# Use of chemotherapy in patients with oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian cancer: an International Cancer Benchmarking Partnership (ICBP) population-based study

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## Summary

**Background** There are few data on international variation in chemotherapy use, despite it being a key treatment type for some patients with cancer. Here, we aimed to examine the presence and size of such variation.

**Methods** This population-based study used data from Norway, the four UK nations (England, Northern Ireland, Scotland, and Wales), eight Canadian provinces (Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan), and two Australian states (New South Wales and Victoria). Patients aged 15–99 years diagnosed with cancer in eight different sites (oesophageal, stomach, colon, rectal, liver, pancreatic, lung, or ovarian cancer), with no other primary cancer diagnosis occurring from within the 5 years before to 1 year after the index cancer diagnosis or during the study period were included in the study. We examined variation in chemotherapy use from 31 days before to 365 days after diagnosis and time to its initiation, alongside related variation in patient group differences. Information was obtained from cancer registry records linked to clinical or patient management system data or hospital administration data. Random-effects meta-analyses quantified interjurisdictional variation using 95% prediction intervals (95% PIs).

**Findings** Between Jan 1, 2012, and Dec 31, 2017, of 893 461 patients with a new diagnosis of one of the studied cancers, 111 569 (12·5%) did not meet the inclusion criteria, and 781 892 were included in the analysis. There was large interjurisdictional variation in chemotherapy use for all studied cancers, with wide 95% PIs: 47·5 to 81·2 (pooled estimate 66·4%) for ovarian cancer, 34·9 to 59·8 (47·2%) for oesophageal cancer, 22·3 to 62·3 (40·8%) for rectal cancer, 25·7 to 55·5 (39·6%) for stomach cancer, 17·2 to 56·3 (34·1%) for pancreatic cancer, 17·9 to 49·0 (31·4%) for lung cancer, 18·6 to 43·8 (29·7%) for colon cancer, and 3·5 to 50·7 (16·1%) for liver cancer. For patients with stage 3 colon cancer, the interjurisdictional variation was greater than that for all patients with colon cancer (95% PI 38·5 to 78·4; 60·1%). Patients aged 85–99 years had 20-times lower odds of chemotherapy use than those aged 65–74 years, with very large interjurisdictional variation in this age difference (odds ratio 0·05; 95% PI 0·01 to 0·19). There was large variation in median time to first chemotherapy (from diagnosis date) by cancer site, with substantial interjurisdictional variation, particularly for rectal cancer (95% PI –15·5 to 193·9 days; pooled estimate 89·2 days). Patients aged 85–99 years had slightly shorter median time to first chemotherapy compared with those aged 65–74 years, consistently between jurisdictions (–3·7 days, 95% PI –7·6 to 0·1).

**Interpretation** Large variation in use and time to chemotherapy initiation were observed between the participating jurisdictions, alongside large and variable age group differences in chemotherapy use. To guide efforts to improve patient outcomes, the underlying reasons for these patterns need to be established.

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## Introduction

For many patients with cancer, systemic anti-cancer therapy (hereafter referred to as chemotherapy) is a key type of treatment. Differences in the use of chemotherapy between patient groups have been described, typically within individual countries. The

## Research in context

### Evidence before this study

We searched PubMed on Jan 31, 2023, without language or year of publication restrictions for population-based studies examining the use of chemotherapy in patients with the eight studied cancers in jurisdictions of more than one country. We used the search terms "chemotherapy use", "population-based", and "international comparison" and previous searches to derive a core group of so-called seeded papers. These were used to propagate the inquiry through searches of lead authors or key words included in already identified papers, articles appearing in similar and cited by PubMed lists, and inspection of the 30 most relevant papers using inciteful.xyz graphs, a citation network exploration tool. We identified 18 primary studies examining use of chemotherapy in up to 12 jurisdictions, typically within a single continent (Europe), for patients with five of the studied cancer sites (oesophageal, stomach, colon, rectal, and pancreatic). The relevant evidence currently available did not formally quantify the size of interjurisdictional variation in chemotherapy use, or of related age inequalities, and did not encompass time-to-chemotherapy initiation.

### Added value of this study

To our knowledge, this is the first population-based study that establishes the frequency of chemotherapy use and time-to-chemotherapy initiation in patients diagnosed in the last decade with eight common cancers (oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian) across international jurisdictions in multiple continents. We identified wide variation in chemotherapy use and age-related disparities, following broad jurisdictional patterns. The findings highlight the value of incorporating measures of chemotherapy use in international studies comparing cancer treatment and outcomes, and of population-based surveillance of treatment patterns and related disparities both within and between countries.

### Implications of all the available evidence

The findings highlight the need to understand the causes of international variation in chemotherapy use, and the implications of such variation for patient outcomes and international differences in cancer survival. Future work should examine tumour, patient, and health-care factors underlying chemotherapy use in different countries and health systems. Health-care factors to be examined should encompass potential differences in clinical guidelines and their implementation, service organisation, system capacity, health-care professional cultures, patient treatment preferences, and access to trial protocols. Incorporating measures of chemotherapy use in both international comparative survival studies and in routine cancer surveillance is warranted.

reasons for such differences are unclear but persist after accounting for clinical and patient factors.[1,2] International variations in chemotherapy use and related patient group differences are probable, but there is little relevant evidence. Time to first chemotherapy treatment is an important corollary of treatment use, particularly in neo-adjuvant or adjuvant contexts. Although measures of timeliness of cancer treatment are reported in different countries, there is little evidence comparing time to chemotherapy initiation internationally.[3,4]

Here, we examined the variation in overall use and time to chemotherapy between several high-income jurisdictions, alongside related interjurisdictional variation by age group, sex, and cancer site. We acknowledge that a detailed understanding of specific factors that drive interjurisdictional variation in chemotherapy use, where present, will be subsequently required.

The study forms part of the International Cancer Benchmarking Partnership, a collaboration of clinicians, policy makers, researchers, and data experts in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK), seeking to explain cancer survival differences between high-income countries with comprehensive cancer registries, similar health system expenditure, and universal health care, to help improve cancer care and outcomes globally.[5–7]

## Methods

### Data

This population-based study used data from Norway, the four UK nations (England, Northern Ireland, Scotland, and Wales), eight Canadian provinces (Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan), and two Australian states (New South Wales and Victoria). All participating jurisdictions were covered by high-quality population-based cancer registries (appendix p 3).[5,8] Chemotherapy use was ascertained from cancer registry records, linked as applicable to data from clinical or patient management systems, or hospital administration data (appendix p 4).

Inclusion criteria were a new primary diagnosis of oesophageal, stomach, colon, rectal, liver, pancreatic, lung, or ovarian cancer (based on International Classification of Diseases tenth revision definitions; appendix p 5) during the study period within the populations covered by the participating cancer registries, in patients aged 15–99 years at diagnosis, without cancer site-sex discordance (applicable to ovarian cancer only), not registered solely from a death certificate, and without other primary cancer diagnosis occurring within 5 years before to 1 year after the index cancer diagnosis or during the study period. Patients were diagnosed between Jan 1, 2012, and Dec 31, 2017, with some variability in study year periods between jurisdictions, reflecting data

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See Online for appendix

For the **inciteful.xyz graphs** see https://inciteful.xyz/about

availability. A federated or distributed analysis model was used, whereby standardised patient-level datasets were prespecified, and then created and quality-assured in participating analytical hubs in each jurisdiction.[9,10] This step included the assessment of probable sources of bias, and checks on the distribution of key variables, helping to identify and correct occasional coding errors or misspecifications in jurisdictional datasets. Data were subsequently analysed within each participating hub, using centrally developed R Markdown code. Aggregate group-level data, suitable for publication, were subsequently shared with the central team, without the transfer of patient-level data. Data were checked further for internal consistency during collation, tabulation, and meta-analysis; any queries raised were discussed with the jurisdictional teams and resolved.

We examined the use of chemotherapy, defined as at least one administration of chemotherapy from 31 days before to 365 days after the date of diagnosis in the cancer registry record; and time to first chemotherapy treatment from diagnosis date during the same period. Including a month of observation before the registered diagnosis date allows for the inclusion of neo-adjuvant chemotherapy initiated before the final histological diagnosis. All patients were followed up for up to 1 year post-diagnosis or death if it occurred earlier, according to the standard practice of participating cancer registries.

In our definition of chemotherapy, we aimed to include all types of systemic anticancer therapy, including immunotherapy, regardless of administration setting (eg, hospital or community facility) or route (eg, intravenous or oral). In most jurisdictions all types, settings, and administration routes of chemotherapy were captured, but in some jurisdictions one or more of these components were not included in the data sources used. Most patients receive chemotherapy of more than one type, in different administration settings, and through different administration routes. Therefore, the overall estimates of chemotherapy use are probably unaffected by missing one or more components of the definition, except for cancer sites where oral chemotherapy as monotherapy was a treatment option during the study period and oral chemotherapy activity was not captured, as described later.

