# Colon and rectal cancer survival in seven high-income countries 2010–2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project)

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## Abstract

**Objectives** As part of the International Cancer Benchmarking Partnership (ICBP) SURVMARK-2 project, we provide the most recent estimates of colon and rectal cancer survival in seven high-income countries by age and stage at diagnosis.

**Methods** Data from 386 870 patients diagnosed during 2010–2014 from 19 cancer registries in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the UK) were analysed. 1-year and 5-year net survival from colon and rectal cancer were estimated by stage at diagnosis, age and country,

**Results** (One1-year) and 5-year net survival varied between (77.1% and 87.5%) 59.1% and 70.9% and (84.8% and 90.0%) 61.6% and 70.9% for colon and rectal cancer, respectively. Survival was consistently higher in Australia, Canada and Norway, with smaller proportions of patients with metastatic disease in Canada and Australia. International differences in (1-year) and 5-year survival were most pronounced for regional and distant colon cancer ranging between (86.0% and 94.1%) 62.5% and 77.5% and (40.7% and 56.4%) 8.0% and 17.3%, respectively. Similar patterns were observed for rectal cancer. Stage distribution of colon and rectal cancers by age varied across countries with marked survival differences for patients with metastatic disease and diagnosed at older ages (irrespective of stage).

**Conclusions** Survival disparities for colon and rectal cancer across high-income countries are likely explained by earlier diagnosis in some countries and differences in treatment for regional and distant disease, as well as older age at diagnosis. Differences in cancer registration practice and different staging systems across countries may have impacted the comparisons.

## Introduction

Colon and rectal cancers (CRC) were the third most common cancer (1.8 million cases) and the second most common cause of cancer-related death (881 000 deaths) for both men and women worldwide in 2018.[1] Most of this burden is concentrated in high and very high-income countries, where incidence is high and the prospects of cure are considerably better than in other regions of the world.[2] Yet, marked survival differences have long existed across high-income countries.[3] In an effort to drive change, the International Cancer Benchmarking Partnership (ICBP) brings together clinicians, policy-makers, researchers and cancer data experts seeking to explain cancer survival differences between high-income countries with similar health systems, for example, similar healthcare expenditure, universal healthcare coverage and population coverage through cancer registries.[3]

In previous analyses of CRC survival for patients diagnosed in 2000–2007, 1-year net survival from colon cancer ranged between 80.2% in Australia and 67.4% in the UK, whereas for rectal cancer it was highest in Sweden (84.4%) and lowest in the UK (75.2%).[4] For both cancers, between-country differences in net survival were largest for the oldest age groups and for patients with more advanced stage of disease at diagnosis. For example, 1-year net survival for patients with colon cancer with 'localised' stage ranged between 95.1% in Canada and 91.3% in the UK, compared with 'distant' stage ranging between 42.0% in Australia and 34.2% in the UK. Differences in uptake and coverage of new treatment advances such as improved surgical techniques,[5] adjuvant chemotherapy,[6] preoperative radiotherapy[7] or the use of palliative chemotherapy[8] and multimodal treatment approaches for resectable metastases[9] might explain some of these survival differences. In addition, differences in time (delays) to diagnosis and in access to cancer care (from primary healthcare) may partly contribute to the observed survival variation.[10] Monitoring survival by stage at diagnosis remains vital to identify drivers of overall differences and to assess the effectiveness of national health systems.

In this study and as part of the ICBP SURVMARK-2 project,[3] we provide the most recent estimates of CRC survival by age and stage at diagnosis, using population-based data from 19 cancer registries in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the UK). We compare distributions of stage at diagnosis and examine overall and stage-specific survival at 1 and 5 years after diagnosis.

# Methods

### Data sources

During the course of the ICBP SURVMARK-2 project, data for patients diagnosed with CRC were collected from 21 population-based cancer registries in seven countries. Data submitted included information on histology, morphology, basis of diagnosis, stage at diagnosis and treatment. A number of quality control measures were carried out on each dataset. This included screening data for specific anomalies including instances of negative survival duration, out-of-range dates of diagnosis and/or dates of death, availability of stage at diagnosis information and invalid vital status codes. Cases were selected and coded according to the following International Classification of Diseases, Tenth Revision rubrics[11]: colon (C18-19) and rectum (C20) including all morphologies. In the current analyses, we included patients diagnosed during 2010–2014 from the following 19 registries that provided sufficient information on stage at diagnosis (≥50% of cases with known stage; online supplementary table 1A,B): Australia (New South Wales, Victoria), Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan), Ireland (2010–2013), Denmark, New Zealand, Norway and the UK (England, Scotland, Wales, Northern Ireland). Out of 405 255 patients with colon and rectal cancer (colon cancer: 294 996; rectal cancer: 110 259) diagnosed during 2010–2014, we excluded cases diagnosed based on death certificate only (DCO) or at autopsy (n=4613, 1.1%), below the age of 15 or above age 99 at diagnosis (n=448, 0.1%), with inconsistencies in stage information (n=1302, 0.3%), with in situ tumours (n=373, 0.1%), and second or higher sequenced cancers diagnosed at the same site (n=11 649, 2.9%). Using these criteria, a total of 386 870 (95.5% of those eligible) (colon cancer: 280 251; rectal cancer: 106 619) patients diagnosed during 2010–2014 were included in the analyses.

Each participating cancer registry provided information on pretreatment pathological and clinical tumour (T), node (N), metastases (M) records, grouped TNM stage, Surveillance, Epidemiology, and End Results (SEER) summary stage 2000 (SEER SS2000) and/or Duke's stage (online supplementary figure 1A). A previously developed algorithm[12] was used to translate both grouped TNM and/or Dukes' as well as individual T, N, M elements to SEER Summary Staging (categorised into localised, regional, distant and missing), enabling us to include all seven countries in comparative analyses. A flowchart of how registry-specific staging information was mapped to SEER staging is available in online supplementary figure 1A,B. All analyses were carried out using grouped TNM where possible and mapped SEER stage for all countries and jurisdictions. We present survival estimates for colon and rectal cancers separately, for all ages combined and four age groups at diagnosis: 15–49, 50–64, 65–79 and 80–99 years. For simplicity, we used stages I–IV when referring to TNM stage, and 'localised', 'regional' and 'distant' when referring to SEER SS2000.

