SYSTEMATIC REVIEWS AND META-ANALYSES

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Global Distribution of Colorectal Cancer Staging at Diagnosis: An Evidence Synthesis

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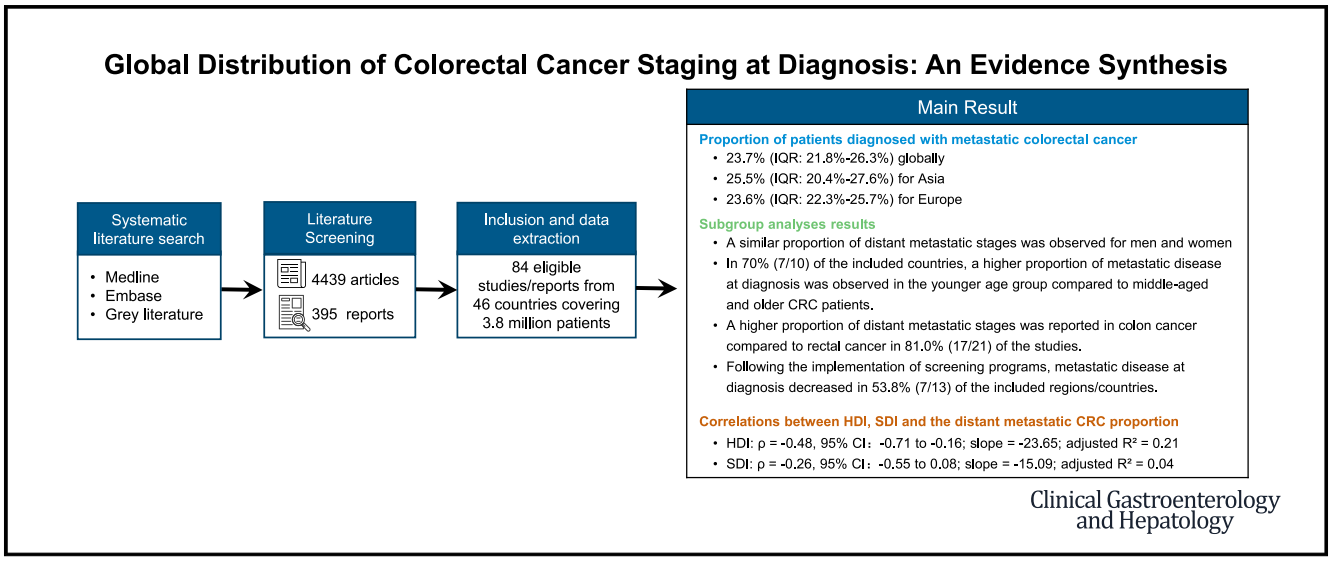

BACKGROUND & AIMS: **Stage at diagnosis is a key prognostic factor for colorectal cancer (CRC) survival. We aimed to assess the global distribution of CRC staging at diagnosis using population-based or hospital-based registry data.**

METHODS: **We systematically searched in MEDLINE and Embase from their inception until December 6, 2023. Gray literature was searched through published cancer reports. Studies from population-based or hospital-based cancer registries reporting the stage distribution of diagnosed CRC were included. We extracted stage-specific proportions among patients with CRC based on TNM; Surveillance, Epidemiology, and End Results; or Dukes staging systems. Subgroup analyses by sex, age, tumor site, calendar period, and status of population-based screening were performed. Correlations between the Human Development Index (HDI), Socio-Demographic Index (SDI), and the distant metastatic CRC proportion were also evaluated.**

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Abbreviations used in this paper: CRC, colorectal cancer; HDI, human development index; IQR, interquartile range; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SDI, sociodemographic index; SEER, Surveillance; Epidemiology, and End Results Program.

Most current article

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RESULTS: **A total of 84 eligible studies/reports from 46 countries were analyzed, covering 3.8 million patients. Among 36 countries included in the main analysis, the most recent distant metastatic CRC proportions varied from 16.2% in Puerto Rico to 28.2% in Oman and Latvia, with a median of 23.7% (interquartile range, 21.8%–26.3%). Higher metastatic proportions were observed in younger patients, those with colon cancer, and those without screening implementation, with no apparent difference between males and females. Over time, some countries/regions, such as Southern Portugal (36.5% in 2000 to 22.2% in 2016), showed declining proportions of metastatic CRC, whereas others remained stable (eg, Austria, Belgium) or increased (eg, United States, Slovenia, Spain). Higher HDI and SDI were correlated with lower proportions of distant metastatic CRC (HDI: $\rho = -0.48$; SDI: $\rho = -0.26$).**

CONCLUSIONS: **Global disparities in CRC staging exist, indicating a need for targeted interventions to enhance early detection and management, especially in high-metastasis areas.**

Keywords: Colorectal Cancer; Stage; Systematic Review.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with over 1.9 million new cases and 0.9 million CRC-related deaths occurring in 2022, accounting for 9.3% of all cancer deaths.[1] Significant variations in CRC survival were observed across countries, with the 5-year survival rates ranging from 12% in South Africa to 76% in Jordan for colon cancer and 9% in South Africa to 76% in Cyprus for rectal cancer during 2010 through 2014.[2] Stage at diagnosis is significantly related to CRC survival. The 5-year survival rate varies from over 90% for patients with TNM stage I to below 10% for patients with TNM stage IV.[3]

The stage at diagnosis of CRC is the basis for treatment strategies at the clinical level[4] and an important index to measure the effectiveness of early detection at the population level.[5] Currently, national population-based CRC screening is mainly available in developed countries, such as the United States and European countries.[6] A previous international comparative study from Europe has shown that the proportion of metastatic stage CRC diagnoses was lower in countries with established colonoscopy- and fecal test-based screening programs.[7] Hence, a comprehensive understanding of the variance in the global distribution of CRC stage at diagnosis is crucial to aid decision-making for national cancer control planning.