The diagnosis date for each patient was assigned by participating registries following standard practices.[11–13] Generally, the recorded diagnosis dates precede or coincide with the start of treatment, but occasionally, asynchronous data flows mean that treatment information is unavailable when the tumour is initially registered, based on the date of histological verification, but made available subsequently. In such instances, when the tumour record is completed, the first treatment date might precede the registered diagnosis date by a few days. Therefore, to avoid underestimating chemotherapy use, we included patients with diagnosis-to-chemotherapy intervals of up to 31 days before diagnosis.[14] Across all jurisdictions, patients with a treatment date before the recorded diagnosis date comprised fewer than 5% of all cases.

Jurisdiction-level data, in the form of percentages or odds ratios (OR) for chemotherapy use and in the form of number of days or coefficients for the time to first chemotherapy treatment, were available for all patients, and stratified by age group, sex or gender (depending on registry; ie, male or female, using information in the cancer registry records), and diagnosis year across all cancer sites and for each cancer site individually. Information was also available on stage at diagnosis (typically TNM stage), although there were missing data for this variable, with some variation in availability and completeness by jurisdiction and cancer type (appendix p 6). The approach to selecting exposure variables was guided by feasibility and data availability across the jurisdictions. For example, no comparable information was available on comorbidity, performance status, or treatment intent.

### Analysis

Random effects meta-analysis characterised inter-jurisdictional variation through a direct central estimate of the outcome of interest and the calculation of 95% prediction intervals (95% PIs) which denote the range of outcomes we would expect to observe in similar jurisdictions not included in the analysis. Additionally, tau values (representing the SD) are reported as direct measures of the magnitude of interjurisdictional variability. Results are likely to be applicable to jurisdictions with high human development index values and universal health-care coverage, such as those included in this study, but not other settings.

We did not attempt to formally identify high or low chemotherapy use jurisdictions, because: (1) there is no global consensus about the optimal amounts of chemotherapy use in a population, and such amounts cannot be inferred confidently without information about the use of other treatment methods, and a range of tumour and patient characteristics; (2) small potential differences in the ascertainment of chemotherapy use might lead to large differences between specific jurisdictions, while having a minimal effect on overall interjurisdictional variation; and (3) because the sample of jurisdictions is small, it cannot be assumed that the observed value ranges between the participating jurisdictions represent the range across all high-income jurisdictions with universal health-care coverage.

For chemotherapy use, meta-analyses encompassed the percentage of patients treated with chemotherapy, both for all eight cancer sites considered together and for each individual site separately, using the observed values without casemix adjustment; and the ORs of chemotherapy use by sex (female compared with male), and by age group (15–64 years, 75–84 years, and 85–99 years, compared with 65–74 years [the most

common age group in our analysis sample]), adjusted for sex, age, cancer site, and diagnosis year. We used categorical groupings of age to aid interpretation and simplify the federated analysis. There were no missing data in the analysis sample for age group, sex, cancer site, and diagnosis year, although information for stage at diagnosis was incomplete for 17·3% (135 206) of patients in the analysis sample. Therefore, the primary analysis did not adjust for stage at diagnosis, although the results for stage-adjusted ORs of chemotherapy use by patient group were also presented only for jurisdictions with high stage completeness (>70%) for every individual cancer site. We additionally examined chemotherapy use in patients with stage 3 colon cancer, because colon cancer had high completeness of information on cancer stage, and indications for chemotherapy use in this patient group have long been established.[15,16] No information was collected on patient race or ethnicity.

For time to first chemotherapy treatment, meta-analyses primarily encompassed the median time to first chemotherapy treatment (from diagnosis date), both for all eight cancer sites considered together and each individual site separately, using the observed values, without casemix adjustment; and differences in median time to first chemotherapy treatment by sex and by age group, adjusted for sex, age group (reference groups as above), cancer site, and diagnosis year.

Meta-analysis of the overall percentage of patients treated with chemotherapy assessed the log odds of such treatment, which were then back-transformed to the percentage scale. Meta-analyses of adjusted ORs of chemotherapy use by patient group (from logistic regression) and of patient group differences in median time to first chemotherapy treatment (from quantile regression) used the model coefficients and SEs reported by each jurisdiction, from regression models specified by the central team. For chemotherapy use, meta-analyses were fitted via restricted maximum likelihood using the R package metafor (version 3.4-0).[17] For median time to chemotherapy, meta-analysis was performed using the quantile estimation method,[18] implemented in the R package metamedian (version 1.0.0). Additional analytical software information is included in the appendix (p 7).

We compared observed chemotherapy use against estimated population health need for chemotherapy by cancer site using estimates from evidence-based indications or comparative epidemiological data. Chemotherapy use data were deemed incomplete in Newfoundland and Labrador (all sites) and Saskatchewan (ovarian cancer only) on the basis of local knowledge of data collection systems. The estimates for Prince Edward Island for ovarian and liver cancer were not available because of the small numbers of patients. These jurisdiction–cancer site strata (and associated all-eight-site-combined strata) were excluded from the meta-analyses of overall use and overall

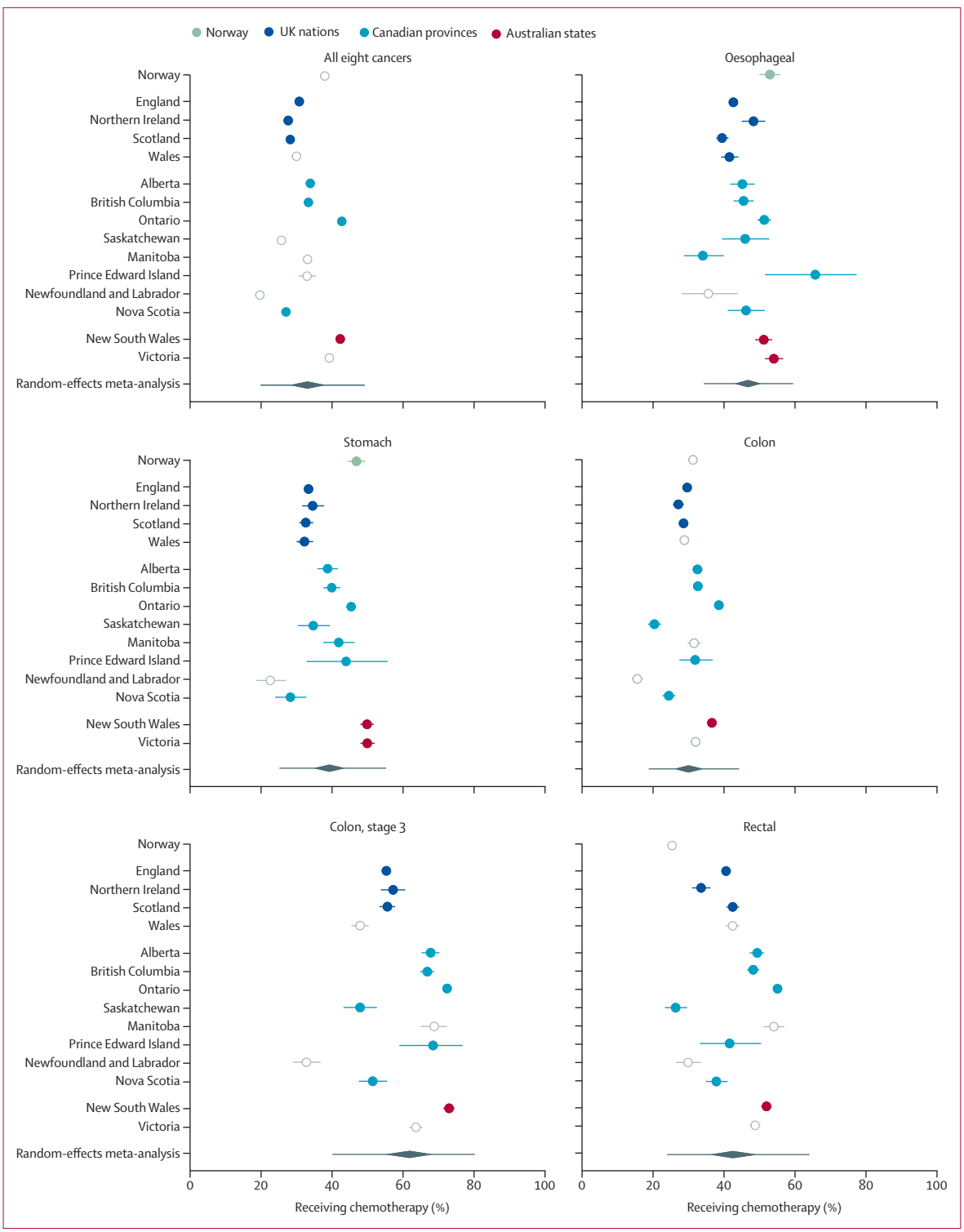
| | All jurisdictions (N=781 892) | Norway (N=37 185) | UK | | | Canada | | | | | | | | Australia | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | England (N= 373 194) | Northern Ireland (N= 15 501) | Scotland (N= 45 027) | Wales (N= 26 139) | AB (N= 25 093) | BC (N= 40 064) | MB (N= 9957) | NL (N= 6160) | NS (N= 10 130) | ON (N= 92 447) | PE (N= 1365) | SK (N= 8220) | NSW (N= 53 198) | VIC (N= 38 212) |
| Oesophageal | 44 425 (5·7%) | 1089 (2·9%) | 27 274 (7·3%) | 972 (6·3%) | 3377 (7·5%) | 1703 (6·5%) | 889 (3·5%) | 1398 (3·5%) | 286 (2·9%) | 141 (2·3%) | 377 (3·7%) | 3099 (3·4%) | 50 (3·7%) | 224 (2·7%) | 1970 (3·7%) | 1576 (4·1%) |
| Stomach | 44 022 (5·6%) | 1884 (5·1%) | 19 813 (5·3%) | 990 (6·4%) | 2337 (5·2%) | 1656 (6·3%) | 1293 (5·2%) | 1934 (4·8%) | 528 (5·3%) | 398 (6·5%) | 428 (4·2%) | 6465 (7·0%) | 70 (5·1%) | 450 (5·5%) | 3179 (6·0%) | 2597 (6·8%) |
| Colon | 198 987 (25·4%) | 12 091 (32·5%) | 88 219 (23·6%) | 3846 (24·8%) | 9599 (21·3%) | 6142 (23·5%) | 6403 (25·5%) | 10 501 (26·2%) | 2445 (24·6%) | 2077 (33·7%) | 2541 (25·1%) | 24 481 (26·5%) | 399 (29·2%) | 2180 (26·5%) | 16 316 (30·7%) | 11 747 (30·7%) |
| Rectal | 73 772 (9·4%) | 4556 (12·3%) | 33 905 (9·1%) | 1376 (8·9%) | 3535 (7·9%) | 2577 (9·9%) | 2486 (9·9%) | 3913 (9·8%) | 1108 (11·1%) | 632 (10·3%) | 1000 (9·9%) | 7845 (8·5%) | 123 (9·0%) | 819 (10·0%) | 5459 (10·3%) | 4438 (11·6%) |
| Liver | 37 302 (4·8%) | 972 (2·6%) | 17 699 (4·7%) | 582 (3·8%) | 2340 (5·2%) | 1155 (4·4%) | 1333 (5·3%) | 2377 (5·9%) | 395 (4·0%) | 206 (3·3%) | 365 (3·6%) | 4129 (4·5%) | NA | 271 (3·3%) | 3155 (5·9%) | 2323 (6·1%) |
| Pancreatic | 61 673 (7·9%) | 2945 (7·9%) | 30 442 (8·2%) | 1162 (7·5%) | 3054 (6·8%) | 1965 (7·5%) | 2114 (8·4%) | 3286 (8·2%) | 833 (8·4%) | 289 (4·7%) | 698 (6·9%) | 6456 (7·0%) | 101 (7·4%) | 658 (8·0%) | 4498 (8·5%) | 3172 (8·3%) |
| Lung | 281 233 (36·0%) | 11 547 (31·1%) | 135 396 (36·3%) | 5752 (37·1%) | 18 662 (41·4%) | 9365 (35·8%) | 9408 (37·5%) | 14 739 (36·8%) | 3920 (39·4%) | 2197 (35·7%) | 4340 (42·8%) | 35 092 (38·0%) | 622 (45·6%) | 3239 (39·4%) | 16 334 (30·7%) | 10 620 (27·8%) |
| Ovarian | 40 478 (5·2%) | 2101 (5·7%) | 20 446 (5·5%) | 821 (5·3%) | 2123 (4·7%) | 1576 (6·0%) | 1167 (4·7%) | 1916 (4·8%) | 442 (4·4%) | 220 (3·6%) | 381 (3·8%) | 4880 (5·3%) | NA | 379 (4·6%) | 2287 (4·3%) | 1739 (4·6%) |