**Statistical analyses**

For cases with missing stage at diagnosis, stage information was imputed using the multiple imputation (*mi*) command with the following covariates: sex, age, year of diagnosis, survival time and the Nelson-Aalen estimator of the cumulative hazard. We ran the imputation procedure 30 times and combined the results using Rubin's rules to estimate net survival and 95% CI.[13]

We reported net survival with accompanying 95% CIs, which is the probability of survival for patients with cancer in a hypothetical situation where cancer is considered the only possible cause of death. Background mortality in the general population of each jurisdiction was obtained from lifetables of all-cause death rates during 1995–2014 by sex, single year of age and calendar year for the respective study period. Follow-up was available until 31 December 2015, for all patients except for those in Ontario, where follow-up was limited to 31 December 2014. Net survival estimates at 1 and 5 years after diagnosis were computed by age, sex, stage at diagnosis and cancer site for each jurisdiction and for the Canadian, Australian and UK registries combined using Pohar Perme estimators,[14] which has been shown to be an unbiased method to estimate cancer-specific survival.[15] We used the period approach for patients diagnosed in 2010–2014 (period window: 2012–2014) which has been shown to perform particularly well in the prediction of up-to-date cancer survival.[16] Age standardisation was carried out using the International Cancer Survival Standard weights.[17] While in the main manuscript we report stage-specific survival estimates by stage at diagnosis after imputation, we also present results based on original, non-imputed, stage categories in online supplementary tables.

**Patient and public involvement**

The ICBP is a multipartner collaboration that involves clinicians, policy-makers, researchers and cancer data experts. While patients were not directly involved in the analytical phase of the study, we will incorporate survival estimates into a publicly available website (http://gco.iarc.fr/survival/survmark/) to support dissemination of findings to patient and public via simple user-generated and automatic graph layouts.

# Results

## Age at diagnosis and cancer stage by country

The median age and distribution of cases by cancer site, country and stage at diagnosis for TNM stage and mapped SEER stage are given in table 1. For both colon and rectal cancers, the median age at diagnosis was slightly higher in New Zealand, Norway and the UK when compared with Australia, Denmark, Ireland and Canada. Among jurisdictions included in this study, the proportion of patients with colon cancer with missing stage at diagnosis was highest in the UK (TNM: 39.5%; SEER: 37.2%) and lowest in Canada (TNM: 7.5%; SEER: 6.4%). For rectal cancer, a similar pattern was seen, that is, proportion with missing TNM stage was 39.4% (SEER: 37.0%) in the UK and 10.8% (SEER: 6.8%) in Canada. Multiple imputation did not substantially alter the distribution of stage for colon or rectal cancer (table 1).

**Table 1** Median age at diagnosis, number of cases and imputed proportion (%) of colon and rectal cancers by stage and country, 2010–2014

