Agreement between questionnaires and registry data on routes to diagnosis and milestone dates of the cancer diagnostic pathway

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Abbreviations: A&E: accident and emergency department; CCC: Lin's concordance correlation coefficient; CI: confidence Interval; GP: general practitioner; ICBP4: International Cancer Benchmarking Partnership, Module 4; IQI: inter quartile interval; n/a: not available; SP: cancer treatment specialist

Abstract

Background: The routes to diagnosis and the time intervals along the diagnostic pathway affect cancer outcomes. Some data on routes to diagnosis and milestone dates can be extracted from registries or databases. When this data is incomplete, inaccurate or non-existing, other data sources are needed. This study investigates the agreement between multiple data sources on routes to diagnosis and milestone dates of cancer pathway.

Methods: Information on routes to diagnosis and milestone dates were compared across four data sources (cancer patients, general practitioners, cancer specialists and registries) for breast, colorectal, lung and ovarian cancers across the UK, Scandinavia, Canada and Australia. Agreement on routes to diagnosis and milestone dates was assessed by Kappa and AC1 coefficients and Lin's concordance correlation coefficient (CCC).

Results: 4,502 patients were included in the analysis of routes to diagnosis. The agreement was almost perfect (kappa=0.15-0.88, AC1=0.86-0.91) for breast cancer, substantial to almost perfect (kappa=0.07-0.86, AC1=0.74-0.93) for colorectal and ovarian cancers, and substantial (kappa=0.09-0.11, AC1=0.65-0.74) for lung cancer. 2,287 patients were included in the analysis of milestone dates. The agreement was adequate for all cancer types (CCC=0.88-0.99); highest agreement was seen for date of diagnosis (CCC=0.94-0.99).

Conclusion: We found a reasonable agreement between patient/physician questionnaires and registry data for routes to diagnosis and milestone dates. The agreement on routes to diagnosis was generally higher for breast cancer than for colorectal, ovarian and lung cancers. Lower agreement was seen on date of first presentation to primary care and date of treatment initiation compared to date of diagnosis.

Keywords: Early Detection of Cancer, Data Accuracy, Surveys and Questionnaires, Registries, Breast Neoplasms, Colorectal Neoplasms, Lung Neoplasms, Ovarian Neoplasms

1. Introduction

Cancer outcomes are influenced by the route to diagnosis and the time intervals in the diagnostic pathway (e.g. the interval between first presentation to healthcare and diagnosis). Patients diagnosed with cancer through emergency presentation have poorer clinical and patient-reported outcomes than patients diagnosed through non-emergency presentation or screening [1]. Advanced staging at diagnosis and increased mortality have been associated with the time to diagnosis, and some cancers have been shown to progress during the interval between diagnosis and treatment [2],[3],[4],[5].

Information on the routes to diagnosis and milestone dates can sometimes be established from registries, which are generally accepted as the most accurate sources of information [6]. However, other data sources may be required when registry data are not available. Detailed information about the pre-diagnostic phase is particularly important and may be obtained from questionnaires completed by patients and physicians.

The growing interest in research on routes to diagnosis and time delays brings a need to establish the level of agreement between registry data and questionnaire instruments on this type of data. Moreover, it is important to explore whether combining data from multiple sources can be used to map the routes to diagnosis and measure the time intervals in the diagnostic pathway.

Existing studies on concordance of routes to diagnosis and milestone dates have compared data from various data sources, but these studies have primarily focussed on a single combination of data sources (e.g. self-report and medical record), a single object (e.g. date of diagnosis) or a single disease (e.g. breast cancer) [7],[8],[9],[10],[11],[12]. To our knowledge, no previous studies have explored the agreement between several data sources on several objects and diseases across several countries.

The International Cancer Benchmarking Partnership (ICBP) explores cancer outcomes variation between comparable countries [13],[14],[15]. Module 4 (ICBP4) was established to describe cancer pathways and investigate the association between the diagnostic time intervals and outcomes of breast, colorectal, lung and ovarian cancer in six countries [16]. This ICBP4 study aims to investigate the agreement on routes to diagnosis and milestone dates in the cancer diagnostic pathway by comparing data from patients, general practitioners (GPs), cancer specialists (SPs) and cancer registries.

2. Methods

2.1 Setting and population

This ICBP4 population-based cohort study included patients with newly diagnosed breast, colorectal, lung or ovarian cancer recorded in cancer- and hospital-based registries in 10 jurisdictions across the UK (Wales,

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England, Scotland, Northern Ireland), Denmark, Sweden, Norway, Canada (Ontario, Manitoba) and Australia (Victoria) during 2013-2015. Patients below age 40 years and with a history of a cancer in the same organ or two or more primary cancers were ineligible.

2.2 Data collection

A questionnaire was sent to eligible patients, their GP and their main SP. Three strategies for contacting patients were used. Participating registries (a) forwarded the patient's details to the local ICBP4 team, who sent the questionnaire directly to the patient; (b) sent a letter to the relevant GP with a request to forward a pre-addressed envelope to the patient or; (c) the questionnaire was directly sent to the patient after contacting the patient's treating clinician to confirm study eligibility. The material provided a detailed description of routes to diagnosis, milestone dates, symptoms and informed consent. The teams obtained information on screening status and date of diagnosis from cancer registries and clinical databases.

Patients with missing information on gender, age, date of consent and diagnosis were excluded. To reduce recall bias, patients completing the questionnaire more than nine months after diagnosis were excluded. Additionally, patients from Sweden and Norway were excluded from the analysis, as only patients completed the survey in Sweden, whereas Norway provided no registry data. The data collection and management has been described in further detail elsewhere [16].