Data are n (%). AB=Alberta. BC=British Columbia. MB=Manitoba. NA=not available. NL=Newfoundland & Labrador. NS=Nova Scotia. ON=Ontario. PE=Prince Edward Island. SK=Saskatchewan. NSW=New South Wales. VIC=Victoria.

***Table 1:*** **Analysis sample composition by jurisdiction and cancer site**

time to first chemotherapy, but included in those examining variation by age and sex.

Supplementary post-hoc analysis suggested that if oral chemotherapy was used as monotherapy, the potential under-counting of such use would substantially underestimate the overall chemotherapy use for colon, rectal, and liver cancer, but not the other cancer sites (appendix p 8). Therefore, estimates for colon, rectal, and

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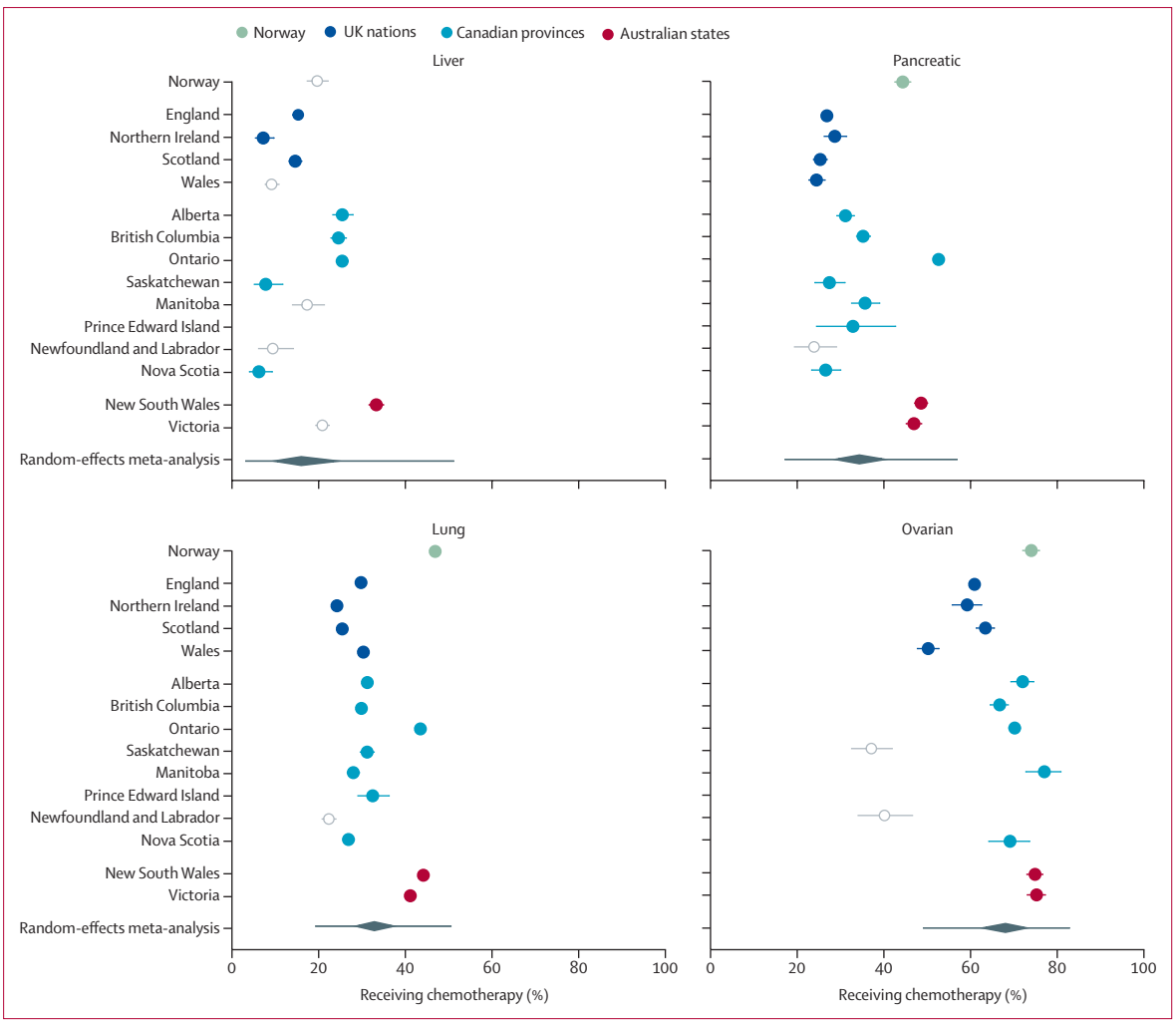


***Figure 1:*** **Overall crude proportion of patients treated with chemotherapy in each jurisdiction, by cancer site**
Circles show proportions, and lines show the associated 95% CIs. Grey diamonds show the meta-analysis estimates; the width of the diamonds shows the related 95% CIs; the wider grey lines show the associated 95% prediction intervals. Site-specific jurisdictional estimates not included in producing meta-analysis estimates (see methods section) are shown as hollow light grey circles. For the stage 3 colon cancer analysis, the regional spread (to lymph nodes) category was used in New South Wales (appendix pp 12–13); estimates for Norway are not included in this meta-analysis because the regional category could correspond to either TNM 2 or 3.

liver cancer, as well as all sites combined, were reported but not included in the meta-analyses of overall use and overall time to chemotherapy for Manitoba, Norway, Victoria, and Wales, where oral chemotherapy use was either not captured during the study period or not included in the study analysis samples. Supplementary analysis examined the potential effect of differences in the age and cancer site composition of jurisdictional samples, fitting one-stage individual participant data meta-analysis models to the aggregate treatment use data (appendix p 9).