| | Colon cancer | | | | | | | | Rectal cancer | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TNM stage | | | | Mapped SEER | | | | TNM stage | | | | Mapped SEER | | | |
| Country | Stage | Median age (IQR) | No of cases (%) | Imputed (%) | Stage | Median age (IQR) | No of cases (%) | Imputed (%) | Stage | Median age (IQR) | No of cases (%) | Imputed (%) | Stage | Median age (IQR) | No of cases (%) | Imputed (%) |
| Australia* | All | 72 (62–80) | 12 932 | | All | 72 (62–80) | 30 802 | | All | 67 (57–77) | 4 877 | | All | 67 (58–76) | 11 058 | |
| | I | 70 (62–79) | 2455 (21.2) | 20.8 | Localised | 72 (63–80) | 10743 (38.0) | 37.7 | I | 67 (58–76) | 1360 (35.0) | 34.8 | Localised | 67 (59–76) | 4173 (44.4) | 45 |
| | II | 74 (65–81) | 3684 (31.8) | 31.7 | Regional | 72 (63–80) | 11477 (40.6) | 40.8 | II | 69 (60–77) | 847 (21.8) | 21 | Regional | 66 (57–76) | 3595 (38.3) | 37.3 |
| | III | 71 (61–79) | 3076 (26.6) | 26.4 | Distant | 70 (60–79) | 6028 (21.3) | 21.5 | III | 65 (56–76) | 1009 (26.0) | 25.9 | Distant | 66 (57–76) | 1629 (17.3) | 17.7 |
| | IV | 69 (59–78) | 2364 (20.4) | 21.1 | | | | | IV | 65 (56–75) | 665 (17.1) | 18.3 | | | | |
| | Missing | 76 (63–85) | 1353 (10.5) | | Missing | 74 (63–84) | 2554 (8.3) | | Missing | 70 (58–81) | 996 (20.4) | | Missing | 68 (57–79) | 1661 (15.0) | |
| Canadian provinces† | All | 71 (61–80) | 58,749 | | All | 71 (61–80) | 58,749 | | All | 66 (57–76) | 20,271 | | All | 66 (57–76) | 20,271 | |
| | I | 70 (61–79) | 11842 (21.8) | 22.3 | Localised | 71 (62–80) | 20435 (37.2) | 38 | I | 67 (58–76) | 4637 (25.6) | 25.3 | Localised | 67 (58–76) | 6917 (36.6) | 36.3 |
| | II | 73 (63–81) | 15414 (28.4) | 27.9 | Regional | 71 (61–80) | 21934 (39.9) | 39.2 | II | 68 (59–77) | 3742 (20.7) | 19.6 | Regional | 65 (57–75) | 8333 (44.1) | 43.6 |
| | III | 70 (61–79) | 15161 (27.9) | 27.8 | Distant | 69 (60–79) | 12592 (22.9) | 22.8 | III | 65 (56–74) | 6327 (35.0) | 35.7 | Distant | 65 (56–75) | 3637 (19.3) | 20 |
| | IV | 69 (60–79) | 11912 (21.9) | 21.9 | | | | | IV | 66 (56–75) | 3372 (18.7) | 19.4 | | | | |
| | Missing | 76 (63–85) | 4420 (7.5) | | Missing | 76 (64–86) | 3788 (6.4) | | Missing | 68 (56–81) | 2193 (10.8) | | Missing | 70 (57–82) | 1384 (6.8) | |
| Denmark | All | 72 (65–79) | 14,690 | | All | 72 (65–79) | 14,690 | | All | 69 (62–77) | 7,584 | | All | 69 (62–77) | 7,584 | |
| | I | 71 (64–78) | 1561 (12.6) | 14 | Localised | 72 (65–79) | 4799 (38.8) | 40.8 | I | 69 (63–76) | 1148 (18.2) | 19.9 | Localised | 69 (63–76) | 2499 (39.6) | 42.1 |
| | II | 73 (66–80) | 4093 (33.1) | 34.2 | Regional | 71 (64–79) | 4058 (32.8) | 32.8 | II | 70 (63–77) | 1649 (26.1) | 26.9 | Regional | 68 (61–76) | 2360 (37.4) | 35.9 |
| | III | 71 (63–78) | 3196 (25.9) | 25.4 | Distant | 71 (63–78) | 3500 (28.3) | 26.4 | III | 68 (61–75) | 2060 (32.7) | 31.3 | Distant | 69 (62–76) | 1452 (23.0) | 21.9 |
| | IV | 71 (63–78) | 3500 (28.3) | 26.5 | | | | | IV | 69 (62–76) | 1452 (23.0) | 21.9 | | | | |
| | Missing | 75 (67–83) | 2340 (15.9) | | Missing | 75 (67–83) | 2333 (15.9) | | Missing | 72 (64–81) | 1275 (16.8) | | Missing | 72 (64–81) | 1273 (16.8) | |
| Ireland‡ | All | 71 (62–79) | 6,863 | | All | 71 (62–79) | 6,863 | | All | 67 (59–76) | 2,637 | | All | 67 (59–76) | 2,637 | |
| | I | 70 (62–78) | 897 (14.3) | 14.3 | Localised | 71 (64–79) | 2304 (36.8) | 37 | I | 69 (61–77) | 437 (18.5) | 18.6 | Localised | 69 (62–77) | 857 (36.2) | 35.7 |
| | II | 73 (64–80) | 1905 (30.5) | 30.8 | Regional | 70 (62–78) | 2360 (37.7) | 37.5 | II | 70 (63–77) | 502 (21.2) | 20.6 | Regional | 66 (57–75) | 1047 (44.3) | 45.3 |
| | III | 70 (61–78) | 1859 (29.7) | 29.4 | Distant | 71 (61–78) | 1593 (25.5) | 25.5 | III | 65 (57–74) | 965 (40.8) | 41.7 | Distant | 66 (57–75) | 462 (19.5) | 19.1 |
| | IV | 71 (61–78) | 1593 (25.5) | 25.5 | | | | | IV | 66 (57–75) | 462 (19.5) | 19.1 | | | | |
| | Missing | 75 (62–84) | 609 (8.9) | | Missing | 75 (62–84) | 606 (8.8) | | Missing | 69 (59–78) | 271 (10.3) | | Missing | 69 (59–78) | 271 (10.3) | |
| New Zealand | | | | | All | 73 (64–81) | 11 049 | | | | | | All | 69 (60–77) | 3 811 | |
| | | | | | Localised | 73 (65–79) | 2644 (26.8) | 25.4 | | | | | Localised | 70 (61–78) | 667 (31.2) | 30.5 |
| | | | | | Regional | 73 (65–80) | 4581 (46.4) | 46.5 | | | | | Regional | 69 (61–78) | 888 (41.6) | 43.7 |
| | | | | | Distant | 71 (62–79) | 2641 (26.8) | 28.2 | | | | | Distant | 68 (58–77) | 581 (27.2) | 25.8 |
| | | | | | Missing | 78 (69–85) | 1183 (10.7) | | | | | | Missing | 68 (58–77) | 1675 (44.0) | |
| Norway | All | 73 (64–81) | 13875 | | All | 73 (64–81) | 13 875 | | All | 69 (61–78) | 5 334 | | All | 73 (64–81) | 5 334 | |
| | I | 74 (65–80) | 1734 (13.9) | 14.3 | Localised | 74 (65–81) | 5519 (44.1) | 43.7 | I | 69 (62–77) | 1130 (29.1) | 29.2 | Localised | 70 (62–78) | 1972 (50.8) | 51 |
| | II | 73 (66–81) | 4279 (34.2) | 33.5 | Regional | 72 (64–80) | 3568 (28.5) | 28.3 | II | 70 (62–78) | 913 (23.5) | 24.1 | Regional | 69 (61–78) | 918 (23.6) | 24.3 |
| | III | 72 (64–80) | 3074 (24.6) | 24.2 | Distant | 71 (63–80) | 3414 (27.3) | 28 | III | 69 (61–78) | 847 (21.8) | 22.1 | Distant | 70 (60–78) | 992 (25.6) | 24.7 |
| | IV | 71 (63–80) | 3414 (27.3) | 27.9 | | | | | IV | 67 (58–76) | 992 (25.6) | 24.6 | | | | |
| | Missing | 77 (67–85) | 1374 (9.9) | | Missing | 77 (67–85) | 1374 (9.9) | | Missing | 70 (61–78) | 1452 (27.2) | | Missing | 70 (61–78) | 1452 (27.2) | |
| UK registries§ | All | 73 (64–81) | 144223 | | All | 73 (64–81) | 144,223 | | All | 70 (61–78) | 55,924 | | All | 70 (61–78) | 55,924 | |
| | I | 70 (63–78) | 13194 (15.1) | 14.4 | Localised | 72 (64–79) | 35982 (39.8) | 37.7 | I | 69 (62–77) | 8300 (24.5) | 23.8 | Localised | 70 (62–78) | 15108 (42.9) | 41.5 |
| | II | 73 (65–81) | 25798 (29.6) | 28.9 | Regional | 72 (63–80) | 30866 (34.1) | 33.6 | II | 71 (62–78) | 6859 (20.2) | 19.8 | Regional | 68 (60–76) | 13343 (37.9) | 38 |
| | III | 71 (63–79) | 23927 (27.4) | 26.9 | Distant | 73 (63–81) | 23666 (26.1) | 28.6 | III | 68 (59–76) | 11776 (34.7) | 35 | Distant | 70 (60–78) | 6785 (19.3) | 20.5 |
| | IV | 73 (63–81) | 24289 (27.9) | 29.7 | | | | | IV | 70 (60–78) | 6954 (20.5) | 21.4 | | | | |
| | Missing | 74 (65–82) | 57015 (39.5) | | Missing | 74 (65–82) | 53709 (37.2) | | Missing | 71 (62–80) | 22035 (39.4) | | Missing | 71 (62–80) | 20688 (37.0) | |

*Australia registries included Victoria (data on both TNM and SEER) and New South Wales (data on SEER only).
†Canadian provinces included Alberta, British Columbia, New Brunswick, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island and Saskatchewan.
‡Ireland (2010–2013).
§UK registries included England, Northern Ireland, Scotland and Wales.
TNM, tumour–node–metastases.