2.3 Routes to diagnosis

We focused on screening, symptomatic presentation and other presentation to the healthcare system as reported by patient and GP and recorded in the registry. The SP was not asked about routes to diagnosis.

Screening

Screening was an option for breast and colorectal cancer patients only, as no national screening programmes existed for lung and ovarian cancers at the time of the patient recruitment. In some jurisdictions, patients could be offered screening as part of an organised programme, or screening could be requested by their GP. The latter test was not used in the agreement analysis.

Symptomatic route

Information about symptomatic presentation was available from patient and GP questionnaires. Symptomatic presentation was defined as to include patients with any reported symptoms or presented through 'visit to GP', 'visit to GP and accident and emergency department (A&E)', 'A&E' or 'visit to doctor for other health problem'.

Other route

The data on other routes was available from patient and GP questionnaires.

2.4 Milestone dates

We focused on three selected milestone dates: date of first cancer-related visit to primary care, date of diagnosis and date of treatment initiation.

Date of first visit

The patients and GPs were asked about the exact date of the first visit to primary care for a specific cancer. Breast and colorectal cancer patients were excluded from the analysis if their route to diagnosis was screening.

Date of diagnosis

Patient questionnaire and registry records included single items on the date of cancer diagnosis, whereas the date of diagnosis in GP and SP questionnaires was defined as: date of histological confirmation, date of biopsy, date of results of investigation, date of hospital admission, date of confirmation by multidisciplinary team, date when "patient was told" or other date of diagnosis (in declining order of priority).

Date of treatment

Date of treatment was collected from patient and SP questionnaires. For patient data, the date was defined as the earliest date of either surgery, chemotherapy, radiology or other treatment.

If the difference between two dates for the same milestone was more than one year when reported by different sources, such milestone was considered a potential outlier and excluded from the analysis.

2.5 Statistical analyses

The agreement for nominal variables on routes to diagnosis was assessed by chance-corrected agreement in the form of kappa coefficients [17] and Gwet's AC1 [18]. Cohen's kappa statistics is widely used to compute agreement between raters on nominally scaled data. However, it is known to be affected by an unbalanced prevalence of the trait, i.e. in a situation where a large proportion of ratings is either positive or negative, kappa may then yield a low value despite high overall percentage agreement [19]. We used AC1 as an alternative agreement coefficient to remediate this issue. Agreement measured by kappa and AC1 was interpreted as: *poor* (below 0), *slight* (0–0.2), *fair* (0.2–0.4), *moderate* (0.4–0.6), *substantial* (0.6-0.8) and *almost perfect* (above 0.8) [20].

The difference between dates could be approximated as following a normal distribution. The agreement for dates was measured by Lin's concordance correlation coefficient (CCC) [21]. We interpreted agreement measured by CCC as: *poor* (below 0.4), *moderate* (0.4-0.7) and *good* (above 0.7) [22].

The analysis was based on the combined dataset across all jurisdictions and was performed for each type of cancer and for the total dataset. The complete-case approach was used in the analyses. Several sensitivity analyses tested the robustness of the results. Statistical analyses were carried out in Stata, version 15.

3. Results

The flow of patients and the exclusion criteria are outlined in Fig. 1. A total of 4,502 (57%) fulfilled the inclusion criteria for the analyses of routes to diagnosis and 2,287 (29%) patients for the analyses of dates.

While the gender and age distribution of included patients were comparable to that of identified patients, included patients were more likely to be women and aged 60-69 years. Included patients were more likely to have less advanced stage than identified patients and therefore more likely to be alive one year after diagnosis (Table A.1 in Appendix A).