Primary data used in the study were collected under jurisdiction-specific regulations enabling cancer registration and the collection of administrative data on hospital admissions or treatments. No participant consent was applicable. No identifiable data were shared for this project. In England, Northern Ireland, Scotland, Wales, British Columbia, Newfoundland and Labrador, and Prince Edward Island, no additional approvals were necessary given the nature of the study and its alignment with the routine surveillance function of cancer registries. In Ontario, research ethics board approval was obtained by the University of Toronto Research Ethics Board. In Alberta, health research ethics board (cancer committee) approval was obtained by the Alberta Health Services (reference CC-16–0868). In Manitoba, this study was approved by the University of Manitoba's health research ethics board and CancerCare Manitoba's research and resource impact committee (reference HS24284 [H2020:416]). In Nova Scotia, the study was endorsed by the Nova Scotia health research ethics board (Research Ethics Board file number 1022055). In Norway, the Norwegian regional ethics committee concluded that no approval was needed for this study (reference 2017/428REK sør-øst A), thus giving the authors exemption from the

statutory duty of confidentiality; approval for handling indirect identifiable data was obtained from the data protection officer (*Personvernombud*) of Oslo University Hospital (reference 2017/6597). In New South Wales, approval for the linkage of the underlying data was granted by the New South Wales population and health services research ethics committee (reference HREC/15/CIPHS/15) and the Australian Institute of Health and Welfare ethics committee (reference EO2016/1/224). In Saskatchewan, approval was obtained from the University of Saskatchewan research ethics board. In Victoria, approval for the data linkage and use of the data from Victoria to study patterns of care was granted by the Cancer Council Victoria's human research ethics committee (reference HREC #1312 and HREC #1412).

### Role of the funding source

The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report, although they have facilitated resources for data collection and analysis.

## Results

Between Jan 1, 2012, and Dec 31, 2017, there were 893 461 patients with a new diagnosis of one of the studied cancers, of whom 111 569 (12·5%) did not meet the inclusion criteria, and 781 892 were included in the analysis. Sample compositions by cancer site, age group, and sex were broadly similar between the jurisdictions (table 1; appendix pp 10–11).

Chemotherapy use varied largely by cancer site; although patterns of variation by cancer site were consistent between the jurisdictions, there was large cancer-specific interjurisdictional variation in chemotherapy use, as indicated by wide 95% PIs (figure 1; table 2; appendix pp 12–13). Specifically, the 95% PIs were 47·5–81·2 (pooled estimate 66·4%) for ovarian cancer, 34·9–59·8 (47·2%) for oesophageal cancer, 22·3–62·3 (40·8%) for rectal cancer, 25·7–55·5 (39·6%) for stomach cancer, 17·2–56·3 (34·1%) for pancreatic cancer, 17·9–49·0 (31·4%) for lung cancer, 18·6–43·8 (29·7%) for colon cancer, and 3·5–50·7 (16·1%) for liver cancer. As denoted by the corresponding tau values, the interjurisdictional variation was largest for liver (tau value 0·702), pancreatic (0·411), and rectal cancer (0·374), and smallest for oesophageal (0·229), colon (0·262), and stomach cancer (0·288). For patients with stage 3 colon cancer, interjurisdictional variation was larger than that observed for all patients with colon cancer (95% PI 38·5–78·4; pooled estimate 60·1%;

| | Percentage of patients treated* | | | | | | Odds ratio for patient group differences in chemotherapy use† | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pooled estimate | 95% CI | 95% PI‡ | Tau log-odds scale§ | $I^2$¶ | Observed jurisdictional range | Pooled estimate | 95% CI | 95% PI‡ | Tau log-odds scale§ | $I^2$¶ | Observed jurisdictional range |
| **Site** | | | | | | | | | | | | |
| All eight sites | 34·1% | 30·0–38·5 | 21·0–50·3 | 0·274 | 99·9 | 28·1–43·9 | .. | .. | .. | .. | .. | .. |
| Oesophageal | 47·2% | 44·0–50·4 | 34·9–59·8 | 0·229 | 96·4 | 34·6–66·0 | 1·94 | 1·69–2·23 | 1·11–3·39 | 0·249 | 95·8 | 1·33–3·52 |
| Stomach | 39·6% | 35·9–43·4 | 25·7–55·5 | 0·288 | 98·0 | 28·7–50·2 | 1·55 | 1·40–1·71 | 1·05–2·28 | 0·173 | 92·9 | 1·23–2·24 |
| Colon | 29·7% | 26·4–33·3 | 18·6–43·8 | 0·262 | 99·5 | 20·2–38·2 | 0·95 | 0·82–1·11 | 0·51–1·79 | 0·282 | 99·0 | 0·54–1·32 |
| Colon stage 3 | 60·1% | 54·3–65·6 | 38·5–78·4 | 0·376 | 99·0 | 46·2–71·2 | .. | .. | .. | .. | .. | .. |
| Rectal | 40·8% | 35·2–46·5 | 22·3–62·3 | 0·374 | 99·3 | 24·7–53·3 | 1·30 | 0·98–1·72 | 0·40–4·22 | 0·530 | 99·5 | 0·31–2·74 |
| Liver | 16·1% | 10·8–23·5 | 3·5–50·7 | 0·702 | 99·5 | 6·6–33·1 | 0·35 | 0·27–0·45 | 0·13–0·96 | 0·447 | 98·4 | 0·15–0·67 |
| Pancreatic | 34·1% | 29·4–39·2 | 17·2–56·3 | 0·411 | 99·2 | 24·4–52·0 | 1·20 | 1·06–1·35 | 0·74–1·93 | 0·213 | 96·1 | 0·80–1·63 |
| Lung | 31·4% | 27·7–35·3 | 17·9–49·0 | 0·334 | 99·7 | 22·9–45·3 | 1‖ | ref | ref | ref | ref | ref |
| Ovarian | 66·4% | 61·8–70·7 | 47·5–81·2 | 0·345 | 98·5 | 48·7–75·3 | 3·91 | 2·93–5·22 | 1·20–12·70 | 0·525 | 99·0 | 1·11–8·44 |
| **Sex**** | | | | | | | | | | | | |
| Male | 34·0% | 29·8–38·4 | 20·7–50·3 | 0·276 | 99·8 | 28·1–43·7 | 1 | ref | ref | ref | ref | ref |
| Female | 34·3% | 30·2–38·7 | 21·2–50·4 | 0·271 | 99·8 | 28·1–44·2 | 0·97 | 0·95–1·00 | 0·89–1·07 | 0·040 | 76·0 | 0·91–1·07 |
| **Age** | | | | | | | | | | | | |
| 15–64 years | 51·4% | 48·5–54·3 | 41·4–61·4 | 0·166 | 99·2 | 44·5–58·3 | 1·54 | 1·46–1·64 | 1·23–1·94 | 0·102 | 94·2 | 1·31–1·89 |
| 65–74 years | 39·4% | 35·0–44·0 | 25·0–55·9 | 0·273 | 99·7 | 32·2–49·9 | 1 | ref | ref | ref | ref | ref |
| 75–84 years | 19·7% | 15·3–25·1 | 7·7–42·2 | 0·444 | 99·8 | 13·1–31·7 | 0·37 | 0·34–0·41 | 0·25–0·55 | 0·174 | 97·3 | 0·28–0·50 |
| 85–99 years | 3·2% | 1·5–6·9 | 0·2–33·9 | 1·112 | 99·7 | 0·0–14·0 | 0·05 | 0·04–0·07 | 0·01–0·19 | 0·595 | 98·6 | 0·02–0·17 |

PI=prediction interval. *Meta-analysis summaries of the percentage of patients treated with chemotherapy, overall and by cancer site, sex, and age group. Results are not adjusted for sex, age (in years), cancer site, or any other variable. †Meta-analysis summaries for patient group differences in chemotherapy use. Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. ‡PIs show the range that 95% of new jurisdictions are expected to fall into and incorporates both the uncertainty around the overall average and the spread of the included jurisdictions. §The estimated SD of the included jurisdictional estimates, directly measuring the spread of jurisdictions. ¶The proportion of total variation not due to sampling variation. || Comparisons against lung cancer are used as a means of indirectly considering the consistency of patterns of variation in chemotherapy use between different cancer sites across the jurisdictions. **Relates to biological sex in some registries, but gender at diagnosis of cancer in others.

*Table 2:* **Meta-analysis summaries of patients treated with chemotherapy**

tau 0·376; table 2). Typically, 95% PIs were similar to the observed interjurisdictional ranges, though slightly wider (table 2). The use of chemotherapy was stable during the study period across all studied cancer sites (appendix p 14).