The distribution of stage at diagnosis (localised, regional and distant) also varied across countries (table 1, figure 1). For example, the proportion of patients with 'distant' stage colon cancer was lowest in Australia (21.5%) and Canada (22.8%) and highest in the UK (28.6%), followed by New Zealand (28.2%). For rectal cancer, the proportion of patients diagnosed with 'distant' stage was lowest in Australia (17.7%) and highest in New Zealand (25.8%).

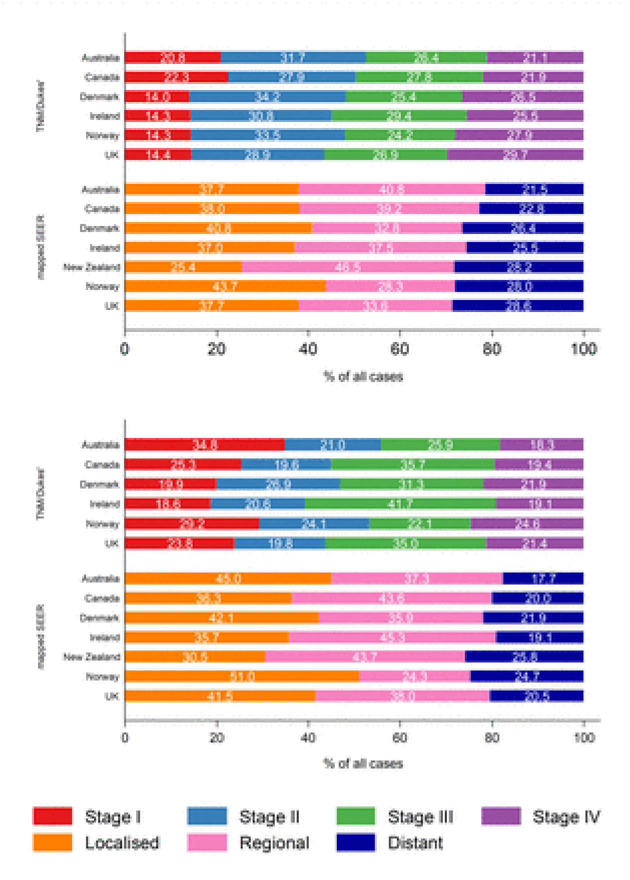


**Figure 1**: **Distribution of (imputed) stage at diagnosis of (A) colon cancer and (B) rectal cancer by country, 2010–2014. TNM, tumour–node–metastases.**

**1-year and 5-year net survival by country**

Overall, 1-year age-standardised net survival from colon cancer ranged from 77.1% in the UK to 87.5% in Australia compared with 80.0%–84.2% elsewhere (online supplementary table 2A). One-year age-standardised net survival from rectal cancer ranged from 84.8% in the UK to 90.0% in Australia compared with 85.9%–89.1% elsewhere (online supplementary table 3A). For both colon and rectal cancers, similar patterns of net survival across countries were observed 5 years after diagnosis (online supplementary tables 2B and 3B). Five-year survival from colon cancer ranged from 59.1% in the UK to 70.9% in Australia (online supplementary table 2B). Five-year survival from rectal cancer ranged from 61.6% in Ireland to 70.9% in Canada (online supplementary table 3B).

1-year and 5-year net survival by age and country

1-year and 5-year net survival from both cancers decreased with increasing age at diagnosis while international differences in survival were largest for the oldest patient groups (80–99 years). For example, 1-year survival for patients with colon cancer aged 15–49 years ranged between 84.8% (New Zealand) and 92.0% (Australia) while survival for patients aged 80–99 years ranged between 57.7% (UK) and 76.9% (Australia) (online supplementary table 2A). Similar age patterns were also seen for rectal cancer; for example, 1-year survival for patients with rectal cancer aged 15–49 years ranged between 90.4% (New Zealand) and 95.9% (Australia), and 69.0% (Ireland) and 80.2% (Australia) for patients aged 80–99 years (online supplementary table 3A).

**1-year and 5-year net survival by stage and country**

International differences in age-standardised net survival were evident, in particular for patients with regional/stage III and distant/stage IV colon and rectal cancers (figures 2 and 3). For example, using SEER stage, 1-year survival for patients with colon cancer with ‘localised’ disease ranged between 96.0% (Canada/UK) and 98.3% (New Zealand), whereas for ‘regional’ colon cancer it ranged between 86.0% (UK) and 94.1% (Australia), and for ‘distant’ stage it ranged between 40.7% (UK) and 56.4% (Australia) (online supplementary table 2A; figure 3). Patterns were similar for survival for patients with colon cancer 5 years after diagnosis (online supplementary table 2B, figure 3). For rectal cancer, the international differences in net survival across stage also varied by country, with similar patterns as those observed for colon cancer (online supplementary table 3A,B, and figures 2 and 3).

