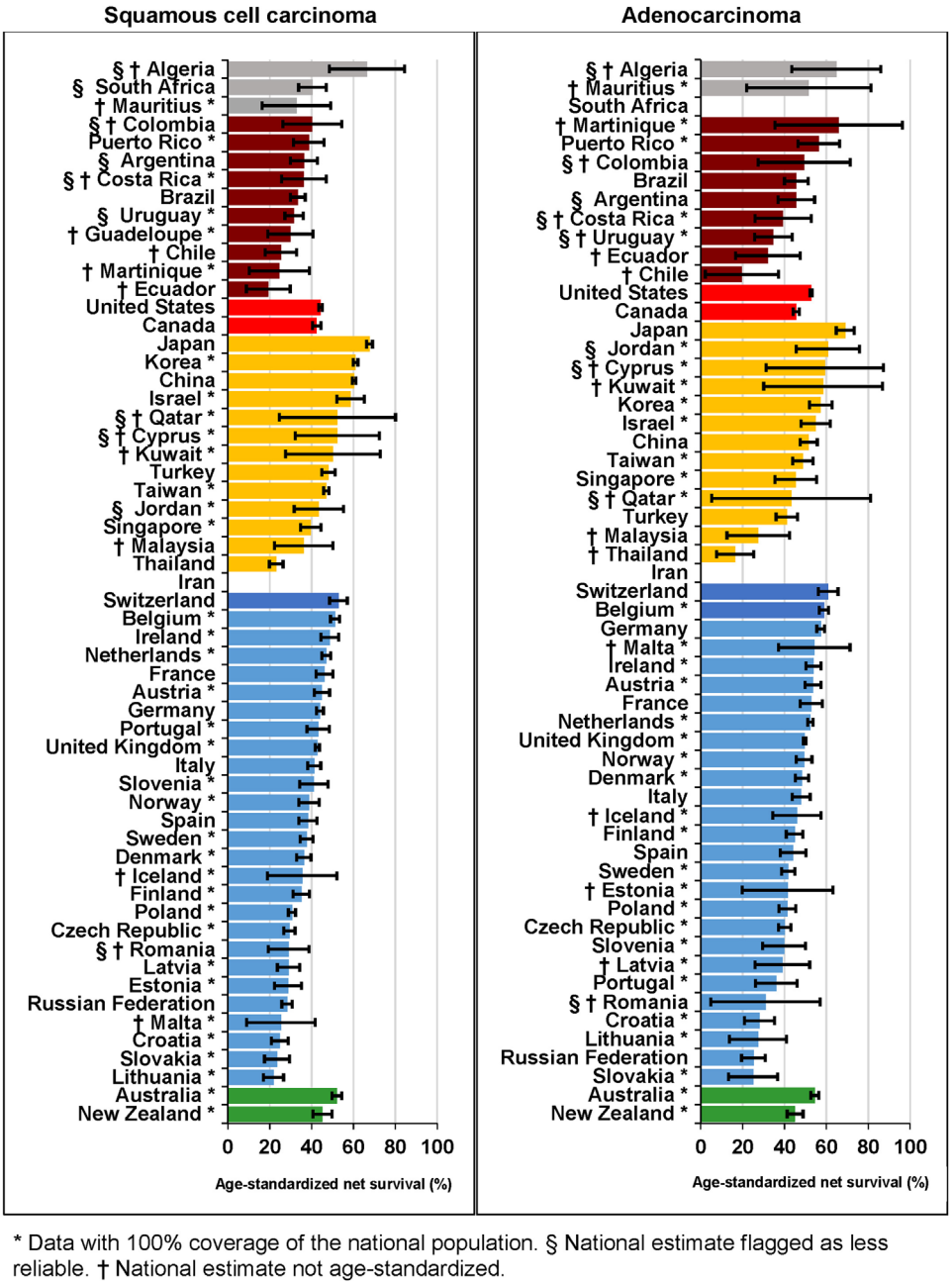


FIGURE 4 Age-standardized one-year net survival (%) by morphological sub-type and country: adults (15-99 years) diagnosed with esophageal cancer during 2010-2014.

* Data with 100% coverage of the national population. § National estimate flagged as less reliable. † National estimate not age-standardized. The different colors represent the types of countries in terms of continental/geographical location, e.g., Africa, South America, North America, Asia, Middle East, Europe, etc.

If we disregard tumors that were coded as not morphologically verified or unknown whether or not they were morphologically verified, the proportion coded to a non-specific morphology was less than 5% in 53 of 58 countries with data for 2010-2014. The proportion of tumors of non-specific morphology (ICD-O-3 codes 8000-8005) remained relatively stable in most countries, though there were large decreases in China, Japan, and Latvia. In these three countries, the proportions of squamous cell carcinoma and adenocarcinoma increased, suggesting improvement in diagnostic techniques. However, for 51 of the 60 countries, the proportions of squamous cell carcinoma and adenocarcinoma showed opposite trends, where an increase in one sub-type corresponded with a decrease in the other.