Among the 271 121 patients who received chemotherapy, after adjustment for age group, cancer site, and diagnosis year, female patients had similar odds of chemotherapy use compared with male patients (table 2; figure 2). Patients aged 85–99 years had 20 times lower odds of receiving chemotherapy than those aged 65–74 years (OR 0·05; 95% PI 0·01–0·19; table 2). These age differences varied substantially between the jurisdictions (table 2; figure 2). Adjustment for stage made little difference to these findings (figure 2).

The pooled estimate of the median time to first chemotherapy treatment by cancer site ranged from 38·0 days for ovarian cancer (95% PI 32·7 to 43·3) to 89·2 days for rectal cancer (–15·5 to 193·9 days), without an apparent association between chemotherapy use and median time to first chemotherapy by cancer site (table 3; figure 3, appendix pp 15–16). Although patterns of variation by cancer site were overall consistent between the jurisdictions, 95% PIs and accompanying tau values indicated that variation in these data was largest for rectal cancer compared with all other cancers (table 3; figure 3).

There was no evidence for differences in time to first chemotherapy treatment by sex (table 3; appendix p 17). Patients aged 85–99 years had slightly shorter median time to first chemotherapy compared with those aged

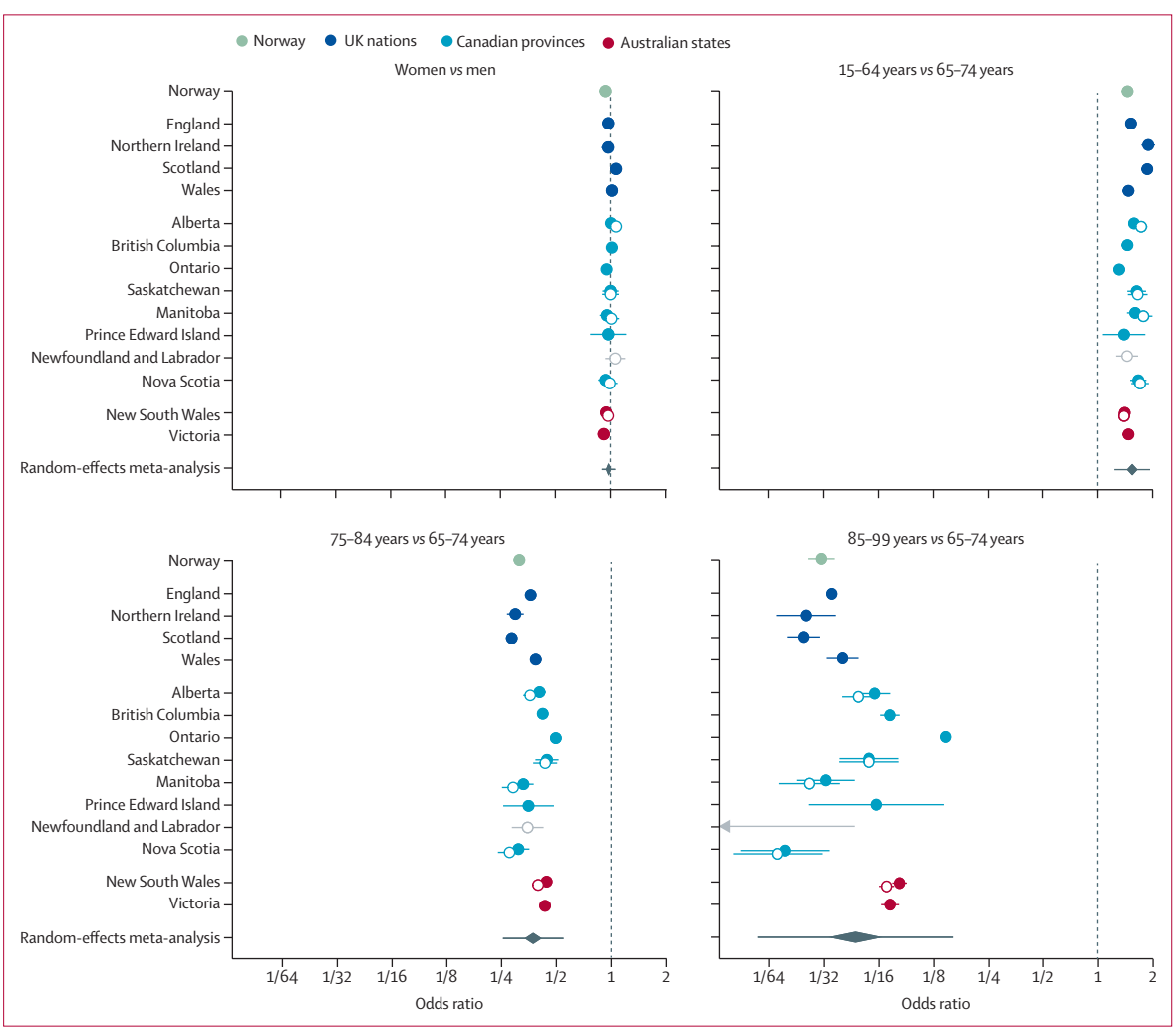


***Figure 2:*** **Variation in use of chemotherapy by sex and age group, by jurisdiction**
Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. Circles show jurisdictional odds ratios, and lines show the associated 95% CIs. Grey diamonds show the meta-analysis estimates; the width of the diamonds shows the related 95% CIs; wider grey lines show the associated 95% prediction intervals. Site-specific jurisdictional estimates not included in producing meta-analysis estimates (see methods section) shown in light grey. White circle estimates are adjusted for stage at diagnosis; this is only shown for jurisdictions with more than 70% completeness of information on stage at diagnosis for every cancer site. These are adjusted for stage categories used by the jurisdiction including a missing stage indicator (TNM stage 1, 2, 3, and 4, and missing stage data, except for New South Wales where the categories were localised, regional [in adjacent organs], regional [in lymph nodes], distant, and missing; appendix pp 12–13).

| | Median time-to-treatment* | | | | | | Difference in median time-to-treatment by patient group† | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pooled estimate, days | 95% CI | 95% PI‡ | Tau natural scale, days§ | $I^2$¶ | Observed jurisdictional range | Pooled estimate, days | 95% CI | 95% PI‡ | Tau natural scale, days§ | $I^2$¶ | Observed jurisdictional range |
| **Site** | | | | | | | | | | | | |
| All eight sites | 55·3 | 50·2 to 60·5 | 37·3 to 73·3 | 7·4 | 99·8 | 43·0 to 65·0 | .. | .. | .. | .. | .. | .. |
| Oesophageal | 55·7 | 49·7 to 61·7 | 30·9 to 80·6 | 11·2 | 99·4 | 34·0 to 71·0 | 11·3 | 7·0 to 15·5 | −5·8 to 28·4 | 7·7 | 97·7 | −1·0 to 33·1 |
| Stomach | 51·3 | 45·7 to 56·9 | 28·4 to 74·2 | 10·3 | 99·0 | 31·0 to 67·0 | 7·7 | 3·6 to 11·7 | −8·4 to 23·8 | 7·2 | 97·1 | −6·0 to 19·0 |
| Colon | 78·7 | 69·4 to 88·0 | 44·1 to 113·3 | 14·8 | 99·8 | 58·0 to 113·0 | 31·6 | 26·1 to 37·1 | 8·9 to 54·3 | 10·2 | 99·1 | 18·0 to 55·5 |
| Rectal | 89·2 | 61·2 to 117·2 | −15·5 to 193·9 | 44·8 | 99·9 | 47·0 to 167·5 | 35·1 | 16·6 to 53·5 | −42·1 to 112·3 | 34·7 | 99·9 | 2·0 to 122·1 |
| Liver | 58·9 | 50·2 to 67·6 | 29·6 to 88·3 | 12·2 | 94·8 | 43·0 to 84·0 | 14·1 | 8·8 to 19·5 | −5·0 to 33·3 | 8·4 | 89·7 | −11·2 to 36·3 |
| Pancreatic | 50·6 | 44·2 to 57·0 | 24·2 to 77·0 | 11·9 | 98·9 | 28·0 to 74·0 | 6·3 | 1·0 to 11·7 | −15·5 to 28·2 | 9·8 | 98·1 | −10·0 to 25·5 |
| Lung | 44·5 | 39·2 to 49·9 | 22·1 to 67·0 | 10·1 | 99·7 | 27·0 to 66·0 | 0‖ | ref | ref | ref | ref | ref |
| Ovarian | 38·0 | 32·7 to 43·3 | 16·8 to 59·2 | 9·3 | 99·5 | 28·0 to 62·0 | −4·2 | −11·0 to 2·6 | −31·9 to 23·5 | 12·3 | 99·2 | −24·0 to 14·5 |
| **Sex** | | | | | | | | | | | | |
| Male | .. | .. | .. | .. | .. | .. | 0 | ref | ref | ref | ref | ref |
| Female | .. | .. | .. | .. | .. | .. | −0·4 | −0·9 to 0·0 | −1·2 to 0·4 | 0·3 | 12·9 | −1·5 to 5·5 |
| **Age** | | | | | | | | | | | | |
| 15–64 years | .. | .. | .. | .. | .. | .. | −2·2 | −2·8 to −1·6 | −3·9 to −0·6 | 0·7 | 54·7 | −3·7 to 0·5 |
| 65–74 years | .. | .. | .. | .. | .. | .. | 0 | ref | ref | ref | ref | ref |
| 75–84 years | .. | .. | .. | .. | .. | .. | −0·1 | −0·5 to 0·3 | −0·7 to 0·4 | 0·2 | 2·6 | −3·5 to 6·0 |
| 85–99 years | .. | .. | .. | .. | .. | .. | −3·7 | −5·6 to −1·8 | −7·6 to 0·1 | 1·5 | 20·5 | −9·5 to 36·5 |