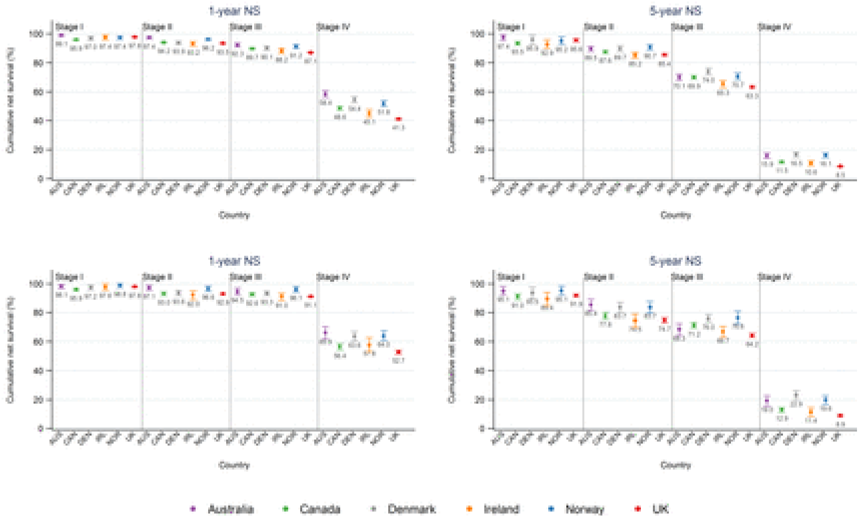


**Figure 2**: **1-year and 5-year age-standardised net survival (NS) and corresponding 95% CIs from (A) colon cancer and (B) rectal cancer by (imputed) tumour–node–metastases stage and country, 2010–2014.**

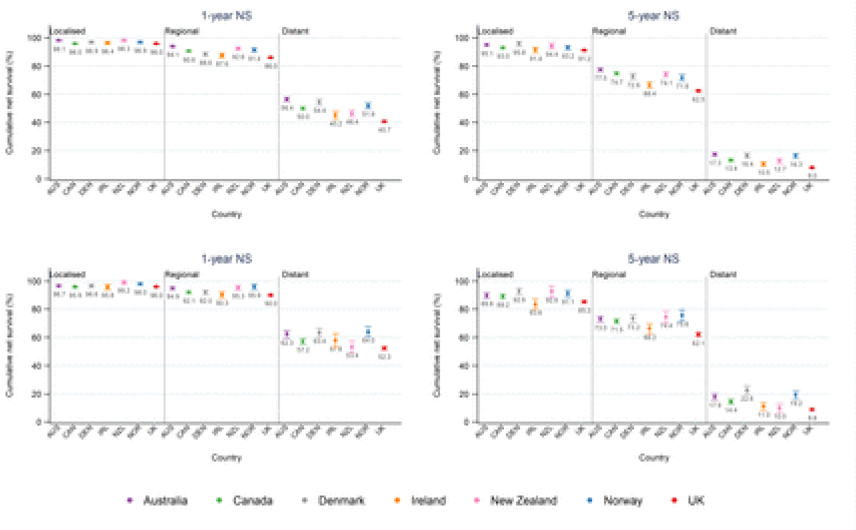


**Figure 3: 1-year and 5-year age-standardised net survival (NS) and corresponding 95% CIs from (A) colon cancer and (B) rectal cancer by (imputed) mapped SEER stage and country, 2010–2014.**

**1-year and 5-year net survival by age, stage and country**

Overall, international differences in 1-year and 5-year net survival from both colon and rectal cancers were more pronounced with increasing age and especially for those with regional and advanced stage of disease (figures 4–7). 1-year and 5-year survival for the oldest patients with colon cancer with ‘distant’ stage ranged between 17.7% (Ireland) and 30.2% (Denmark), and 1.3% (UK) and 8.3% (Denmark), respectively (online supplementary table 2A,B). 1-year and 5-year survival for patients with rectal cancer with ‘distant’ stage aged 80–99 years ranged between 29.0% (Ireland) and 37.7% (Denmark), and 1.1% (UK) and 7.2% (Denmark), respectively (online supplementary table 3A,B). Figures 4–7 also present the proportion of patients by stage category across age groups; for example, the proportion of patients with colon cancer with ‘distant’ stage among those aged 80–99 years was highest in the UK (32.5%) and between 20.8% and 28.1% elsewhere, whereas the proportion of patients with rectal cancer with ‘distant’ stage in this oldest age group was highest in New Zealand (28.7%) and between 18.7% and 25.0% elsewhere (figures 6 and 7, and online supplementary figures 2 and 3).

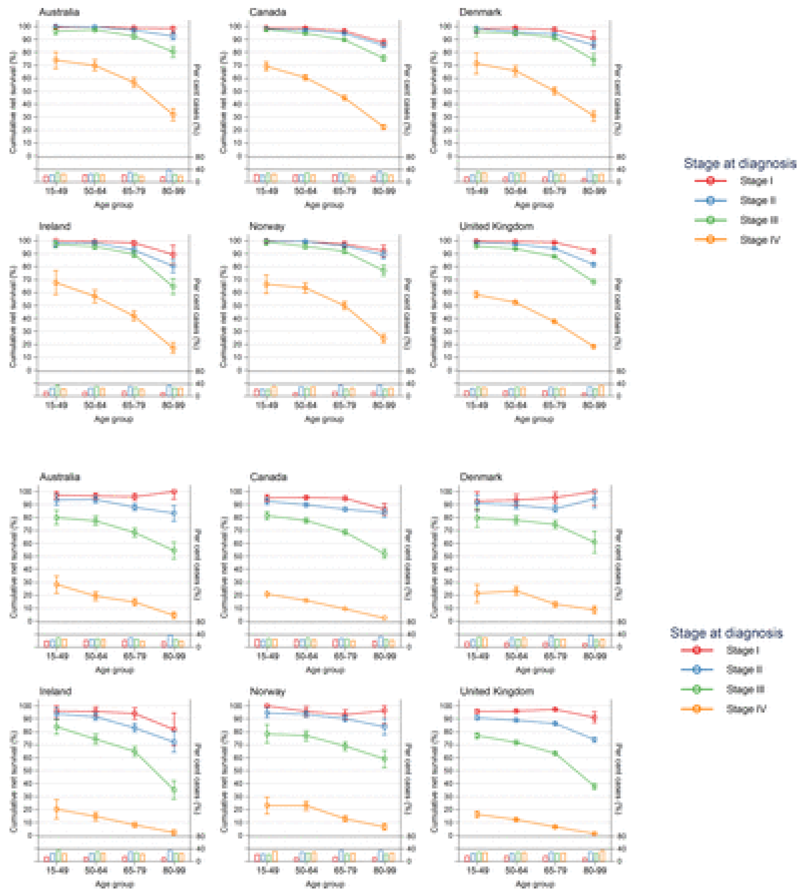


**Figure 4: (A) 1-year and (B) 5-year age-standardised net survival and corresponding 95% CIs from colon cancer by age and (imputed) tumour–node–metastases stage and country, 2010–2014.**