Some previous studies have evaluated the distribution of CRC stages at diagnosis, but they were limited by the study design, small number of countries, and lack of temporal analysis.[2,8–11] Therefore, we conducted this systematic review on published studies and cancer reports primarily from population-based cancer registries and supplemented with hospital-based cancer registries to comprehensively evaluate the stage distribution of diagnosed CRC across countries. Additionally, we examined the variations in stage distribution by sex, age, tumor site, period of diagnosis, and other demographic factors. Our aim was to provide timely evidence on the global distribution of CRC staging at diagnosis to inform the design of effective strategies for reducing the burden of late-stage CRC.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[12] and was prospectively registered in the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42023487010, December 7, 2023).

Search Strategy and Selection Criteria

A systematic literature search of MEDLINE via PubMed and Embase via embase.com was conducted to identify relevant literature pertaining to the global distribution of CRC staging at diagnosis. Both free text words and medical subject heading terms were used, including "colorectal neoplasms," "neoplasm staging," and "cancer registry." The detailed search strategy is presented in Supplementary Table 1. The searches were limited to human studies published from the databases' inception until December 6, 2023. Titles and abstracts were independently screened by 2 investigators (L.C. and C.Z.), and differences were resolved by a third investigator (H.C.). To capture the most recently available cancer registry data that are not always published in peer-reviewed journals, we performed a supplemental gray literature search in cancer registries to maximize the completeness of our evidence sources. We used a comprehensive list of all existing cancer registries with their corresponding websites provided by the Global Initiative for Cancer Registry Development (https://gicr.iarc.fr/) as well as Global Burden of Disease (https://ghdx.healthdata.org/countries) as the source of cancer reports. Two authors (L.W. and W.G.) reviewed the lists, performed searches using the listed registry names, and reviewed official registry websites. This list was then divided among 4 investigators (L.W., L.C., W.G., and C.Z.), who accessed and searched the websites for official statistical reports and documents containing CRC staging data, which, if available, were extracted.

The following inclusion criteria were applied: population-based registry data of patients diagnosed with primary malignant CRC (International Classification of Disease-10: C18–C21), with reported numbers of cases and/or incidence rates by stage at diagnosis; if the population-based registry data was not available in the country, hospital-based cancer registry data would be extracted for our analysis. The following exclusion criteria were applied: (1) studies that included advanced adenoma or neuroendocrine tumors without the possibility of separation from malignant CRC cases; (2) studies exclusively examining specific health conditions, occupations, or employment status; (3) duplicate publications; (4) studies lacking detailed distant metastatic stages data; (5) studies exclusively reporting on CRC cases diagnosed before the year 2000; (6) publications presented as reviews, case reports, editorials, letters, or conference abstracts. Language restrictions were not imposed.

What You Need to Know

Background

The stage at diagnosis is a crucial prognostic factor for colorectal cancer (CRC) survival, yet there is limited evidence on the global distribution of CRC staging at diagnosis.

Findings

Our analysis of over 3.8 million cases of CRC from 46 countries provides a comprehensive overview on stage distribution patterns and trends. This study identified wide regional disparities in the proportion of distant metastatic CRC and revealed variations of staging by various factors, such as age and tumor site. Countries with low human development index and sociodemographic index were also observed to have higher proportions of metastatic CRC.

Implications for patient care

This study provides critical evidence for cancer control planning, highlighting the need for tailored interventions to reduce the burden of metastatic CRC.

Data Extraction

Initial paper screening was conducted based on titles and abstracts to identify potentially relevant citations, followed by a full-text assessment of the selected studies to determine their eligibility based on the established inclusion and exclusion criteria. Data were extracted by L.W., L.C., W.G., and C.Z. using a standardized extraction form, and reviewed by L.G., X.F., and H.C.. Discrepancies were resolved through panel discussions within the research team. Data extracted from eligible studies included information on study characteristics (eg, first author, publication year, study design, population demographics, and geographical region), patient information (sex, age at diagnosis, and tumor site), and stage distribution data (eg, stage system used (American Joint Committee on Cancer/Union for International Cancer Control TNM, Surveillance, Epidemiology, and End Results Program [SEER] summary, or Dukes staging), number of cases, and percentage by stage).

Outcome Definition

In the data extraction and categorization of cancer stage data from various studies, priority was given to data categorized by TNM classification as stages I, II, III, and IV, with attention paid to cases in which the stage was unknown. Studies utilizing different staging systems, including the SEER summary stage and Dukes staging, were categorized separately, with the SEER summary stage divided into local, regional, distant categories and unknown, and Dukes staging divided into stages A, B, C, D, and unknown. The summarization of stage data involved an initial assessment of the distribution of metastatic vs non-metastatic groups, with the metastatic category encompassing TNM stage IV, M1, SEER distant stage, or Dukes stage D, labeled as distant metastatic or metastatic stage for standardization purposes. This approach facilitates comparison among international benchmarking studies.[13] A detailed analysis was conducted using the TNM and SEER summary stage categories, allowing for a comprehensive understanding of cancer stage distribution across 6 world regions: Africa, Asia, Europe, Latin America and the Caribbean, Northern America, and Oceania.

Except for time-trend analysis, in instances where there were 2 (or more) sets of estimates from the same population or time period, the most relevant, high-quality, available data based on a set of hierarchical rules were included (sorted from highest): (1) largest population coverage, that is, national, subnational, and regional; (2) most recent calendar period of diagnosis; and (3) widest age range. We pooled the estimates that were available annually to present the most robust estimate for that period, with a minimum of 4 years.

Main, Subgroup, and Time-trend Analysis

Countries with the most recent data having more than 20% of cases with unknown stage or exclusively reporting on CRC cases diagnosed before the year 2010 were excluded from the main analysis but were retained in the Supplementary File for other analyses. Subgroup analyses by sex, age group, anatomic tumor site (colon and rectum), and status of population-based screening were presented for the most recently available period. Time-trend analysis was performed for countries with data across multiple periods. Proportions of distant metastatic stage and early/localized stage were

recalculated after excluding the CRC cases with unknown stage in the above-mentioned analysis.