PI=prediction interval. *Meta-analysis summaries for time-to-first chemotherapy, overall and by cancer site (method by McGrath and colleagues[21]). Results are not adjusted for sex, age, cancer site, or any other variable. †Meta-analysis summary for differences in median time-to-chemotherapy in patients who received chemotherapy by sex, age group, and cancer site. Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. ‡PIs show the range that 95% of new jurisdictions are expected to fall into and incorporates both the uncertainty around the overall median and the spread of the included jurisdictions. Negative values at the lower bound of the 95% PI can occur because, according to our definition, chemotherapy could have been administered from −31 days to +365 from the recorded date of diagnosis by the cancer registry. The inclusion of the −31 day interval before diagnosis allows for instances where a patient is treated with chemotherapy after a clinical diagnosis but before the date of cancer registration. §The estimated SD of the included jurisdictional estimates, directly measuring the spread of jurisdictions. ¶The proportion of total variation not due to sampling variation. ‖Comparisons against lung cancer are used as a means of indirectly considering the consistency of patterns of variation in chemotherapy use between different cancer sites across the jurisdictions.

*Table 3:* **Meta-analysis summaries for time-to-first-chemotherapy**

65–74 years, consistently between jurisdictions (−3·7 days; 95% PI −7·6 to 0·1; table 3; appendix p 17).

Considering jurisdictional patterns, Ontario, New South Wales, and Victoria typically had higher chemotherapy use than the average jurisdiction across the eight cancer sites; Norway also had higher than average chemotherapy use for oesophageal, stomach, pancreatic, lung, and ovarian cancer. UK jurisdictions had typically lower use than the average jurisdiction (figure 1; appendix pp 12–13). Canadian jurisdictions other than Ontario either had higher than average or lower than average chemotherapy use, with some variability by cancer site. The decrease in chemotherapy use with increasing age group tended to be less steep in Ontario, Alberta, British Columbia, New South Wales, and Victoria, and steeper in Norway and UK jurisdictions (figure 2). Regarding time to first chemotherapy, Norway and the two Australian jurisdictions typically had the shortest recorded median times (figure 3). For all studied cancer sites other than pancreatic cancer, theoretical estimates of optimal use exceeded those observed in the jurisdiction with the highest chemotherapy use (appendix p 18).

In the supplementary analysis exploring compositional differences in jurisdictional analysis samples, adjustment for cancer site or age group made little difference to the estimated interjurisdictional variation, as evidenced by comparisons of the tau statistic (appendix p 9). Additional results are provided in the appendix (pp 19–49). Morphology type distributions were similar among participating jurisdictions (appendix p 50).

## Discussion

We used population-based data from 15 international jurisdictions with similar health systems to characterise interjurisdictional variation in use and time-to-chemotherapy in patients with cancers of eight different organs. Patterns of variation in chemotherapy use by cancer site were consistent across the jurisdictions, but with large cancer-specific interjurisdictional differences. Patterns of variation between included Australian, Canadian, and European jurisdictions were also apparent. Older patients were less likely to be treated with chemotherapy, with the magnitude of these differences varying substantially between the jurisdictions, particularly among patients aged 75 years or older. Time-to-chemotherapy initiation varied substantially between the jurisdictions, although without substantial sex and age group differences.

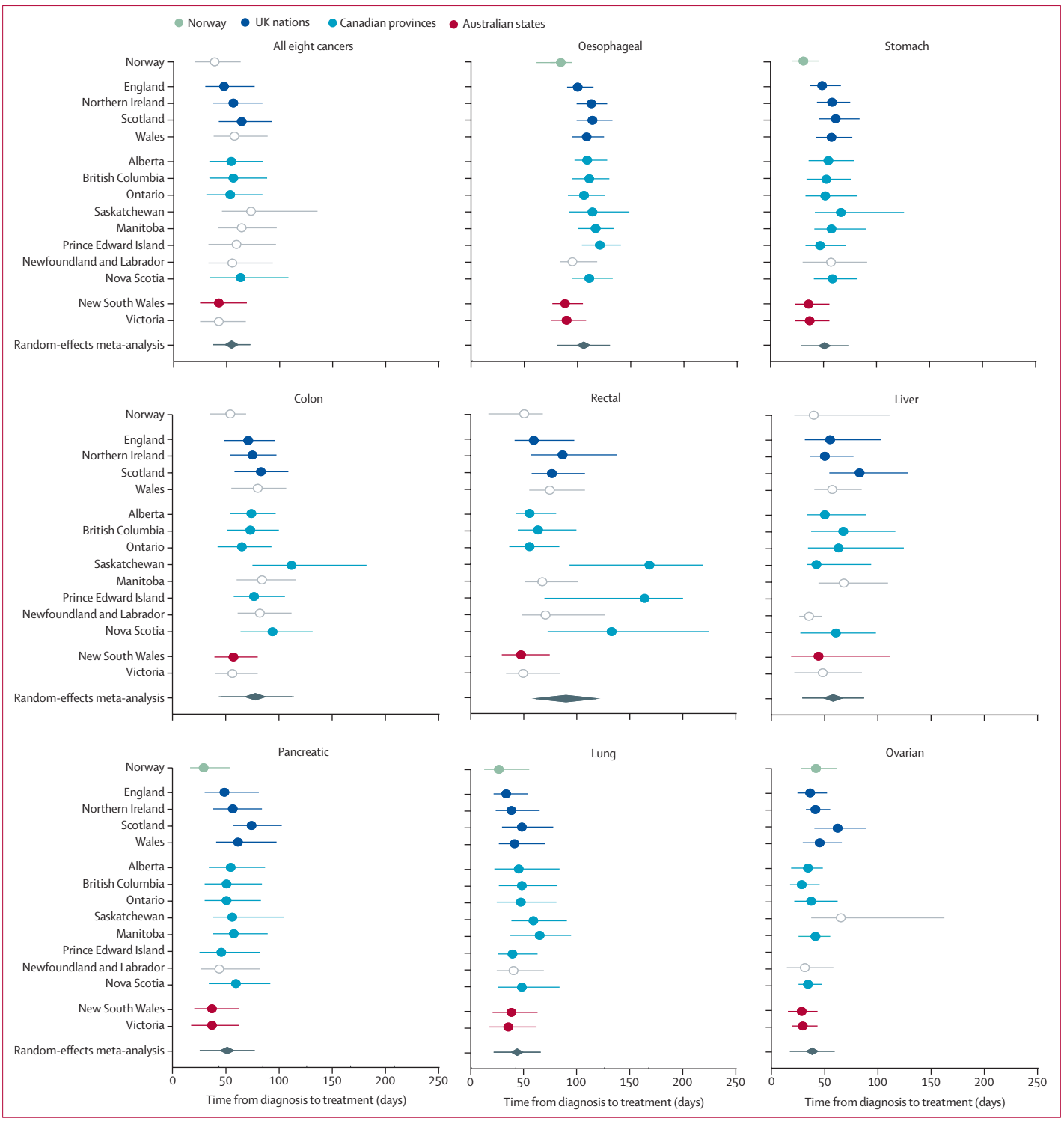


***Figure 3:*** **Median time-to-chemotherapy for each jurisdiction, by cancer site**
Circles show medians and related lines show the IQR. Grey diamonds show the meta-analysis estimates; the width of the diamonds shows the related 95% CIs; wider grey lines show the associated 95% prediction intervals. Highly uncertain estimates have been suppressed from visualisation but included in the meta-analysis. Site-specific jurisdictional estimates not included in producing meta-analysis estimates (see methods section) are shown as light grey circles.

To our knowledge, the study for the first time establishes the frequency of chemotherapy use, alongside time-to-chemotherapy initiation, in patients diagnosed in the last decade with eight common cancers in international jurisdictions from three continents. Previous evidence on international variation in chemotherapy use is typically concentrated on single cancer sites and European countries, without considering treatment timeliness.[19–22] Although differences between patient groups (eg, by age) or hospital providers have been documented in single-country studies, we have described the presence and heterogeneity (across jurisdictions) of patient group differences in use and time-to-chemotherapy across multiple jurisdictions and cancer sites.[1,2,23–27] Theoretical estimates of population health need for chemotherapy use were higher than the observed use, across jurisdictions and cancer sites other than pancreatic cancer.