Included patients with breast or ovarian cancer were generally younger and had less comorbidity (Table 1). Slightly more than half of the patients with colorectal or lung cancer were men. The clinical features were similar for each jurisdiction, but the number of Ontario residents with lung or ovarian cancer used in the analysis of dates was low (Table A.2 in Appendix A).
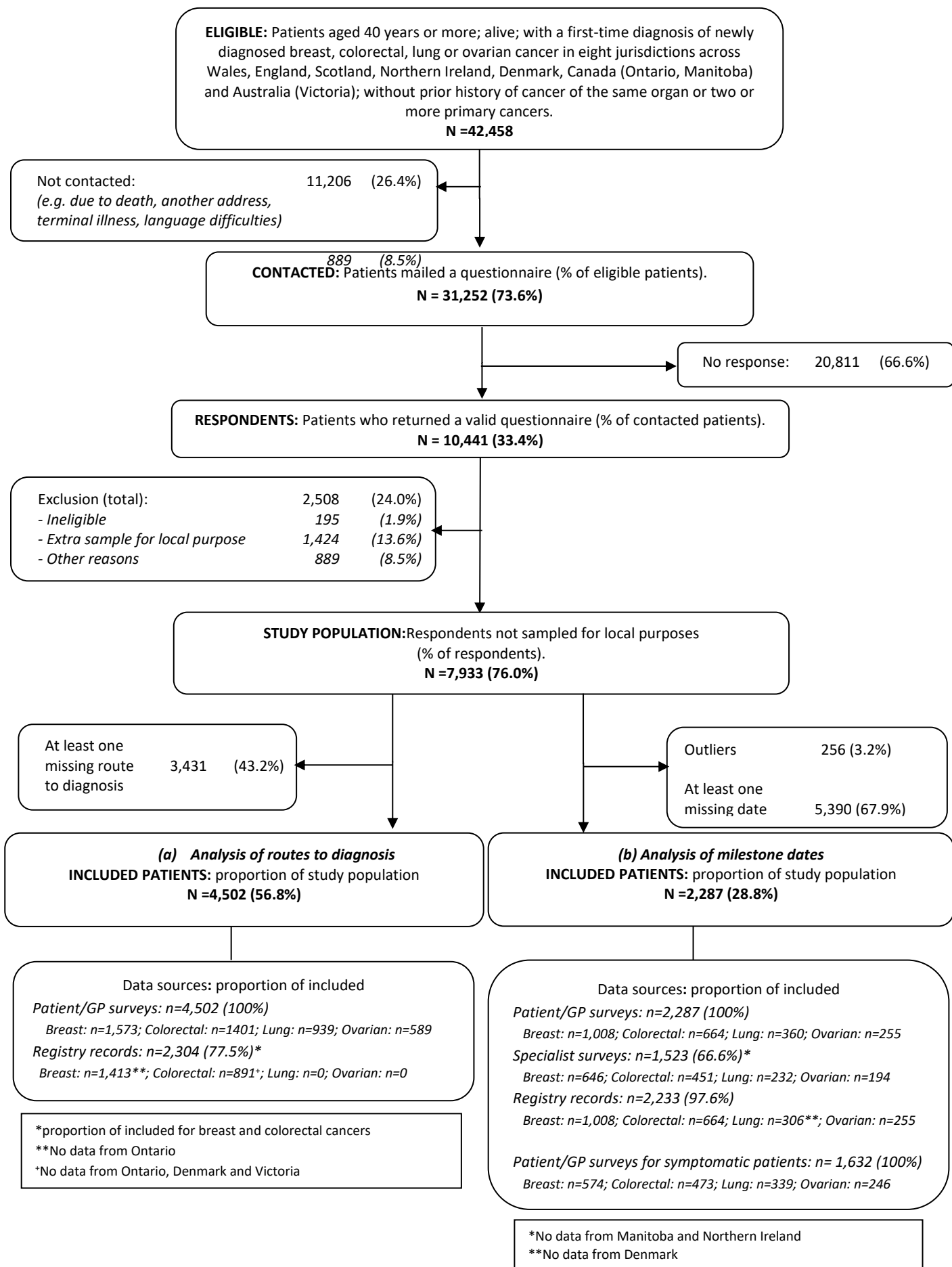
3.1 Agreement on routes to diagnosis

Approximately 45% of breast cancers were detected by screening, 53% by symptomatic presentation and 5% by other routes (Table 2). Approximately 20% of colorectal cancers were detected by screening, 73% by symptomatic presentation and 11% by other routes. Some patients reported multiple routes to diagnosis.

The agreement on screening route was almost perfect (kappa ≥ 0.86 for breast cancer; overall agreement ≥ 0.90, AC1 ≥ 0.85 for colorectal cancer) (Table 3). The agreement on symptomatic presentation was almost perfect for breast and ovarian cancers (kappa = 0.88 for breast cancer; overall agreement = 86%, AC1 = 0.84 for ovarian cancer) and substantial for colorectal and lung cancers (overall agreement ≥ 80%, AC1 = 0.74). The agreement on other routes was high for breast cancer (overall agreement = 92%, AC1 = 0.91) and lower for the other three types of cancer (overall agreement ranged from 74% and AC1 from 0.65 for lung cancer to 83% and 0.78, respectively, for colorectal cancer).

In case of substantial discrepancy between kappa and AC1 coefficients, the result was interpreted as a good agreement if overall agreement and AC1 was high despite low kappa. In this situation, the proportion of patients using a specific route to diagnosis was either very low or very high, and the kappa coefficient was thus considered to be artificially low due to the unbalanced trait prevalence [19],[18].

3.2 Agreement on milestone dates

Adequate agreement was achieved across all data sources for all milestone dates when the four types of cancer were assessed together (CCC = 0.92 for date of first presentation to primary care; 0.96 ≤ CCC ≤ 0.98 for date of diagnosis and CCC = 0.90 for date of treatment initiation) (Table 4). After stratification by type of

ELIGIBLE: Patients aged 40 years or more; alive; with a first-time diagnosis of newly diagnosed breast, colorectal, lung or ovarian cancer in eight jurisdictions across Wales, England, Scotland, Northern Ireland, Denmark, Canada (Ontario, Manitoba) and Australia (Victoria); without prior history of cancer of the same organ or two or more primary cancers.
N =42.458

Not contacted: 11,206   (26.4%)
(e.g. due to death, another address, terminal illness, language difficulties)

889   (8.5%)
CONTACTED: Patients mailed a questionnaire (% of eligible patients).
N = 31,252 (73.6%)

No response: 20,811   (66.6%)

RESPONDENTS: Patients who returned a valid questionnaire (% of contacted patients).
N = 10,441 (33.4%)

Exclusion (total):   2,508   (24.0%)
- Ineligible   *195*   *(1.9%)*
- Extra sample for local purpose *1,424*   *(13.6%)*
- Other reasons   *889*   *(8.5%)*

STUDY POPULATION: Respondents not sampled for local purposes (% of respondents).
N =7,933 (76.0%)

At least one missing route to diagnosis   3,431   (43.2%)

Outliers   256 (3.2%)

At least one missing date   5,390 (67.9%)

(a)   Analysis of routes to diagnosis
INCLUDED PATIENTS: proportion of study population
N =4,502 (56.8%)