Ecological Analysis Regarding Associations of Human Development Index, Sociodemographic Index, and Cancer Screening on the Stage Distribution

The human development index (HDI), which was determined by income, period of education, and life expectancy, was extracted from the United Nations Development Programme for the included countries using data from 2022.[14] Sociodemographic index (SDI) data were obtained from the Global Burden of Disease study, which provides comprehensive and comparable estimates of health loss across countries and regions for the included countries using data of 2021.[15] A linear regression model was applied to examine the potential correlation between the HDI/SDI and with the level of distant metastasis proportion in CRC. We also assessed the availability of population-based CRC screening programs within the included data. The initiation year of these screening programs was extracted from the CanScreen5 database.[16]

Risk of Bias Assessment

The risk of bias in eligible studies was evaluated using a modified version of the Joanna Briggs Institute tool for cross-sectional studies.[17] Furthermore, we incorporated data quality indicators from the Cancer Incidence in Five Continents database into the assessment process,[18] enhancing robustness. The risk of bias assessment process was completed by 2 investigators (C.Z. and W.G.) independently, and any discrepancies were resolved by a third senior methodology investigator (Y.Z.). Our assessment tool comprised 6 key questions addressing critical aspects, including population description, data completeness, validity of cancer registrations, missing data proportions, reporting of cancer staging systems, and consistency in statistical reporting. A detailed description of the assessment tool is provided in Supplementary Table 2.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

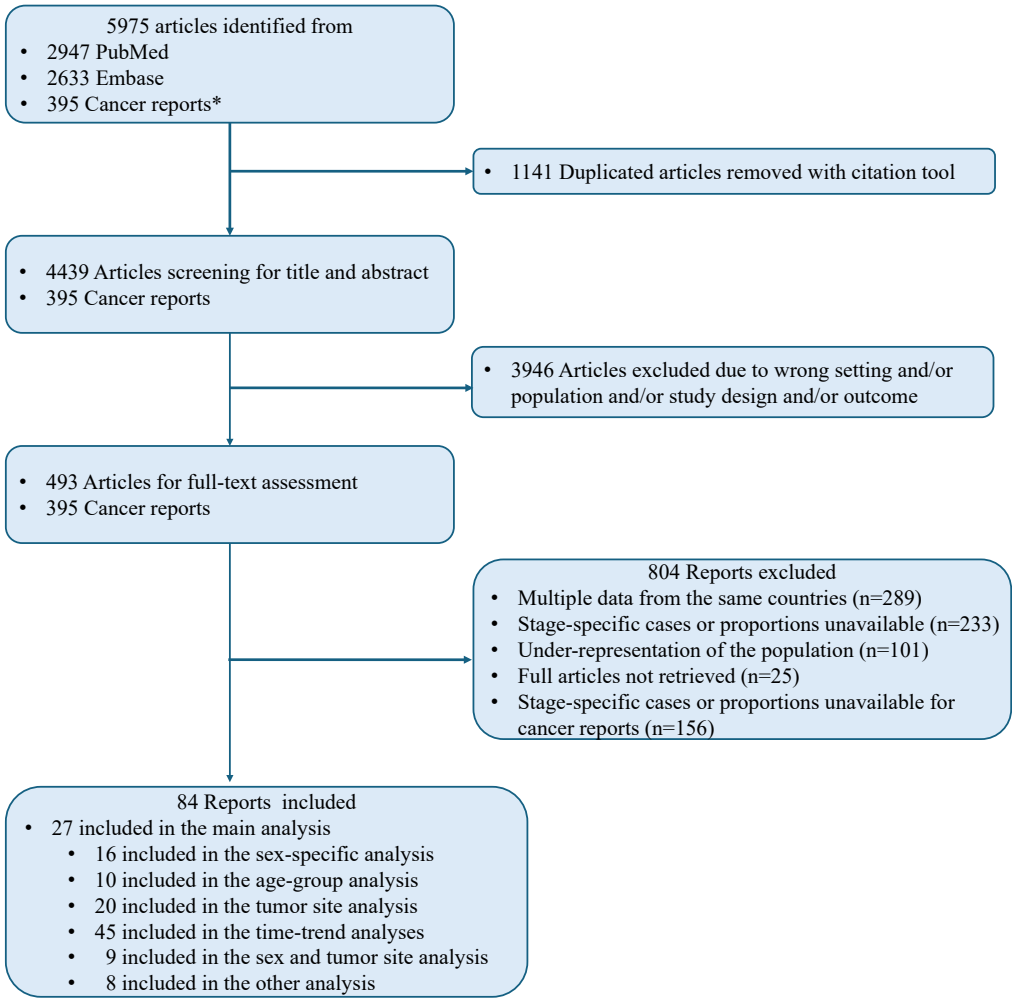
Literature Search

As shown in Figure 1, the search strategy yielded 5580 citations and 395 cancer reports. After screening titles and abstracts, 493 citations and 395 cancer reports were deemed potentially valuable, and the full texts were retrieved for detailed evaluation. Of these, 804 were excluded for the following reasons: 289 were multiple datasets from the same countries, 233 lacked stage-specific cases or proportions, 101 had under-representation of the population, 25 were full reports from MEDLINE and Embase that were not retrieved, and 156 cancer reports lacked stage-specific cases or proportions. Finally, 84 reports (37 published studies and 47 cancer reports) were eligible and included in this systematic review. The full list of eligible studies is provided in Supplementary File 2 (eligible references, 1–84). Of these 84 reports, 27 studies were included for presenting the most recent stage distribution (eligible references, 1–27), 16 for sex-specific analysis (eligible references, 1,8,11,15,16,22–24,26,28–34), 10 for age-specific analysis (eligible references, 8,11,16,17, 24,35–39), 20 for tumor site specific analysis (eligible references, 4,5,7–9,12,15,16,19,20,29,36,40–47), 45 for time-trend analysis (eligible references, 1,4,7,9,11, 12,14,16,21,24,26,34,40,42,48–78), 9 for combined analysis of sex and tumor site (eligible references, 16,20,29,31,33,44,45,79,80), and 8 for other analysis (eligible references, 28,29,40,41,81–84).