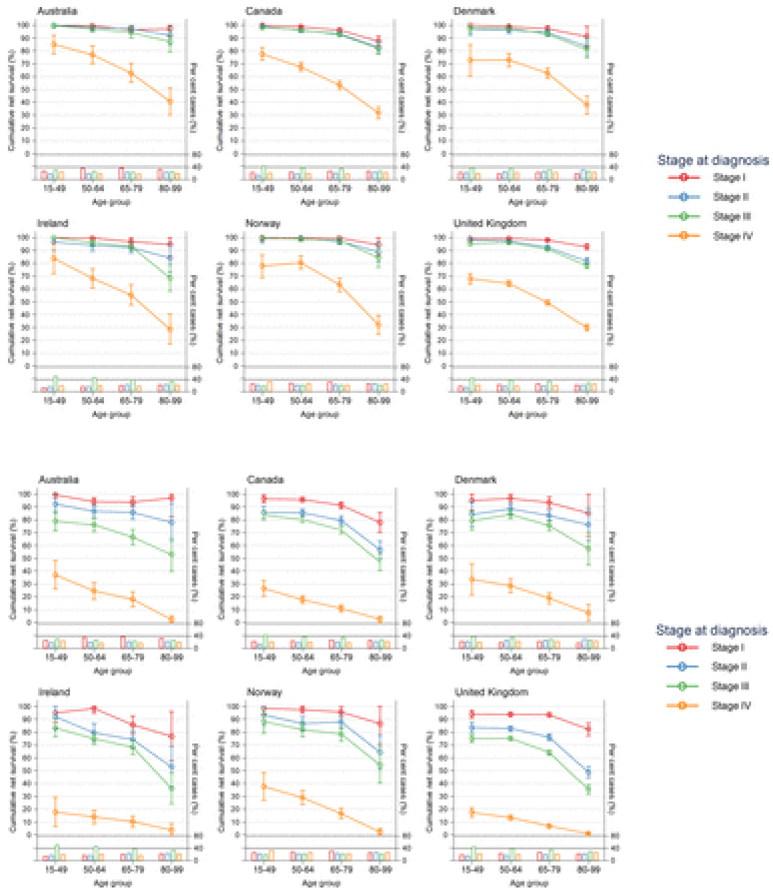


**Figure 5: (A) 1-year and (B) 5-year age-standardised net survival and corresponding 95% CIs from rectal cancer by age and (imputed) tumour–node–metastases stage and country, 2010–2014.**

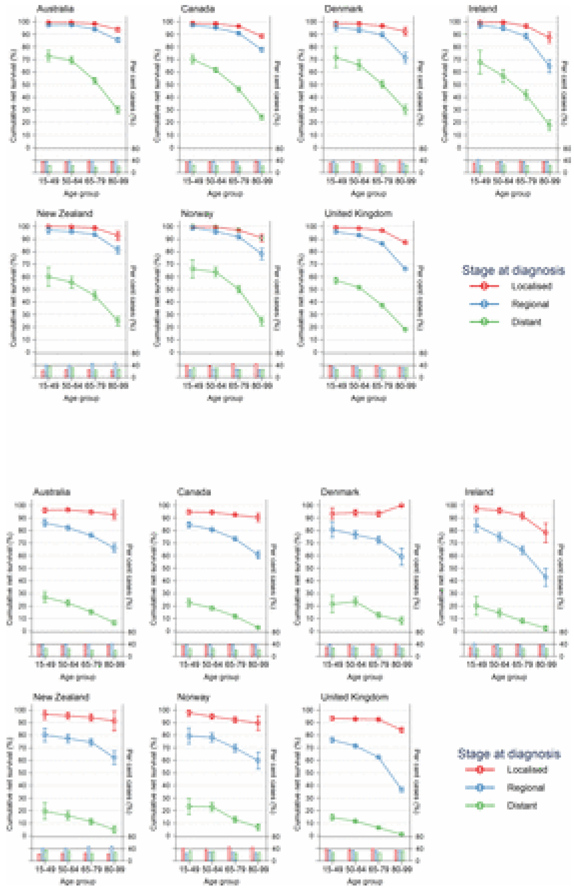


**Figure 6: (A) 1- and (B) 5-year age-standardised net survival and corresponding 95% CIs from colon cancer by age and (imputed) mapped SEER stage and country, 2010–2014.**

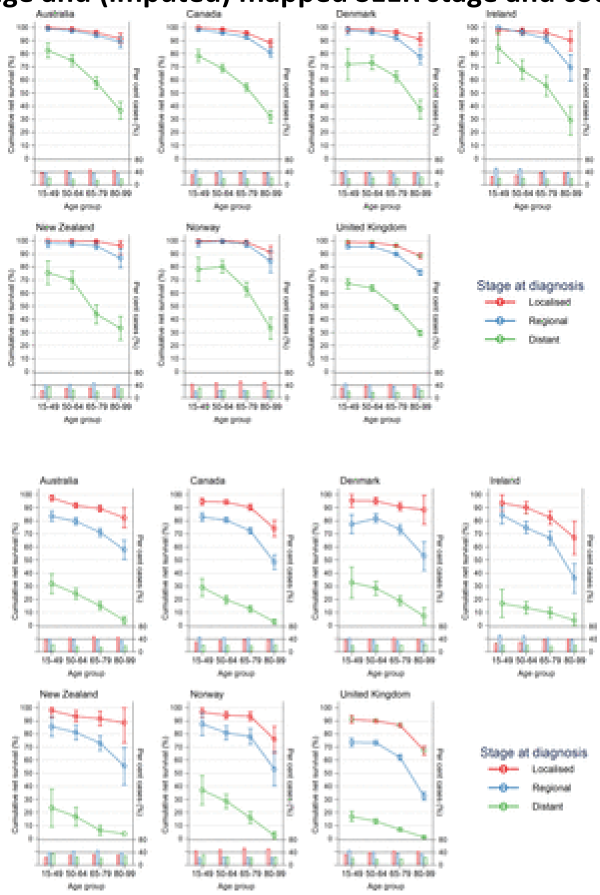

**Figure 7: (A) 1-year and (B) 5-year age-standardised net survival and corresponding 95% CIs from rectal cancer by age and (imputed) mapped SEER stage and country, 2010–2014.**