(b) Analysis of milestone dates
INCLUDED PATIENTS: proportion of study population
N =2,287 (28.8%)

Data sources: proportion of included
Patient/GP surveys: n=4,502 (100%)
  Breast: n=1,573; Colorectal: n=1401; Lung: n=939; Ovarian: n=589
Registry records: n=2,304 (77.5%)*
  Breast: n=1,413**; Colorectal: n=891+; Lung: n=0; Ovarian: n=0

*proportion of included for breast and colorectal cancers
**No data from Ontario
+No data from Ontario, Denmark and Victoria

Data sources: proportion of included
Patient/GP surveys: n=2,287 (100%)
  Breast: n=1,008; Colorectal: n=664; Lung: n=360; Ovarian: n=255
Specialist surveys: n=1,523 (66.6%)*
  Breast: n=646; Colorectal: n=451; Lung: n=232; Ovarian: n=194
Registry records: n=2,233 (97.6%)
  Breast: n=1,008; Colorectal: n=664; Lung: n=306**; Ovarian: n=255

Patient/GP surveys for symptomatic patients: n= 1,632 (100%)
  Breast: n=574; Colorectal: n=473; Lung: n=339; Ovarian: n=246

*No data from Manitoba and Northern Ireland
**No data from Denmark

Fig. 1. Flowchart of patients included in the analysis on (a) routes to diagnosis and (b) milestone dates.

Table 1. Basic characteristics of patients included in the analyses of routes to diagnosis (top) and milestone dates (bottom) (n and % if nothing else stated)

	Analysis of routes to diagnosis				
	Breast cancer **(N=1573)**	**Colorectal cancer** **(N=1413)**	**Lung cancer** **(N=939)**	**Ovarian cancer** **(N=589)**	**Total** **(N=4502)**
Age (years), Median (IQI)	62 (53,70)	69 (62,76)	69 (64,75)	63 (55,71)	66 (58,74)
Gender, Male among colorectal and lung cancer patients	-	816 (58)	495 (53)	-	1311 (56)
Comorbidity[1]					
None	1098 (70)	769 (55)	355 (38)	408 (69)	2,630 (58)
Medium	454 (29)	599 (43)	532 (57)	176 (30)	1,761 (39)
High	11 (1)	31 (2)	52 (5)	5 (1)	99 (2)
Missing	10 (1)	2 (1)	0 (0)	0 (0)	12 (1)

	Analysis of milestone dates				
	Breast cancer **(N=1008)**	**Colorectal cancer** **(N=664)**	**Lung cancer** **(N=360)**	**Ovarian cancer** **(N=255)**	**Total** **(N=2287)**
Age (years), Median (IQI)	62 (52,69)	69 (62,76)	68 (64,75)	63 (55,70)	65 (57,73)
Gender, Male among colorectal and lung cancer patients	-	400 (60)	182 (51)	-	582 (57)
Comorbidity[1]					
None	708 (70)	360 (54)	151 (42)	183 (72)	1402 (61)
Medium	287 (28)	292 (44)	194 (54)	71 (28)	844 (37)
High	10 (1)	12 (2)	15 (4)	1 (1)	38 (2)
Missing	3 (1)	0 (0)	0 (0)	0 (0)	3 (1)

[1]Comorbidity coded as none (none reported), medium (1-2 reported) and high (3+ reported)
Abbreviations: ICI: inter-quartile interval

Table 2. Cancer patients' routes to diagnosis expressed as proportions according to screening, symptomatic presentation or other presentation for each cancer type and data sources available

Data sources	Proportion of cases with screening route (95% CI)	Proportion of cases with symptomatic route (95% CI)	Proportion of cases with other route (95% CI)
Breast cancer			
Patient (n=1573)	0.45 (0.42-0.47)	0.52 (0.50-0.54)	0.07 (0.06-0.08)
GP (n=1573)	0.44 (0.41-0.46)	0.54 (0.52-0.56)	0.03 (0.02-0.04)
Registry (n=1413)	0.44 (0.41-0.46)	n/a	n/a
Colorectal cancer			
Patient (n=1401)	0.24 (0.22-0.27) *	0.71 (0.69-0.73)	0.12 (0.10-0.14)
GP (n=1401)	0.17 (0.15-0.19)	0.75 (0.72-0.77)	0.10 (0.08-0.11)
Registry (n=891)	0.22 (0.19-0.25)	n/a	n/a
Lung cancer			
Patient (n=939)	n/a	0.91 (0.89-0.92)	0.15 (0.13-0.18)
GP (n=939)	n/a	0.84 (0.81-0.86)	0.18 (0.16-0.21)
Ovarian cancer			
Patient (n=589)	n/a	0.91 (0.89-0.93)	0.13 (0.10-0.16)
GP (n=589)	n/a	0.92 (0.89-0.94)	0.11 (0.09-0.14)

*n=1268 due to exclusion of Manitoba as it was unknown whether patients reported screening programme or test organised by GP

Abbreviations: CI: confidence interval, GP: general practitioner, n/a: not available

Table 3. Agreement between different data sources to report if a cancer case was presented through screening, symptomatic or other presentation, for each disease and all four cancers