The characteristics of the studies are summarized in Supplementary Table 3, Supplementary Figure 1, Supplementary Figure 2, and Supplementary Figure 3. We included 46 countries comprising 3.8 million cases of CRC in the overall analysis, with 44 having the most recent data on stage distribution, and 2 countries (Israel and India) included only in the subgroup analysis. The study included 2 countries from Africa, 15 from Asia, 24 from Europe, 2 from North America, 1 from Latin America, and 2 from Oceania, with reporting periods spanning from 2004 to 2023. Of the 44 countries with the most recent data, 39 had population-based cancer registry data, whereas 5 had hospital-based registry data. Additionally, 7 countries reported a high proportion of unknown stage cases exceeding 20%, including Malaysia (63.5%), Thailand (39.6%), Kuwait (38.2%), Jordan (32.7%), Morocco (32.0%), Lithuania (26.9%), and Uganda (23.1%). The TNM staging system was used by 29 countries, whereas the remaining 15 used the SEER staging system.

Most Recent CRC Stage Distribution

As detailed in Figure 2, Supplementary Table 4 and Supplementary Table 5, among the 36 countries having proportion of unknown stage less than 20% and reporting on CRC cases diagnosed after the year 2010, the recalculated metastatic proportion after excluding the unknown stage cases was the lowest in Puerto Rico (16.2%) and the highest in Oman and Latvia (28.2%), with a median of 23.7% (interquartile range [IQR], 21.8%–26.3%) globally, 25.5% (IQR, 20.4%–27.6%) for Asia, and 23.6% (IQR, 22.3%–25.7%) for Europe. The proportion of countries with less than 23.7% of patients



* A comprehensive list of all existing cancer registries, and their corresponding websites, was provided by the Global Initiative for Cancer Registry Development (GICR, https://gicr.iarc.fr/) as well as Global Burden of Disease (https://ghdx.healthdata.org/countries).

Figure 1. Flow diagram for literature search.

diagnosed at the metastatic stage was 37.5% (3/8) in Asia, 47.8% (11/23) in Europe, 50.0% (1/2) in North America, 100% (1/1) in Latin America and the Caribbean, and 50.0% (1/2) in Oceania. For the other 8 countries reporting a high proportion of unknown stage cases exceeding 20% or data before 2010, detailed results are shown in Supplementary Table 6 and Supplementary Table 7.

Sex-specific Analysis

Figure 3*A* and Supplementary Figure 4 present the staging data according to sex. Of the known stages, with data available from 16 countries, we found a similar proportion of distant metastatic stages for men and women, with the ratio of metastatic staging in males to females ranging from 0.9 to 1.1.

Age-specific Analysis

We found a higher proportion of metastatic disease at diagnosis in the younger age group compared with middle-aged and older patients with CRC in 70% (7/10) of the included countries (Figure 3*B*; Supplementary Figure 5 and Supplementary Table 8). For instance, in the United States, the proportions of metastatic staging were 27.1% in the younger group (<50 years), 26.5% in the middle-aged group (50–64 years), and 23.9% in the older group (≥65 years). A similar trend was observed in Singapore, Slovakia, Canada, and Australia.

Tumor Site-specific Analysis

Figure 3*C* and Supplementary Figure 6 show the staging data by tumor site. Among the 21 countries with available data on known stages, 81.0% (17/21) reported a higher proportion of distant metastatic stages in colon cancers compared with rectal cancers. For example, in Germany, 30.8% of colon cancers were classified as metastatic, compared with 26.2% of rectal cancers. In other countries, such as Denmark, Sweden, and New Zealand, the proportion of metastatic rectal cancer was slightly higher than that of colon cancer, although the differences were minimal. In addition, Supplementary