Our study has limitations. Because the latest study year was 2017, the findings might not represent current chemotherapy use in participating jurisdictions, given probable changes over time in health system capacity, and in the type and indications of chemotherapy. Furthermore, the findings are not likely to be generalisable to jurisdictions in low-income and middle-income countries or countries with substantially different health systems to those of the studied jurisdictions.

Regarding treatment variables, no information was available on treatment intent. Stage at diagnosis could be used as a surrogate marker of curative or palliative intent, but its completeness was generally low and variable. Therefore, we have only performed stratified analysis by stage at diagnosis for colon cancer, where stage completeness was high and guideline recommendations supporting chemotherapy use were well established. We could not consider whether surgery and radiotherapy were used in combination with chemotherapy. It is worth noting that if the use of surgery and radiotherapy contributed to the interjurisdictional variation in the use of chemotherapy, their own uses would also have to vary between jurisdictions. We had no information on whether prescribed regimens were completed.

Regarding patient factors, no information was available on patient morbidity status, which is inconsistently coded across the participating jurisdictions.[28] Large variation in morbidity status between participating jurisdictions is unlikely, given their overall similar demographic structures. Similarly, we had no information on patient performance status. Although single-country studies have documented differences in chemotherapy use by socioeconomic status,[2,23–27] there are no consistent measures of socioeconomic status across international jurisdictions. There were no data on patient preference for and acceptability of chemotherapy. The main analysis findings regarding overall use and time-to-chemotherapy were not adjusted for age group, but analysis samples had a broadly similar age composition; furthermore, supplementary analyses indicated that interjurisdictional variation in chemotherapy use seemed to be independent of the age and cancer site casemix of the studied jurisdictional populations. Additionally, we did not want to adjust the observed overall use to avoid obscuring interjurisdictional variation in how patients are managed; for example, by age group, which we examined using meta-analysis.

Regarding health system organisational factors, several factors during the study period (such as how the health system appraised new cancer therapies, how clinical practice guidelines were produced and implemented,[6] and how cancer health-care was delivered through multidisciplinary teams and centralised or regional centres) might have influenced population levels of chemotherapy use; no such information was collected for this study. The participating jurisdictions were served by health-care systems with universal coverage, enabling access to cancer treatment. Therefore, access barriers to chemotherapy are unlikely to have contributed substantially to interjurisdictional variation. Within-jurisdiction differences in use of chemotherapy are probable, for example, between different geographies or hospital providers, but were not examined.

Considering the findings, we posit the following hypotheses. First, that the observed variation is due to confounding. This hypothesis would not deny the presence of variation but might help to explain it; for example, if unmeasured confounder variables were unequally distributed across jurisdictional samples, or if their effect sizes differed interjurisdictionally, or both. Given the large size of the observed variations, distributional and effect size differences of confounder variables would need to be implausibly large to substantially affect the findings. It is unlikely, for example, that variation in the prevalence of morbidity between older patients differs substantially between jurisdictional populations, to the amount needed to produce the large size of observed interjurisdictional variation in age differences. In principle, interjurisdictional variation in tumour morphology in patients with oesophageal, stomach, liver, lung, and ovarian cancer could contribute to variation in chemotherapy use, but morphology type distributions were similar among participating jurisdictions.

Second, that the observed variation is artefactual; for example, because of differences in operational definitions and recording of chemotherapy use in different data sources. This hypothesis is hard to measure empirically, although several considerations suggest that the potential for such biases is unlikely to be the sole cause for the differences. In only a few cases we observed negative time-to-treatment intervals, probably reflecting instances where tumour registration based on the date of histological verification had occurred before the treatment start date was identified. Including these cases prevented a biased estimation of true treatment use

status.[14] Because such instances consistently related to only a few cases, the effect on the overall time-to-treatment distribution was small, and unlikely to materially influence the observed interjurisdictional differences in median time-to-chemotherapy.[29]

Third, that the observed variation is real. Having considered alternative explanations, we posit that, in major part, the observed variation is because of genuine inter-jurisdictional differences in chemotherapy use, not accounted for by other factors. Several considerations support this interpretation. Firstly, because the data sources used in each jurisdiction are the same for all cancer sites, any potential undercount of actual chemotherapy use would be expected to affect estimates across all cancer sites similarly, yet some jurisdictions with comparatively low use for given cancer sites did not have low use for others, and vice versa. Related to this, any potential undercounting of actual chemotherapy use is unlikely to differ by sex or age group because the data collection process is the same across patient groups (except for colon, rectal, and liver cancer in jurisdictions where oral chemotherapy use was not captured, particularly among patients aged 75 years or older). Secondly, stratified analysis revealed a prevailing variability in chemotherapy use in patients with stage 3 colon cancer, a patient group with long-established indications for chemotherapy use, and for which we would have expected interjurisdictional variation to be low, although the opposite is observed. Thirdly, the size of interjurisdictional variation in age differences is such that it most likely indicates genuine differences in decision thresholds for using chemotherapy in older patients between the jurisdictions than any other factors such as (implausibly large) interjurisdictional variation in the morbidity burden among older patients with cancer.

It is not possible to infer from our data the probable causes of such real variation, although several hypotheses can be postulated and examined by future research, both in the epidemiology and health policy fields. These include differences in the content of national clinical guidelines, or their implementation, or both; variable constraints in health-care professional capacity and the availability of treatment facilities; variation in professional culture and norms towards more or less conservative management; the variable extent of differences in clinical practice between providers or hospital teams within the same country; the differences in patient preferences and expectations of cancer care; the geographical location of treatment centres in relation to population residence; variable research infrastructure that could enable access to clinical trial protocols; and differences in the availability and content of national cancer control strategies, which might all be contributing to interjurisdictional differences in chemotherapy use.[6,7,22,23,30]

In our study, interjurisdictional variation in time-to-chemotherapy was generally smaller compared with variation in use. Artefactual causes of such variation are unlikely among patients identified as having received chemotherapy. Interjurisdictional differences in the capacity of specialist imaging services used for staging,[7] the promptness of staging investigations, the distribution of stage at diagnosis, and the use of neo-adjuvant regimens might be contributing to variation in treatment timeliness.

In conclusion, wide variation in the frequency of chemotherapy use, and to a lesser extent the time to first chemotherapy treatment, were observed across included high-income countries, indicating variations in health system propensity for chemotherapy use. There were large age differences in chemotherapy use, with older patients substantially less likely to be treated, and with large variation in age differences between the jurisdictions. The findings show the value of international studies to understand the variation between different jurisdictions in chemotherapy use. To guide efforts to improve patient outcomes, the reasons for such variation need to be established and their probable contribution to interjurisdictional survival differences quantified in future studies.

**ICBP Module 9 Chemotherapy Group**
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**Contributors**
SMcP, MEB, RJST, and GL conceptualised the study. SMcP, SAJ, RS, AB, OB, NC, DWD, NF, SH, LM, CAMcC, GM, YN, NS-J, SS, XT, HW, RRW, and HY curated the data. SMcP, MEB, SAJ, RS, AB, CAD, DWD, LD, SH, CAMcC, YN, NS-J, SS, HW, and RRW did the formal analysis. GL acquired funding. Investigation: SMcP, MEB, SAJ, RS, AB, NC, CAD, RAD, LD, NF, SH, LM, CAMcC, YN, NS-J, XT, RRW, HY, and GL did the investigation. SMcP, MEB, SAJ, RS, AB, NC, NF, SH, YN, RJST, XT, HY, and GL did the methodology. SAJ, RA, OB, NC, CAD, JJD, LD, ATG, DWH, LM, CAMcC, BM, GM, NS-J, LS, CST, RRW, and GL did the project administration. RA, OB, RAD, JJD, ATG, DWH, LM, CAMcC, BM, GM, NS-J, LS, CST, RJST, and RRW produced the resources. SMcP, MEB, SAJ, RS, AB, OB, NC, NF, SH, GM, and YN did the analysis on the software. SMcP, RA, AB, OB, NC, OB, JJD, ATG, SH, DWH, LM, CAMcC, BM, GM, YN, NS-J, LS, CST, RJST, RRW, and GL supervised the study. SMcP, MEB, SAJ, RS, RA, AB, OB, NC, CAD, RAD, DWD, JJD, NF, SH, LM, CAMcC, GM, YN, NS-J, SS, LS, XT, HW, RRW, HY, and GL validated the study. MEB and SAJ were responsible for visualisation. GL and MEB wrote the original draft. SMcP, MEB, SAJ, RS, RA, AB, OB, NC, CAD, RAD, DWD, JJD, LD, NF, ATG, SH, DWH, LM, CAMcC, BM, GM, YN, NS-J, LS, XT, CST, RJST, HW, RRW, HY, and GL reviewed and edited the study. All authors had access to the aggregate jurisdictional data reported in the manuscript. The following authors have accessed and verified the underlying raw data for each jurisdictional substudy: YN and BM (Norway); SMcP and RS (England); DWD (Northern Ireland); CAD and LD (Scotland); LM (Wales); XT (Alberta); RW (British Columbia); GM (Manitoba); HW (Newfoundland and Labrador); NS-J and RAD (Nova Scotia); SH and AB (Ontario); CMcL (Prince Edward Island), SS and AR (Saskatchewan); NC and HY (New South Wales); and NF (Victoria). GL had final responsibility for the decision to submit for publication on behalf of the collaborative authors' group.