Route to diagnosis	Data sources	Overall agreement (%)	Kappa (95%CI)	AC1 (95%CI)
Breast cancer				
	Patient vs GP (n=1573)	93	0.86 (0.84,0.89)	0.86 (0.84,0.89)
Screening	Registry vs Patient (n=1413)	93	0.86 (0.84,0.89)	0.87 (0.84,0.89)
	Registry vs GP (n=1413)	94	0.88 (0.86,0.91)	0.89 (0.87,0.91)
Symptomatic	Patient vs GP (n=1573)	94	0.88 (0.86,0.90)	0.88 (0.86,0.90)
Other	Patient vs GP (n=1573)	92	0.15 (0.07,0.24)	0.91 (0.89,0.93)
Colorectal cancer				
	Patient vs GP (n=1268)	90	0.71 (0.66,0.76)	0.85 (0.83,0.88)
Screening	Registry vs Patient (n=758)	93	0.82 (0.77,0.86)	0.88 (0.85,0.91)
	Registry vs GP (n=891)	95	0.86 (0.82,0.90)	0.93 (0.91,0.95)
Symptomatic	Patient vs GP (n=1401)	84	0.61 (0.56,0.65)	0.74 (0.71,0.78)
Other	Patient vs GP (n=1401)	83	0.09 (0.03,0.15)	0.78 (0.75,0.81)
Lung cancer				
Symptomatic	Patient vs GP (n=939)	80	0.11 (0.04,0.19)	0.74 (0.70,0.78)
Other	Patient vs GP (n=939)	74	0.09 (0.02,0.16)	0.65 (0.60,0.69)
Ovarian cancer				
Symptomatic	Patient vs GP (n=596)	86	0.12 (0.01,0.23)	0.84 (0.80,0.88)
Other	Patient vs GP (n=596)	80	0.07 (-0.02,0.16)	0.75 (0.70,0.80)

Abbreviations: CI: confidence interval, GP: general practitioner

Table 4. Mean difference (in days), proportions of agreement and concordance correlation coefficient (CCC) for dates of first visit to primary care, diagnosis and treatment, for each type of cancer and all cancers

Type of Date	Data sources	Mean difference in days	Fully agree (%)	Agree within 1 week (%)	Agree above 1 week (%)	CCC (95% CI)
Breast cancer						
First visit to PC*	GP vs Patient (n=574)	-5.6	44	24	32	0.95 (0.94,0.95)
	GP vs Patient (n=1008)	1.9	26	37	37	0.97 (0.96,0.97)
	Registry vs Patient (n=1008)	-4.1	21	39	41	0.98 (0.98,0.98)
Diagnosis	Registry vs GP (n=1008)	-6.0	27	41	32	0.98 (0.98,0.98)
	SP vs Registry (n=646)	5.0	16	61	22	0.98 (0.98,0.98)
	SP vs Patient (n=646)	0.6	17	50	33	0.95 (0.94,0.96)
Treatment	SP and Patient (n=646)	4.6	61	16	23	0.88 (0.86,0.90)
Colorectal cancer						
First visit to PC*	GP vs Patient (n=473)	-2.4	25	20	55	0.89 (0.87,0.91)
	GP vs Patient (n=664)	2.2	18	29	53	0.95 (0.95,0.96)
Diagnosis	Registry vs Patient (n=664)	-3.8	22	28	50	0.98 (0.98,0.98)
	Registry vs GP (n=664)	-6.0	28	27	45	0.97 (0.96,0.97)

	SP vs Registry (n=451)	7.1	18	53	30	0.95 (0.94,0.96)
	SP vs Patient (n=451)	2.9	10	43	47	0.95 (0.94,0.96)
Treatment	SP vs Patient (n=451)	4.0	58	18	24	0.89 (0.87,0.91)
Lung cancer						
First visit to PC*	GP vs Patient (n=339)	1.8	19	19	62	0.91 (0.89,0.93)
	GP vs Patient (n=360)	10.9	12	21	66	0.96 (0.95,0.97)
	Registry vs Patient (n=306)	5.9	6	26	68	0.98 (0.97,0.98)
Diagnosis	Registry vs GP (n=306)	-7.2	23	28	49	0.97 (0.97,0.98)
	SP vs Registry (n=178)	11.9	17	37	46	0.95 (0.94,0.97)
	SP vs Patient (n=232)	10.3	9	30	61	0.94 (0.93,0.96)
Treatment	SP vs Patient (n=232)	2.7	47	24	29	0.96 (0.95,0.97)
Ovarian cancer						
First visit to PC*	GP vs Patient (n=246)	6.4	35	18	48	0.91 (0.89,0.93)
	GP vs Patient (n=255)	10.0	9	27	64	0.97 (0.96,0.97)
	Registry vs Patient (n=255)	1.3	7	25	67	0.98 (0.97,0.98)
Diagnosis	Registry vs GP (n=255)	-8.7	28	23	49	0.97 (0.97,0.98)
	SP vs Registry (n=194)	7.5	28	27	44	0.99 (0.98,0.99)
	SP vs Patient (n=194)	5.5	7	30	63	0.98 (0.98,0.98)
Treatment	SP vs Patient (n=194)	8.1	57	17	26	0.93 (0.91,0.95)
All cancers						
First visit to PC*	GP vs Patient (n=1632)	-1.3	32	21	47	0.92 (0.91,0.92)
	GP vs Patient (n=2287)	4.3	19	31	50	0.96 (0.96,0.97)
	Registry vs Patient (n=2233)	-2.0	18	32	50	0.98 (0.98,0.98)
Diagnosis	Registry vs GP (n=2233)	-6.5	27	33	40	0.98 (0.97,0.98)
	SP vs Registry (n=1469)	6.8	18	51	31	0.97 (0.97,0.97)
	SP vs Patient (n=1523)	3.4	12	43	45	0.96 (0.95,0.96)
Treatment	SP vs Patient (n=1523)	4.6	57	18	25	0.90 (0.89,0.91)

*only for symptomatic patients

Abbreviations: CI: confidence interval, GP: general practitioner, PC: primary care, SP: cancer specialist

disease, the agreement was still reasonable. CCC for date of first presentation ranged from 0.89 for colorectal cancer to 0.95 for breast cancer. CCC for date of treatment was about 0.88 for breast and colorectal cancers and above 0.9 for the other two diseases. CCC for date of diagnosis was homogenous across all four cancer types, ranging from 0.94 to 0.99. The mean difference ranged from 0.6 days for diagnosis date of breast cancer between SP and patient to 12 days for diagnosis date of lung cancer between SP and registry.