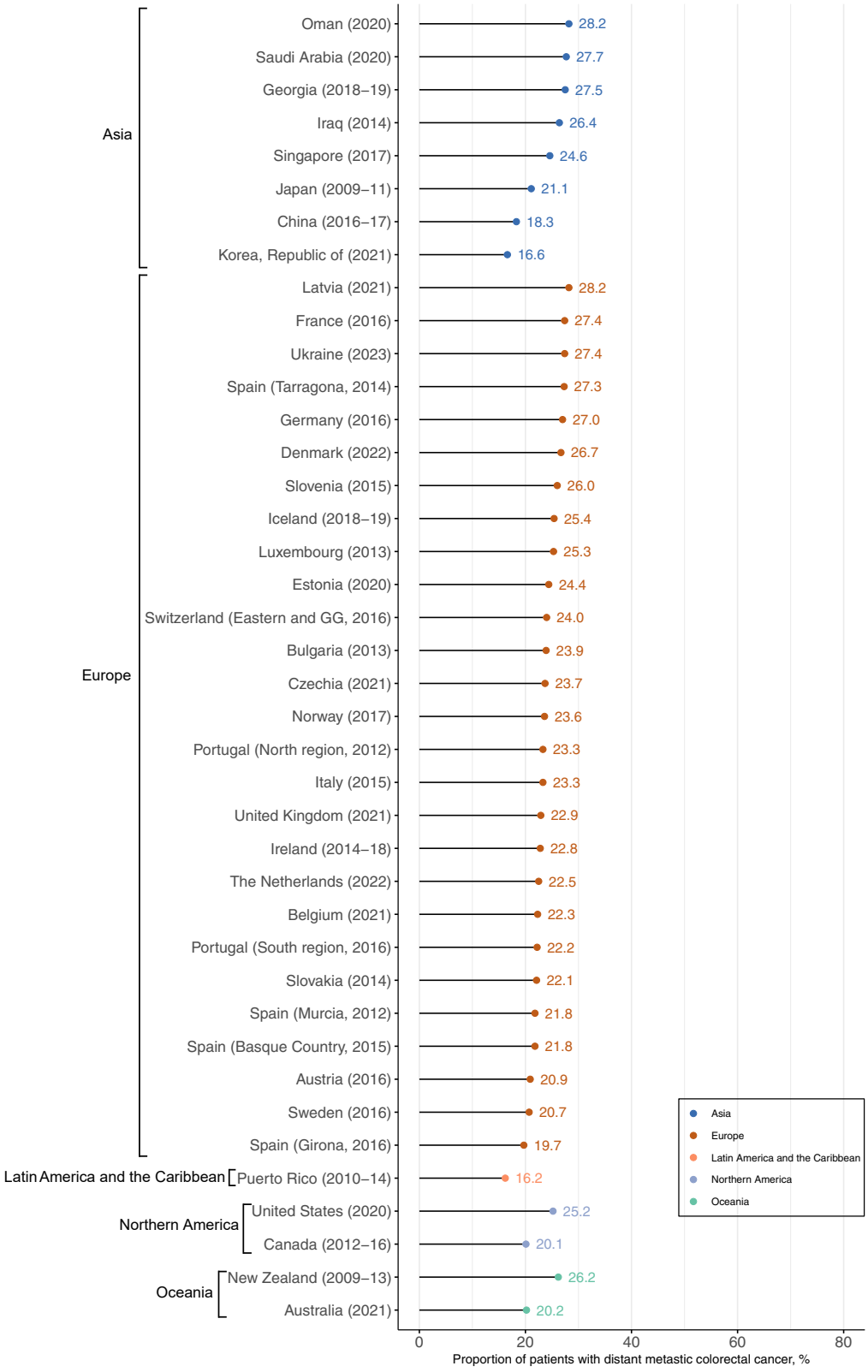


Figure 2. Proportion of patients diagnosed with metastatic CRC in all included countries using the latest available data.

Table 9 further presents the proportion of distant metastatic CRC by gender and tumor site in 9 countries. Both male and female patients showed higher proportions of metastatic colon cancer than for rectal cancer in all these countries.

Status of Screening Analysis

Figure 3*D* presents the staging data stratified by the status of screening programs. We observed a lower proportion of metastatic disease at diagnosis after the

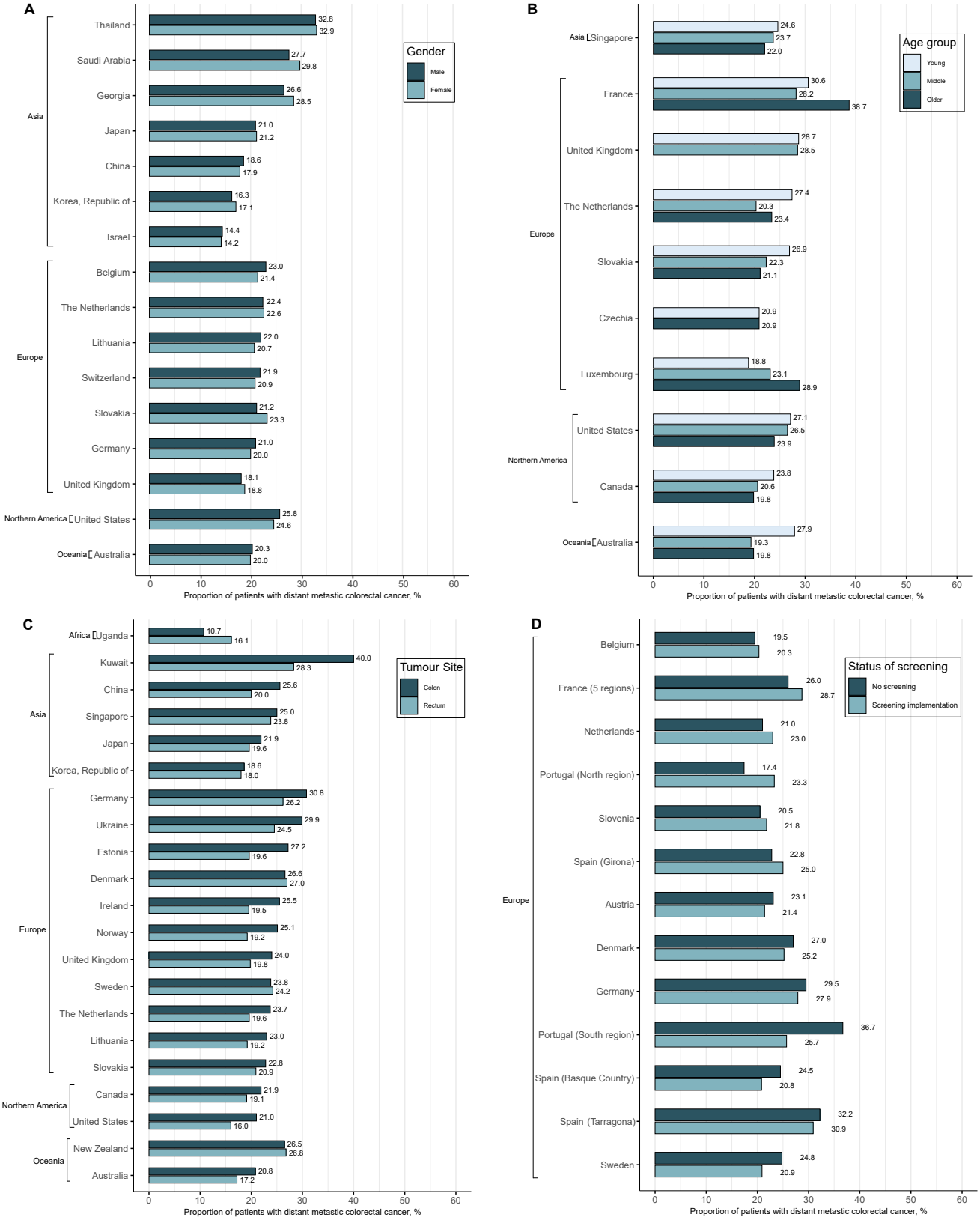


Figure 3. Stratified proportion of patients diagnosed with metastatic CRC in the included countries, categorized by sex (*A*), age group (*B*), tumor site (*C*), and status of population-based screening (*D*). Note: detailed age group definition for panel *B* is provided in the Supplementary Table 8

introduction of screening in 53.8% (7/13) of the included countries/regions. For example, in the South region of Portugal, the proportion of metastatic cases dropped from 36.7% (IQR, 33.9%–39.0%) before the introduction of screening to 25.7% (IQR, 22.2%–29.5%) after screening implementation. A similar trend was