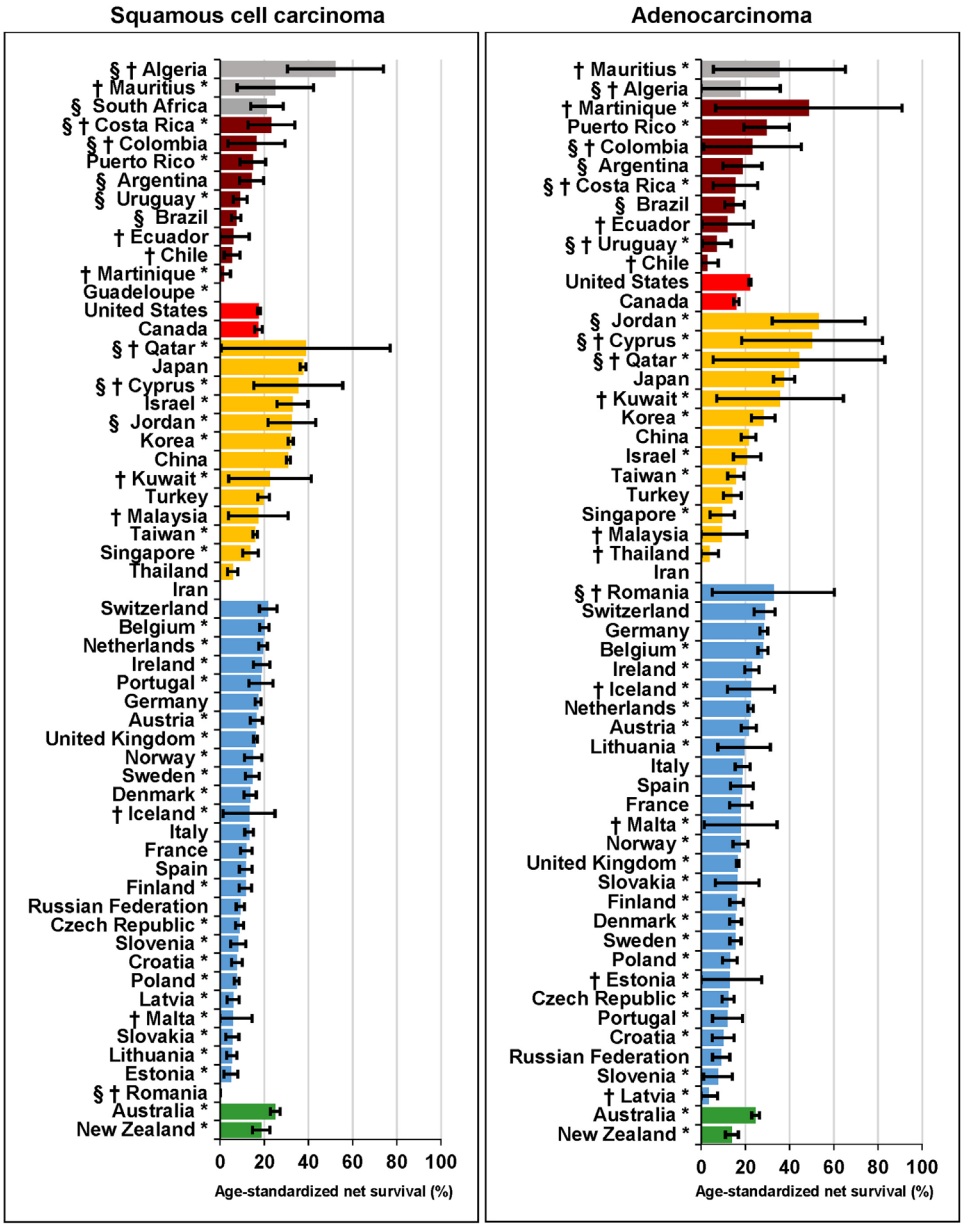


FIGURE 5 Five-year net survival (%) by morphological sub-type and country: adults (15-99 years) diagnosed with esophageal cancer during 2010-2014.

* Data with 100% coverage of the national population. § National estimate flagged as less reliable. † National estimate not age-standardized. The different colors represent the types of countries in terms of continental/geographical location, e.g., Africa, South America, North America, Asia, Middle East, Europe, etc.

In most of these countries, the proportion of tumors with a non-specific morphology code was less than 2% and remained stable over time. Thus, the change in the morphology distributions over time for most countries is less likely to be attributable to improvement in the quality of pathological reporting or changes in the definition of the morphological sub-types and more likely to a true shift in morphological types, in turn presumably attributable to a change in the prevalence of the different risk factors for each sub-type of esophageal cancer [4, 19]. Given the availability of more detailed information on morphology, it may be more beneficial to examine trends in survival by morphological sub-type than by anatomic sub-site.

Smoking is a major risk factor for squamous cell carcinoma. In low- and middle-income countries where smoking is still common, the proportion of squamous cell

carcinoma continues to increase. However, smoking cessation can quickly reduce the risk of developing squamous cell carcinoma, and in countries where smoking cessation programs have been developed, the proportion of these tumors is decreasing [3, 4]. By contrast, risk factors for adenocarcinoma, such as obesity and gastro-esophageal reflux, are increasing in high-income countries; and this may explain the increase in adenocarcinomas in these regions [3]. Examining the trends in the incidence rates of the various sub-types may help explain further the changing distribution over time.