### Declaration of interests

MEB reports personal fees from GRAIL Bio UK, for Independent Data Monitoring Committee membership unrelated to this study. OB and GM report salary compensation for the analysis of trial data in preparation for review by the Data Safety Monitoring Board for the POWERRANGER trial (NCT01404156), unrelated to this study. DWH reports grant support by Moondance Cancer Initiative (to their institution) in relation to exploring bowel cancer audit data. YN reports grant support to The Cancer Registry of Norway by the Norwegian Cancer Society on standardised cancer pathways (no direct payment). RRW reports research grant funding by the Michael Smith Foundation for Health Research, the First Nations Health Authority and Canadian Partnership Against Cancer, and the BC Cancer Foundation for public health research projects unrelated to the present study. GL declares research grant funding by the study sponsors to his employer (University College London). All other authors declare no competing interests.

### Data sharing

Most of the aggregate data are shared in the main text or the appendix, and all R code and aggregate data used for meta-analyses are available on GitHub (https://github.com/MattEBarclay/icbp_chemo_sharing). The following analytical resources are available from the authors: (1) a Microsoft Excel spreadsheet describing the analysis dataset structure (data items and properties), exemplified for a jurisdiction; (2) a write-out of SQL code (in Microsoft Word) that can be used (or adapted) to generate analysis-ready datasets; (3) an R markdown quality assurance code for analysis datasets; (4) an R markdown output of quality assurance of analysis dataset for an exemplar jurisdiction; and (5) an R markdown analysis code designed to be run against analysis datasets and produce aggregate data outputs in comma-separated variable files. Primary data used in this study can be requested following the data access policies of the data owner organisations listed (Cancer Registry of Norway; National Disease Registration Service, NHS England; Northern Ireland Cancer Registry; Scottish Cancer Registry, Public Health Scotland; Welsh Cancer Intelligence and Surveillance Unit, Public Health Wales; Alberta Cancer Registry, Cancer Care Alberta, Alberta Health Services; British Columbia Cancer Registry, BC; Manitoba Cancer Registry, CancerCare Manitoba; Provincial Cancer Care Program, NL; Nova Scotia Cancer Registry; Ontario Health (Cancer Care Ontario); Prince Edward Island Cancer Registry; Saskatchewan Cancer Agency; NSW Cancer Registry, Cancer Institute NSW; and the Victorian Cancer Registry). Additionally, for Ontario, Ontario Health is prohibited from making the data used in this research publicly accessible if it includes potentially identifiable personal health information or personal information, or both, as defined in Ontario law, specifically the Personal Health Information Protection Act and the Freedom of Information and Protection of Privacy Act. Upon request, data de-identified to a level suitable for public release can be provided.

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### References

1 Zavala VA, Bracci PM, Carethers JM, et al. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer* 2021; **124:** 315–32.

2 Henson KE, Fry A, Lyratzopoulos G, Peake M, Roberts KJ, McPhail S. Sociodemographic variation in the use of chemotherapy and radiotherapy in patients with stage IV lung, oesophageal, stomach and pancreatic cancer: evidence from population-based data in England during 2013-2014. *Br J Cancer* 2018; **118:** 1382–90.

3 Khare SR, Batist G, Bartlett G. Identification of performance indicators across a network of clinical cancer programs. *Curr Oncol* 2016; **23:** 81–90.

4 Massarweh NN, Haynes AB, Chiang YJ, et al. Adequacy of the National Quality Forum's colon cancer adjuvant chemotherapy quality metric: is 4 months soon enough? *Ann Surg* 2015; **262:** 312–20.

5 Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol* 2019; **20:** 1493–505.

6 Norell CH, Butler J, Farrell R, et al. Exploring international differences in ovarian cancer treatment: a comparison of clinical practice guidelines and patterns of care. *Int J Gynecol Cancer* 2020; **30:** 1748–56.

7 Lynch C, Reguilon I, Langer DL, et al. A comparative analysis: international variation in PET-CT service provision in oncology-an International Cancer Benchmarking Partnership study. *Int J Qual Health Care* 2021; **33:** mzaa166.

8 Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391:** 1023–75.

9 McPhail S, Swann R, Johnson SA, et al. Risk factors and prognostic implications of diagnosis of cancer within 30 days after an emergency hospital admission (emergency presentation): an International Cancer Benchmarking Partnership (ICBP) population-based study. *Lancet Oncol* 2022; **23:** 587–600.

10 Larønningen S, Skog A, Engholm G, et al. Nordcan.R: a new tool for federated analysis and quality assurance of cancer registry data. *Front Oncol* 2023; **13:** 1098342.

11 Statistics Canada. Canadian Cancer Registry (CCR) system guide – 2010 edition. https://www23.statcan.gc.ca/imdb-bmdi/pub/document/3207_D9_T15_V2-eng.htm (accessed Jan 31, 2024).

12 NSW Government, NSW Cancer Institute. NSW cancer registry – data dictionary. https://www.cancer.nsw.gov.au/getattachment/09728f8b-2a49-4d85-b47b-3f61f20ad1b1/nsw-cancer-registry-data-dictionary.pdf (accessed Jan 31, 2024).

13 European Network of Cancer Registries. Coding incidence date. 2022. https://www.encr.eu/sites/default/files/Recommendations/ENCR%20Recommendation%20DOI_Mar2022_0.pdf (accessed Jan 31, 2024).

14 National Disease Registration Service. Cancer treatments. https://digital.nhs.uk/ndrs/data/data-outputs/cancer-data-hub/cancer-treatments#methodology (accessed Jan 31, 2024).

15 International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995; **345:** 939–44.

16 Jonker DJ, Spithoff K, Maroun J. Adjuvant systemic chemotherapy for stage II and III colon cancer after complete resection: an updated practice guideline. *Clin Oncol (R Coll Radiol)* 2011; **23:** 314–22.

17 Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005; **30:** 261–93.

18 McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. *Biom J* 2020; **62:** 69–98.

19 Huang L, Jansen L, Balavarca Y, et al. Nonsurgical therapies for resected and unresected pancreatic cancer in Europe and USA in 2003–2014: a large international population-based study. *Int J Cancer* 2018; **143:** 3227–39.

20 van den Broek CB, van Gijn W, Bastiaannet E, et al. Differences in pre-operative treatment for rectal cancer between Norway, Sweden, Denmark, Belgium and the Netherlands. *Eur J Surg Oncol* 2014; **40:** 1789–96.

21 Breugom AJ, Bastiaannet E, Boelens PG, et al. Oncologic treatment strategies and relative survival of patients with stage I–III rectal cancer – a EURECCA international comparison between the Netherlands, Belgium, Denmark, Sweden, England, Ireland, Spain, and Lithuania. *Eur J Surg Oncol* 2018; **44:** 1338–43.

22 Ko JJ, Kennecke HF, Lim HJ, et al. Reasons for underuse of adjuvant chemotherapy in elderly patients with stage III colon cancer. *Clin Colorectal Cancer* 2016; **15:** 179–85.

23 Boyle JM, Kuryba A, Cowling TE, et al. Determinants of variation in the use of adjuvant chemotherapy for stage III colon cancer in England. *Clin Oncol (R Coll Radiol)* 2020; **32:** e135–44.

24 Booth CM, Nanji S, Wei X, et al. Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. *J Natl Compr Canc Netw* 2016; **14:** 47–56.

25 Nilssen Y, Brustugun OT, Møller B. Factors associated with emergency-related diagnosis, time to treatment and type of treatment in 5713 lung cancer patients. *Eur J Public Health* 2021; **31:** 967–74.

26 Nilssen Y, Eriksen MT, Guren MG, Møller B. Factors associated with emergency-onset diagnosis, time to treatment and type of treatment in colorectal cancer patients in Norway. *BMC Cancer* 2021; **21:** 757.

27 Habbous S, Yermakhanova O, Forster K, Holloway CMB, Darling G. Variation in diagnosis, treatment, and outcome of esophageal cancer in a regionalized care system in Ontario, Canada. *JAMA Netw Open* 2021; **4:** e2126090.

28 Lüchtenborg M, Morris EJA, Tataru D, et al. Investigation of the international comparability of population-based routine hospital data set derived comorbidity scores for patients with lung cancer. *Thorax* 2018; **73:** 339–49.

29 Myklebust TÅ, Andersson T, Bardot A, et al. Can different definitions of date of cancer incidence explain observed international variation in cancer survival? An ICBP SURVMARK-2 study. *Cancer Epidemiol* 2020; **67:** 101759.

30 Nolte E, Morris M, Landon S, et al. Exploring the link between cancer policies and cancer survival: a comparison of International Cancer Benchmarking Partnership countries. *Lancet Oncol* 2022; **23:** e502–14.