3.3 Sensitivity analyses

The sensitivity analyses, which investigated the implications of including patients with missing information in at least one data source for routes to diagnosis or milestone date, displayed similar findings as the main

analysis (Tables A.3-A.4 in Appendix A). And the basic characteristics of excluded and included patients were similar (Table A.5 in Appendix A).

4. Discussion

4.1 Key findings

The present study assessed the agreement on routes to diagnosis and milestone dates in the diagnostic pathway reported by cancer patients, physicians and cancer registries in several countries. We found almost perfect agreement on routes to diagnosis (screening, symptomatic presentation and other presentation) for breast cancer across all explored data sources. However, the agreement was lower for colorectal, lung and ovarian cancers, ranging from substantial to almost perfect. The lowest level of agreement was seen for lung cancer. A possible explanation for the higher level of agreement in breast cancer is that the diagnostic pathways for this type of cancer may be relatively straightforward; by comparison, symptoms are typically vague in colorectal, lung and ovarian cancers, leading to more convoluted pathways. For example, a survey of patients with newly diagnosed ovarian cancer found that bloating and increased abdominal size were reported three to four times more often than documented in primary-care records [23].

We found good agreement on milestone dates across all data sources and all types of dates. The agreement was highest for date of diagnosis, with almost no variation across different combinations of data sources. Lower agreement was seen for date of first presentation to primary care and date of treatment initiation across all four types of cancers.

4.2 Comparison of findings with existing literature

Some studies have questioned the quality of self-reported data in cancer research. A Canadian study [9] showed low agreement between self-reported history and physician's records on less invasive colorectal cancer screening tests. However, the study was based on a mix of patients with and without cancer, which may explain the different findings in our study. In contrast, Australian researchers [7] showed almost perfect concordance between patient and GP for screen-detected and symptomatic presentation of colorectal cancer and breast cancer. This is consistent with our findings, except for colorectal cancer diagnosed through symptomatic presentation for which we found substantial agreement. The same study reported good concordance between patient and registry/specialist on date of diagnosis and date of treatment initiation, which was supported by our results. In line with our findings, two studies on breast cancer (one in China, one in Canada) reported substantial to almost perfect agreement on treatment initiation date, when comparing women's answers with medical records [8],[12]. Our findings of high levels of agreement between patients and GPs on date of first presentation to primary care align with a Danish study on all newly diagnosed cancers

[10] and an Australian study on colorectal and breast cancer [7], although another Australian study on colorectal cancer found only moderate validity for this date [11].

4.3 Strengths and limitations

A strength of our population-based cohort study is the large number of included patients (4,502 and 2,287). Moreover, the international context allowed data collection in eight jurisdictions with similar healthcare systems. The data on routes to diagnosis and milestone dates were collected from several different sources, including cancer registries and questionnaires completed by patients and their physicians (GP and SP). The ICBP4 surveys are based on state-of-the-art instruments, which undergo extensive translation and adaptation procedures, cognitive testing and pilot testing to ensure standardised high-quality data on routes to diagnosis and milestone dates [16]. The rich database allowed for multiple agreement analysis across several data sources and variables of interest.

A limitation is the variation in some items across data sources used in the agreement analysis. For example, the date of diagnosis was defined by a single general definition in the patient questionnaire and in the registry, whereas this date had to be aggregated in the GP and SP questionnaires using different definitions (for example, date of histological confirmation, date of biopsy undertaken). Additionally, the treatment initiation date was based on a single definition in the questionnaire for SPs, whereas it was defined as the earliest date of either surgery, chemotherapy, radiology or other treatment in the patient questionnaire. Most likely, these issues have led to an underestimated agreement.

Subtle differences between jurisdictions were observed in the understanding of 'screening' in the route to diagnosis. The patients did not always distinguish between screening and tests for symptom-based diagnosis. For example, GPs in Australia and Canada may use faecal occult blood testing (FOBT) for screening during consultations, whereas this is rare in the UK and Scandinavia. To counter these inconsistencies, we did not include screening data in the analysis if not specified whether it formed part of a national screening programme or was requested by the GP.

If two dates for the same milestone differed by more than one year between different sources, this patient was excluded. This approach was taken to as a precaution against severe recall bias and potential misclassifications. Selection bias cannot be ruled out. However, as it accounted for only 3% of the possible cases (Figure 1), this cannot explain the high level of agreement found.

A key limitation, as with many questionnaire-based studies, was the low patient participation rate. About three quarters of eligible patients was contacted, and one third of these completed a questionnaire. This may

have led to selection and non-response bias and has implications for interpretation and generalisation of findings. The analyses were undertaken using a complete case approach, leading to a lower response rate, especially in the analysis of dates. However, the sensitivity analysis confirmed the robustness of the results against missing data. Furthermore, the basic characteristics of excluded and included patients were broadly similar.