**Supplementary analyses**

1-year net survival from colon and rectal cancers was similar for males and females (online supplementary tables 4A-7A); however, 5-year survival was higher for females (online supplementary tables 4B-7B). Stage-specific survival estimates including the missing category (without multiple imputation) were slightly higher compared with survival estimates after multiple imputation. For example, in Canada (with the lowest proportion of missing stage) 1-year survival for imputed distant stage colon cancer was 50.0% and the estimate without imputation was 51.0%. In the UK, where the proportion of those with missing stage information was highest, the respective estimates were 40.7% and 42.9% (online supplementary table 8A; figure 4A). This is due to the somewhat poorer survival for patients with missing stage. For example, among patients with colon cancer for whom SEER stage was missing, the 1-year net survival ranged between 68.5% and 81.6% versus 77.1% and 87.5% for overall colon cancer cases, and 74.3% and 89.3% versus 84.8% and 90.0% for rectal cancer, respectively (online supplementary tables 8A and 9A; figures 4 and 5).

As for specific results by jurisdiction within country, variation in stage distribution was evident; in the UK, the proportions of cases with localised colon and rectal cancers were largest in Scotland (42.0% and 49.9%, respectively; online supplementary table 10). Net survival estimates for rectal cancer were generally better in Scotland (eg, at 5 years for localised disease 88.2% vs 80.3% in Wales) and for colon cancer in Northern Ireland (eg, at 5 years for localised disease 95.2% vs 83.1% in Wales; online supplementary tables 11-14). In Canada, the proportion with localised colon cancer varied from 32.2% to 45.7% and from 29.1% to 45.4% for rectal cancer (online supplementary table 15). Survival also varied; for example, for the larger Canadian provinces 5-year net survival from localised colon cancer ranged between 86.4% (Saskatchewan) and 96.2% (New Brunswick; online supplementary tables 16-19). Similarly, we also observed differences in stage distribution in Australia, for example, 31.3% were localised colon cancer in New South Wales and 46.8% in Victoria (online supplementary table 20), while 5-year net survival was approximately 95% in both jurisdictions (online supplementary tables 21-24). As previously observed, survival differences within countries were largely driven by variations in survival among the older patients with cancer and those with advanced disease.

# Discussion

The current study has shown survival differences for colon and rectal cancers by age and stage at diagnosis across seven high-income countries with similar health systems. For colon cancer, age-standardised 5-year net survival from colon and rectal cancers ranged between 59.1% and 70.9% and 61.6% and 70.9%, respectively, and tended to be higher in Australia and Canada, intermediate in Denmark and Norway and lower in Ireland, New Zealand and the UK. Stage at diagnosis varied by countries, with large proportions with localised colon and rectal cancers in Norway and Australia (as well as the UK for colon cancer) and small proportions with metastatic cancers in Australia and Canada (also Ireland for rectal cancer). Survival differences persisted within each stage at diagnosis and were most pronounced for regional and distant disease as well as with increasing age at diagnosis. Compared with the first phase of ICBP,[4] survival improvements are evident in particular for metastatic disease.

For example in Denmark, 1-year survival of metastatic colon and rectal cancer improved by 14 percentage point (40.7% to 54.4%) and 11 percentage point (52.4% to 63.4%), respectively. A study of CRC cases in the [18]USA showed that 5-year relative survival (colon cancer: 64.4%, rectal cancer: 66.6%) is closer to our estimates for Denmark and Norway. Direct comparison between our study and their estimate needs to also consider differences in various factors including diagnostic and treatment practices as well as access to healthcare system.[19]

Stage at diagnosis is an important determinant of survival and partly explains international differences in survival. Generally we observed smaller proportions of patients with metastatic disease in Australia and Canada, and larger proportions with localised disease in Australia and Norway. The distribution of stage at diagnosis maybe affected by national early detection and screening programmes as well as by country-specific diagnostic pathways and clinical procedures. Gradual implementation of the CRC screening programme started in the mid-2006s (UK), 2006–2020 (Australia, roll-out with additional age groups added each year), 2007–2012 (Canada), 2012 (Ireland and Norway (the latter started with a pilot programme, national programme in 2019)), 2014 (Denmark)[20] and in 2017 in New Zealand.[21] Therefore, the impact of screening activities on stage distributions during the time period covered by this study (2010–2014) is limited to the UK where screening started more than a decade ago. Comparison between country needs to take into account screening uptake, for example, in the case of the UK 52%,[20] and also case mix that follows in populations with screening programme. Screening for CRC typically leads to an initial increase in incidence attributable to a greater detection of, and shift toward, early-stage cancers, followed by decreases in incidence due to removal of premalignant adenomas.[22] Screening programmes for CRC have furthermore been associated with a reduction in colon cancer cases diagnosed as an emergency.[23] Continuous monitoring and quality assurance of early detection and screening programmes and detailed assessment of their impact on survival are therefore warranted.[24]

Another phenomenon that has been proposed to explain differences in international stage distributions and stage-specific survival is stage migration.[25] Thoroughness of examination to determine stage in patients may differ between countries. For example, a study comparing the number of lymph node examinations among patients with cancer across European countries showed that lower number of lymph node examinations led to misclassification of advanced stage cancers (toward early stage), resulting in lower survival in both early and advanced stage categories.[26] International differences in diagnostic guidelines, access to early detection and adherence to protocols could potentially bias stage-specific survival comparisons across countries. In addition, variations in clinical and pathological practice with regards to clinical examinations, nodal assessment and the use of imaging technology to detect small lymph nodes or distant metastases may have contributed to differences in the composition of patients within a specific stage grouping.[27] It is therefore important to interpret findings from our study in light of local clinical practice and to ensure that registries have data collection protocols that are as uniform as possible.[28]

Another potential factor that may influence early detection is patients' behaviours toward symptoms, as these have been linked to diagnostic delays and can impact the time from the first symptoms to diagnosis, as well as time from diagnosis to staging.[29] For example, in the UK, the general population often report 'embarrassment' as the main barrier to going to the doctor when a symptom might be serious.[30] Improved interventions to address barriers to early presentation and increase confidence to approach primary care physicians (particularly for older patients) may potentially reduce delays in diagnosis and ultimately improve survival. Furthermore, changes in regional and national healthcare policies can influence patients' pathways. For example, urgent referrals for cancer investigation have been implemented in Denmark and this has been shown to reduce diagnostic and treatment delays.[31] The use of urgent referrals by general practitioners (GPs) has also proven efficient in improving cancer prognosis.[32] A better understanding of patients' symptoms when presenting to GPs may result in more rapid and accurate diagnosis that will lead to a more efficient diagnostic pathway.[33] Finally, success in implementation of healthcare policies largely depend on contexts of the local setting and its health system and therefore tailoring of strategies is key to ensure effective policy.