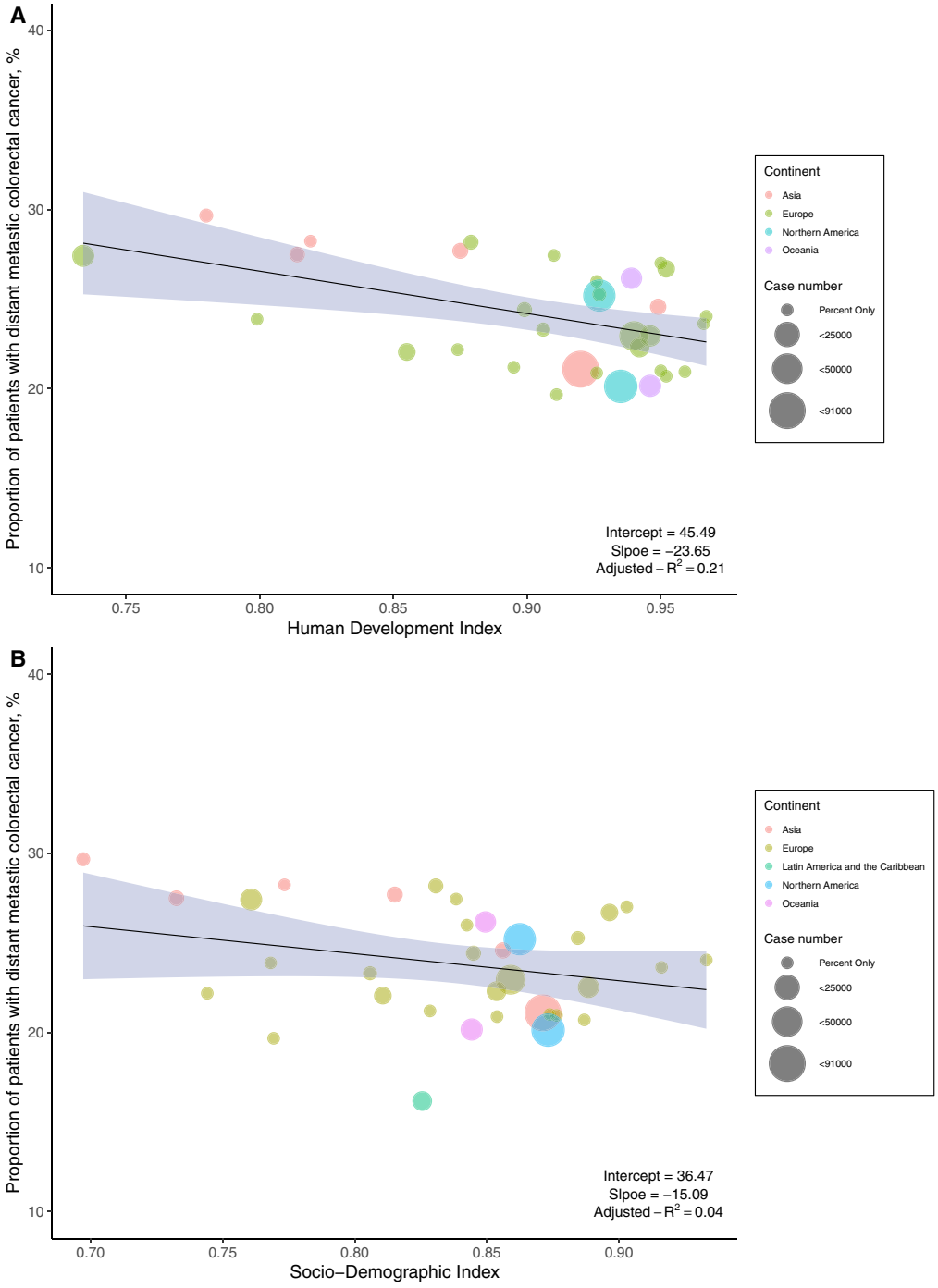


Figure 4. Association between the proportion of patients with metastatic CRC by HDI and SDI. Note: In Panel (*A*) data from Morocco, Uganda, Jordan, Kuwait, Malaysia, Thailand, Lithuania, China, Iraq, the Republic of Korea, and Puerto Rico were excluded due to a high proportion of unknown stage (>20%), hospital-based data, or unavailable HDI. In Panel (*B*) data from the same countries were excluded due to a high proportion of unknown stage (>20%) or hospital-based data.

observed in other regions and countries, including Spain (Tarragona), Germany, Denmark, Sweden, Spain (Basque Country), and Austria.

Correlation Analysis Between HDI and SDI and Metastatic CRC

The analysis is restricted to countries reporting data from population-based cancer registries with a proportion of unknown stage less than 20%. Overall, data from 33 countries (excluding Puerto Rico, where HDI data was unavailable) were included to examine the correlation between HDI and the proportion of metastatic CRC, and 34 countries were included to examine the correlation between SDI and the proportion of metastatic CRC. As shown in Figure 4, higher HDI and SDI were correlated with lower proportions of distant metastatic CRC (HDI: $\rho = -0.48$; 95% CI, -0.71 to -0.16; SDI: $\rho = -0.26$; 95% CI, -0.55 to 0.08). Specifically, the slope was -23.65 (adjusted $R^2 = 0.21$) for HDI and -15.09 (adjusted $R^2 = 0.04$) for SDI.