The ICBP4 recruitment process required the patient to be alive for at least 3-4 months after diagnosis; for some, up to 9 months after diagnosis. This may have led to recall bias and thus possibly underestimated agreement. Also, bias is conceivable as the study didn't include those who experienced dying soon after diagnosis. These may be patients who had fast ('sick-quick' patients) or prolonged pathways leading to advanced stages. Some jurisdictions did not provide all necessary data from the registries and SP questionnaires, which may have caused selection bias. Moreover, the study included data from GP questionnaires, which might have induced selection bias if the non-responding GPs had a different perception of routes to diagnosis and index dates than the responding GPs.

The broad international setting may hold other differences between jurisdictions that were not captured. Nevertheless, the clinical features of the participants were similar across cancer types and jurisdictions. The sample size was not sufficient to perform analyses at the level of each jurisdiction.

4.4 Interpretation and implications

The presented results have implications for research and development using data on the cancer pathway. The findings suggest that combining data from patient/physician questionnaires and nationwide registries can be useful to measure routes to diagnosis and milestone dates. For instance, patient questionnaires can be used when registry data and physician's records do not include data on initial presentation. The present ICBP4 study illustrates that triangulation of data from multiple sources can provide more complete and reliable information on the pathways. To prioritise data sources, we developed hierarchical data rules [24]. We recommend application of similar hierarchical data rules in future projects, and the applied rules should be made publicly available to ease interpretation.

Our findings of good agreement on milestone dates across all data sources and explored types of dates suggest that e.g. patient-reported data could complement cancer registration with patient reported date of first presentation to health care due to symptoms. The increasing use of patient-reported outcome measures (PROMs) in cancer care shows promising results, especially within clinical care [25],[26],[27]. Thus, one way to complement cancer registrations could be to routinely collect PROMs at specific time points [26],[28]. Routine PROM data on milestone dates could also supply public health authorities and clinicians with new

and valuable information on the real timeliness of a cancer diagnosis. This information may serve as an indicator of the responsiveness of the healthcare system when new initiatives are implemented (e.g. to ensure earlier diagnosis). However, the feasibility and validity of routinely collected PROMs need to be established.

5. Conclusions

We found adequate agreement between patient/physician questionnaires and registry data on routes to cancer diagnosis (screening, symptomatic presentation and other presentation) and milestone dates (date of first presentation to primary care, date of diagnosis and date of treatment initiation). The agreement on routes to diagnosis was generally higher for breast cancer than for colorectal, ovarian and lung cancers. The agreement on date of first presentation to primary care and date of treatment initiation was generally lower than the agreement on date of diagnosis.

Our results suggest that combining data from patient/physician questionnaires and from registries may lead to more reliable estimates of routes to diagnosis and milestone dates in the cancer diagnostic pathway.

Ethics approval

Each local data collection involved specific procedures and approvals, including anonymised data transfer to University College London and Aarhus University. Approvals were received from the following institutions: Cancer Council Victoria Human Research Ethics Committee (HREC 112); Health Research Ethics Board, University of Manitoba (HS15227 (H2012:105)); Research Resource Ethics Committee, CancerCare Manitoba (RRIC#28-2012); University of Toronto Research Ethics Board (27881); The Danish Data Protection Agency (2013- 41-2030); Swedish Ethics Review Board, Uppsala (2013/306); Norway Regional committees for medical and health research ethics (2013/136/REK nord); England, Wales and Scotland, NRES Committee East Midlands – Derby 2, local R&D for each health board (11/EM/0420); and Northern Ireland ORECNI Ethical approval, local governance for each health Trust (11/EM/0420). The study was conducted in accordance with the Declaration of Helsinki.

Patient consent

Not required

Collaborators

Online Appendix B contains a list of the full ICBP Module 4 Working Group.

References

[1]   Y. Zhou, G.A. Abel, W. Hamilton, K. Pritchard-Jones, C.P. Gross, F.M. Walter, C. Renzi, S. Johnson, S. McPhail, L. Elliss-Brookes, G. Lyratzopoulos, Diagnosis of cancer as an emergency: A critical review of current evidence, Nat. Rev. Clin. Oncol. (2017). doi:10.1038/nrclinonc.2016.155.

[2]   Z. Chen, W. King, R. Pearcey, M. Kerba, W.J. Mackillop, The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature, Radiother. Oncol. (2008). doi:10.1016/j.radonc.2007.11.016.

[3]   R.D. Neal, P. Tharmanathan, B. France, N.U. Din, S. Cotton, J. Fallon-Ferguson, W. Hamilton, A. Hendry, M. Hendry, R. Lewis, U. Macleod, E.D. Mitchell, M. Pickett, T. Rai, K. Shaw, N. Stuart, M.L. Tørring, C. Wilkinson, B. Williams, N. Williams, J. Emery, Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review, Br. J. Cancer. 112 (2015) S92–S107. doi:10.1038/bjc.2015.48.

[4]   M.L. Tørring, A.Z. Falborg, H. Jensen, R.D. Neal, D. Weller, I. Reguilon, U. Menon, P. Vedsted, Advanced-stage cancer and time to diagnosis: An International Cancer Benchmarking Partnership (ICBP) cross-sectional study, Eur. J. Cancer Care (Engl). (2019). doi:10.1111/ecc.13100.