The existing international variation in survival from CRC could also in part be attributable to national differences in treatment practices, in particular the receipt of surgery and chemotherapy. Surgical resection is widely accepted as standard treatment for localised and regional stages of CRC. Yet, the receipt of surgical treatment varies by country, age and stage. For example, the proportion of patients with colon cancer receiving surgical treatment ranged from 68.4% in England to 81.3% in Sweden, and from 59.9% to 70.8% for rectal cancer.[34] The variation is even larger for patients with CRC older than 75 years; for example, for patients with colon cancer in England this was 59.7% as compared with 80.9% in Sweden.[34] In addition to surgery, systemic therapy is an important treatment modality for regional CRC.[35] Studies have shown large variations in the use of adjuvant chemotherapy[36] and preoperative radiotherapy[37] across countries. For example, 56% of cases with Dukes' stage C colon cancers in the USA received chemotherapy, while only 42% of cases with the same stage received chemotherapy in Northern Europe.[38] These disparities are in general greater for the oldest patient group.[39] Patients with resectable metastases may benefit from multidisciplinary treatment with surgery and chemotherapy, while beneficial effects of chemotherapy—with/without palliative surgery of the primary tumour—have been reported for patients with widespread metastases.[9] Treatment harmonisation between countries in line with recent clinical guidelines should decrease the international survival gap.

When interpreting the study results, differences in registration practice and staging systems need to be considered. As part of the ICBP SURVMARK-2 study protocol, data quality checks using standard indicators were carried out and variables were harmonised in close collaboration with participating cancer registries.[40,41] The overall data quality was high, with fewer than 1.1% of cases registered as DCO, yet differences in data handling and registration practice may still have partially biased the survival comparisons. For example, problematic death linkages may contribute to missing deaths and overestimated survival. To put this in context however, a recent study showed that even under the extreme scenarios for incorrect registration, for example, recording the date of cancer recurrence instead of the date of primary cancer diagnosis, very little of the international differences in survival could be explained by differences in cancer registration.[42] Another study suggested incompleteness of case ascertainment may induce an error in survival time (survival time would be too short due to processing information from death certificates, especially for fatal cancers) by a magnitude of <1.9% for the patients diagnosed with CRC in England.[43]

Data on stage were provided using different classification systems, which required the conversion and mapping of different stage variables to one common classification. The TNM system remains the preferred staging classification; however, for the sake of comparison in this study all cases were mapped to the SEER SS2000 system using previously defined algorithms.[12] Due to inconsistencies in the staging of certain tumour types across staging systems, this process might have resulted in stage misclassification.[44] A previous study showed that transformation of the Duke's system to TNM led to 10% of stage IV colon cancers being misclassified as stage III.[44] In this study, the Duke's system (with or without integrated staging) was used only in the UK (except in England). The staging distribution for Scotland, which uses the Duke's staging system, was shown to be similar to that for England where only integrated staging was used (stage I, II, III and IV were 16%, 29%, 26%, 29% in Scotland and 14%, 29%, 27%, 30% in England, respectively). Differences in the timing of stage data collection processes across registries may, for example, affect staging of patients with rectal cancer who have undergone preoperative radiotherapy or chemotherapy, which can lead to reductions in the tumour size or the number of involved lymph nodes.[37] Although the data collection protocol specified collection of pretreatment stage data, stage comparisons (and survival by stage) need to be interpreted with caution and future work should focus on improvements in this area.[45] Routine collection of information on diagnostic procedures performed to define stage, such as pathological examination of lymph nodes or clinical assessment using imaging for distant metastasis should be considered. In collaboration with the Union for International Cancer Control, the International Agency for Research on Cancer has also proposed the utilisation of essential TNM that will facilitate the collection of stage data in population-based cancer registries, improve international stage comparisons and help to elucidate the causes of international variation in survival.[46]

Finally, to include the totality of diagnosed cases in all participating jurisdictions and hence increase validity in comparative stage-specific survival, we used multiple imputation to deal with the unknown and missing data for stage at diagnosis. While the degree of stage data completeness varied between jurisdictions (online supplementary table 1A,B), we observed that the survival for patients with recorded missing stage was between that for patients with stage III and IV tumours (online supplementary figures 4 and 5), implying a case mix that is not composed of cases with the most advanced stage only. It is important to note that 'unknown' stage does not necessarily imply that clinical stage could not be determined or used for treatment decisions by clinicians at time of diagnosis. Therefore, information on stage may be available from resources other than the registry for cases with 'unknown' stage (data missing at random). In such a situation, multiple imputation has been shown to be a valid method for dealing with unknown stage recorded in population-based cancer registry data.[47] After the inclusion of patients whose stage data were imputed, survival estimates were slightly lower in all stages categories, which could be due to the fact that patients with missing data on stage tended to be older and have lower survival.

In conclusion, differences in survival from CRC remain marked across high-income countries in recent years and are more pronounced for older ages and patients with advanced disease. Similarly, the proportions of cases diagnosed with early and advanced CRC differ across countries and survival estimates tended to be lower for countries that had higher proportions of elderly and patients with advanced stage. Our study suggests that both early detection and optimal treatment are important factors that may explain survival gaps between countries. Evidently the improved collection and standardisation of staging data, and the accrual of additional variables, such as treatment and comorbidities,[48] are critical steps in developing a complete understanding of the underlying mechanisms that explain international differences in cancer survival.

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