Time-trend Analysis

Twenty-nine countries with data across multiple periods were included in the time-trend analysis, of which 13 had nationwide organized screening programs, whereas the remaining 16 did not. Figure 5 shows the time-trend for stage distribution of patients with CRC in 13 countries with nation-wide organized screening programs. The proportion of patients with metastatic disease at diagnosis in 11 countries/regions has decreased each year since screening began, including Australia, Belgium, Czech Republic, France, Germany, Portugal (South region), Spain (Girona), Spain (Tarragona), Sweden, and United Kingdom. Taking Portugal (South region) as an example, the proportion of patients with metastatic disease at diagnosis was 33.5% in 2008, when the organized screening program began, and decreased to 22.2% in 2016. In contrast, a stable or slight increase was observed for a few countries/regions, such as Denmark, Portugal (North region), Spain (Basque Country), and the Netherlands. Notably, there was a considerable increase in the United States (from 19.8% in 2004 to 25.2% in 2020) and Slovenia (from 20.9% in 2009 to 26.0% in 2015). For the 8 countries/regions without nationwide organized screening programs (Supplementary Figure 7), all but Bulgaria and Estonia—such as Norway, Saudi Arabia, Murcia (Spain), Singapore, Switzerland (Eastern and Graubunden-Glarus), and Ukraine—showed a stable or slightly increasing trend in the proportion of metastatic disease.

Other countries lacking detailed year-by-year stage distribution but with data across multiple periods were also summarized, with the results presented in Supplementary Table 10, Supplementary Figure 8, and Supplementary Figure 9. Countries such as China, Japan, Kuwait, Italy, Canada, Australia, and New Zealand also showed increasing trends in metastatic CRC in recent years.

Risk of Bias Assessment

Among the 44 countries included with the most recent CRC stage distribution, the risk of bias was low for 10 countries (22.7%), intermediate for 9 countries (20.5%), and high for 25 countries (56.8%). The primary reasons for classifying countries as high-risk were a high percentage of death certificate only (>20%) and low rates of microscopically verified cases (<75%). A detailed evaluation of key indicators is provided in Supplementary Table 2 and Supplementary Figure 9.

Discussion

To the best of our knowledge, this is the first comprehensive systematic review to estimate the global distribution of CRC stages at diagnosis using data primarily from population-based cancer registries. This study provides an extensive overview of CRC stages at diagnosis across 46 countries, comprising more than 3.8 million patients, and offers valuable insights into the global epidemiology of this disease. Notably, there is considerable regional disparity in the proportion of distant metastatic disease. Higher proportions of metastatic stage were more prevalent among younger patients and those diagnosed with colon cancer. Importantly, countries with low HDI/SDI were also observed to have higher proportions of metastatic CRC. The wide variation in stage distribution across regions underscores the need for targeted interventions to enhance early detection and management, particularly in regions with high metastatic burdens.

Our findings highlight disparities in stage distribution across different countries. European and Oceanian countries predominantly present with localized disease, whereas metastatic stages are more prevalent in Asian countries. Cardoso and colleagues[9] have demonstrated that screening-detected cases had more favorable stage distributions and higher stage-specific survival. The European countries included in our study, except for Iceland, Slovakia, Switzerland, and Ukraine, had all implemented population-based CRC screening programs, which may partly explain the more favorable stage distribution compared with countries without such programs.

However, the association between a high proportion of early staging and screening programs has not been well-established in the literature. Schreuders et al[6] emphasized the effectiveness of screening in reducing the incidence of advanced-stage CRC. However, unlike female breast cancer,[13] there is no clear indication that the diagnosis of CRC at early stages has increased, even in developed countries where CRC screening has been introduced. For example, in the United States, where population-based screening began in 1996, the proportion of localized disease at diagnosis decreased from 42.6% in 2004 to 35.0% in 2020, whereas the proportion of metastatic disease at diagnosis increased from 19.8% in 2004 to 25.2% in 2020. One possible explanation is that our analysis focused on the percentage of cases in prevalent cases rather than incident cases. Thus, even if the proportion of metastatic CRC cases has slightly increased in the United States, absolute rates for metastatic CRC most likely declined substantially in the era of screening.[3] Another potential reason for the somewhat slower decline in metastatic CRC incidence compared with early-stage CRC could be that CRC incidence has declined more sharply among health-conscious individuals who attended screening and were less likely to present with metastatic CRC, even in the absence of screening.

Early-onset CRC (age ≤50 years) is of increasing concern globally.[19] Previous analyses showed that the burden of early-onset CRC was the greatest in the high-middle SDI quintile regions and East Asia.[20] Our analysis also revealed that younger individuals in some high-