Squamous cell carcinomas generally develop in the middle third of the esophagus, while adenocarcinomas tend to develop in the lower third [4]. Thus, the increasing proportion of tumors in the middle third in some Asian countries corresponds to the increase in squamous cell tumors. Similarly, the increase in tumors of the lower third in Central and South America, North America, Europe, and Oceania corresponds with the increase in adenocarcinoma in these regions. There may be some misclassification of adenocarcinomas in the gastro-esophageal junction, with some esophageal tumors reported as arising in the stomach and vice versa. Though the impact of this misclassification is most likely to be small, it may have diminished the increasing trend in adenocarcinomas [20, 21].

While the distributions of anatomic sub-site and morphological sub-type vary worldwide, they do not appear to explain fully the international variations in survival for all esophageal cancers combined. Five-year survival for adults with a middle or lower third tumor was higher (15%-20%) than those with tumors of the upper third or overlapping sub-sites (5%-15%). While Asian countries had high proportions of tumors of the middle third, tumors of the lower third were more common in North America, Europe, and Oceania. Thus, the high survival for all sub-sites combined in Asia is not explained by the high proportion of tumors in the middle third.

A similar conclusion can be drawn for the distribution of morphological sub-type. One-year survival from both squamous cell carcinoma and adenocarcinoma was generally around 30%-50%, while five-year survival ranged from 15%-20%. One- and five-year survival for each morphological sub-type was highest in Asia. Thus, a higher proportion of squamous cell carcinomas does not appear to explain the higher levels of esophageal cancer survival in Asia.

Stage at diagnosis, as with many other cancers, is one of the most important prognostic factors of esophageal cancer, and stage-specific survival has been shown to vary between high-income countries [22]. Treatment for esophageal cancer will depend on the stage at diagnosis and is generally more effective for early-stage disease, which can be curable [3]. Esophageal cancer usually presents at an advanced stage, primarily due to a lack of obvious symptoms for early-stage disease [23]. The most common symptom is difficulty in swallowing, but this only occurs once the tumor is large enough to obstruct passage from the throat to the stomach and is, thus, no longer an early-stage disease [24].

The high proportion of esophageal tumors diagnosed at an advanced stage could also occur because very few countries conduct population-based screening programs for esophageal cancer. Despite precursor lesions existing for both squamous cell carcinoma and adenocarcinoma, many countries do not recommend screening at the population level, focusing instead only on high-risk individuals, including those with Barrett's esophagus [19, 24]. Endoscopic screening at the population level can be costly, while cheaper non-endoscopic techniques may not be accurate [25, 26].

However, higher survival in some Eastern Asian countries may be partially explained by comprehensive screening programs for esophageal and gastric cancers. Since 1983, gastric cancer screening has been offered to all adults aged 40 years or older in Japan [27, 28]. In 2006, free endoscopic screening was offered to the population in Yangzhong County, China. In this high-risk population, screening effectively detected early-stage tumors, which could then be treated with curative intent [29]. In South Korea, endoscopic screening for gastric cancer was incorporated in 1999 as part of the National Cancer Screening Programme [30]. Both countries, as well as other eastern Asian countries with population-based gastric cancer screening programs, have experienced massive improvements in esophageal cancer survival over the past few decades and have achieved the highest levels of esophageal cancer survival worldwide.

In conclusion, the distributions of esophageal cancer by anatomic sub-site and morphological sub-type differ between continents and countries, but international variation in esophageal cancer survival does not appear to be explained by these differences. Further examination of survival by stage at diagnosis and trends in the incidence and mortality rates of the various sub-site and sub-types may help explain international variations in esophageal cancer survival.

DISCLOSURES

The interpretation of the findings in this report and the opinions, conclusions, and recommendations are those of the authors and do not necessarily reflect the views or official position of the British Columbia Cancer Agency or Cancer Care Ontario (Canada); the Centers for Disease

Control and Prevention, the National Cancer Institute, Maryland Cancer Registry, New Hampshire Department of Health and Human Services, New York City Department of Health and Mental Hygiene, Ohio Department of Health, Pennsylvania Department of Health or West Virginia Cancer Registry (USA); the Health Directorate of the Australian Capital Territory, or the Institut National Du Cancer (France).

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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The Cancer Survival Group maintains approval for processing sensitive personal data for the CONCORD programme from the UK's statutory Health Research Authority (reference ECC 3-04(i)/2011; last update 17 October 2022), the UK National Health Service Research Ethics Service (11/LO/0331; 2 November 2022), and the Ethics Committee of the London School of Hygiene & Tropical Medicine (12171; 1 September 2022).

CONSENT FOR PUBLICATION

Consent for publication is not applicable because the data are anonymized by the source registries.

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***CONCORD Steering Committee**

DATA AVAILABILITY STATEMENT

Research data are not shared due to the ethical and legal constraints that apply to sensitive personal data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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