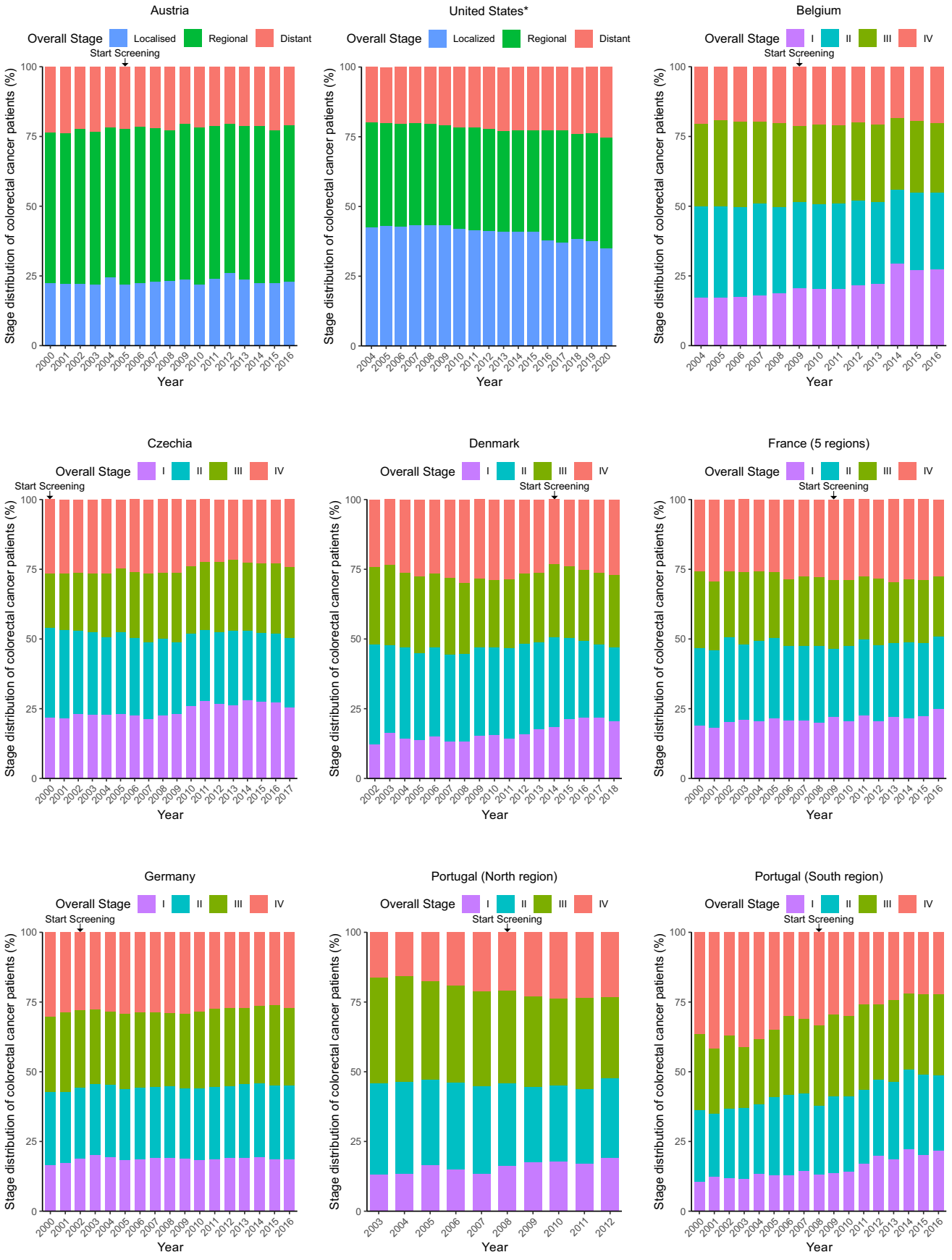


Figure 5. Stage distribution of colorectal cancer patients over different years in countries with available nationwide screening programs. Note: The *arrow* indicates the start year of nationwide screening in each respective country. Countries with start years beyond the included data: the United States in 1996, United Kingdom (England) in 2006 and United Kingdom (Scotland) in 2007.

Figure 5. (*continued*).

income countries, such as Australia and Canada, had a higher proportion of metastatic cases compared with older individuals. Current guidelines typically recommend screening for average-risk populations aged 50 years or older, which do not cover the younger individuals.[21] Therefore, targeted preventive efforts are needed to reduce the disease burden among younger populations.

We observed a higher proportion of distant metastatic stages in colon cancer compared with rectal cancer, with variations at the country level. Unlike patients with colon cancer, those with late-stage rectal cancer often undergo neoadjuvant therapy,[22] which leads to tumor shrinkage before surgery and results in downstaging of the disease.[23] Another possible explanation is that rectal cancer may present with earlier symptoms compared with colon cancer, leading to a more favorable clinical stage at diagnosis. Moreover, left-side colon, right-side colon, and rectal cancer have been demonstrated to exhibit different molecular characteristics and histology, which may also contribute to the variation in stage at diagnosis and overall prognosis.[19,24]

Although countries with high HDI/SDI bear a greater burden of CRC compared with those with low HDI/SDI,[25] the proportion of metastatic CRC is relatively low. The observed correlation between HDI/SDI and the proportion of metastatic stage underscores inequalities in access to screening and early detection, as well as differences in exposure to risk factors such as unhealthy diet and sedentary lifestyle.[26] CRC disparities arise from factors across individual, provider, health system, community, and policy levels. Multilevel interventions, combining health care and community efforts with policy changes, can reduce disparities in stage at diagnosis and prognosis by promoting healthy behaviors and ensuring access to high-quality CRC care.

Strengths and Limitations

This study has several strengths. First, a systematic literature search, including both published studies and gray literature, was conducted to ensure the study's comprehensiveness. Second, data were primarily extracted from population-based cancer registries, ensuring that the reported stage distributions were representative of the population and minimizing potential selection bias. Third, we conducted comprehensive subgroup and ecological analyses to examine the factors correlated with stage distribution.

When interpreting our results, several limitations must be acknowledged. First, due to variations in data availability, the years of the most recent data for the included countries were not consistent. However, given that stage distribution is unlikely to change significantly over a few years—as evidenced by our time-trend analysis—our analysis still provides a robust comparison between different countries. Second, 2 staging systems (TNM and SEER) were used in the included countries. Despite the minimal misclassification risk when defining the metastatic group, as suggested by previous studies,[27] efforts to enhance the global comparability of stage need to be advocated in the future. The International Agency for Research on Cancer (IARC) recommends using the TNM classification to improve the quality and completeness of stage data, which is crucial for evaluating and planning cancer control strategies globally. Third, due to the lack of cancer registries and data, high-quality estimates from African and South American countries are missing. Some countries only had hospital-based subnational data, which may be subject to significant selection bias. As a result, these data were not included in the main analysis. Efforts to improve the quality of cancer registries and expand data coverage are essential for more accurate and comprehensive global estimates. Fourth, the subgroup analyses were conducted only in a few countries with available data. Potential variations in stage distribution among different ethnic and racial groups could not be evaluated due to the lack of detailed data in most included countries. Nonetheless, we acknowledge that ethnicity and race are important determinants in this context.[28] Fifth, the impact of CRC screening on stage distribution could not be separately evaluated for each included country due to the lack of individual-level data, which should be addressed in future studies with high-quality data.

In conclusion, this study reveals global disparities in CRC staging, influenced by factors such as age, anatomical site, HDI, SDI, and screening status. To reduce the proportion of metastatic cases, targeted strategies, including the implementation of population-based screening, are essential for improving early detection and management, particularly in regions with a high metastatic burden. Future improvements in the registration and dissemination of cancer stage information, along with the harmonization of staging systems, are necessary to support effective policies, cancer control plans, and international comparisons.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.11.019.

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Data Availability
Requests to access the whole datasets regarding the manuscript should be directed to Dr Hongda Chen (Email: chenhongda@pumch.cn).