[5]   J. Wang, P. Mahasittiwat, K.K. Wong, L.E. Quint, F.M.S. Kong, Natural growth and disease progression of non-small cell lung cancer evaluated with 18F-fluorodeoxyglucose PET/CT, Lung Cancer. 78 (2012) 51–56. doi:10.1016/j.lungcan.2012.06.010.

[6]   S.R. Jensen OM, Parkin DM, MacLennan R, Muir CS, Cancer Registration: Principles and Methods, IARC Scien, International Agency for Research on Cancer, Lyon, France, 1991. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Cancer-Registration-Principles-And-Methods-1991.

[7]   R.J. Bergin, J. Emery, R.C. Bollard, A.Z. Falborg, H. Jensen, D. Weller, U. Menon, P. Vedsted, R.J. Thomas, K. Whitfield, V. White, Rural-urban disparities in time to diagnosis and treatment for colorectal and breast cancer, Cancer Epidemiol. Biomarkers Prev. 27 (2018). doi:10.1158/1055-9965.EPI-18-0210.

[8]   V. Gupta, K. Gu, Z. Chen, W. Lu, X.O. Shu, Y. Zheng, Concordance of self-reported and medical chart information on cancer diagnosis and treatment, BMC Med. Res. Methodol. 11 (2011). doi:10.1186/1471-2288-11-72.

[9]   S. Khoja, S.E. McGregor, R.J. Hilsden, Validation of self-reported history of colorectal cancer screening, Can. Fam. Physician. 53 (2007) 1192–1197.

[10]   M.B. Larsen, R.P. Hansen, I. Sokolowski, P. Vedsted, Agreement between patient-reported and doctor-reported patient intervals and date of first symptom presentation in cancer diagnosis - A population-based questionnaire study, Cancer Epidemiol. 38 (2014) 100–105.

doi:10.1016/j.canep.2013.10.006.

[11] B.M. Lynch, D. Youlden, L. Fritschi, B. Newman, K.I. Pakenham, B. Leggett, N. Owen, J.F. Aitken, Self-reported information on the diagnosis of colorectal cancer was reliable but not necessarily valid, J. Clin. Epidemiol. 61 (2008) 498–504. doi:10.1016/j.jclinepi.2007.05.018.

[12] E. Maunsell, M. Drolet, N. Ouhoummane, J. Robert, Breast cancer survivors accurately reported key treatment and prognostic characteristics, J. Clin. Epidemiol. 58 (2005) 364–369. doi:10.1016/j.jclinepi.2004.09.005.

[13] M.P. Coleman, D. Forman, H. Bryant, J. Butler, B. Rachet, C. Maringe, U. Nur, E. Tracey, M. Coory, J. Hatcher, C.E. McGahan, D. Turner, L. Marrett, M.L. Gjerstorff, T.B. Johannesen, J. Adolfsson, M. Lambe, G. Lawrence, D. Meechan, E.J. Morris, R. Middleton, J. Steward, M.A. Richards, Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the international cancer benchmarking partnership): An analysis of population-based cancer registry data, Lancet. 377 (2011) 127–138. doi:10.1016/S0140-6736(10)62231-3.

[14] J. Butler, C. Foot, M. Bomb, S. Hiom, M. Coleman, H. Bryant, P. Vedsted, J. Hanson, M. Richards, The International Cancer Benchmarking Partnership: An international collaboration to inform cancer policy in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom, Health Policy (New. York). 112 (2013) 148–155. doi:10.1016/j.healthpol.2013.03.021.

[15] M. Arnold, M.J. Rutherford, A. Bardot, J. Ferlay, T.M.-L. Andersson, T.Å. Myklebust, H. Tervonen, V. Thursfield, D. Ransom, L. Shack, R.R. Woods, D. Turner, S. Leonfellner, S. Ryan, N. Saint-Jacques, P. De, C. McClure, A. V Ramanakumar, H. Stuart-Panko, G. Engholm, P.M. Walsh, C. Jackson, S. Vernon, E. Morgan, A. Gavin, D.S. Morrison, D.W. Huws, G. Porter, J. Butler, H. Bryant, D.C. Currow, S. Hiom, D.M. Parkin, P. Sasieni, P.C. Lambert, B. Møller, I. Soerjomataram, F. Bray, Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study, Lancet Oncol. (2019). doi:10.1016/s1470-2045(19)30456-5.

[16] D. Weller, P. Vedsted, C. Anandan, A. Zalounina, E.O. Fourkala, R. Desai, W. Liston, H. Jensen, A. Barisic, A. Gavin, E. Grunfeld, M. Lambe, R.J. Law, M. Malmberg, R.D. Neal, J. Kalsi, D. Turner, V. White, M. Bomb, U. Menon, An investigation of routes to cancer diagnosis in 10 international jurisdictions, as part of the International Cancer Benchmarking Partnership: Survey development and implementation, BMJ Open. 6 (2016). doi:10.1136/bmjopen-2015-009641.

[17] J. Cohen, A Coefficient of Agreement for Nominal Scales, Educ. Psychol. Meas. 20 (1960) 37–46. doi:10.1177/001316446002000104.

[18] K.L. Gwet, Computing inter-rater reliability and its variance in the presence of high agreement, Br. J. Math. Stat. Psychol. 61 (2008) 29–48. doi:10.1348/000711006X126600.

[19] D. V. Cicchetti, A.R. Feinstein, High agreement but low kappa: II. Resolving the paradoxes, J. Clin. Epidemiol. 43 (1990) 551–558. doi:10.1016/0895-4356(90)90159-M.

[20]   J.R. Landis, G.G. Koch, The Measurement of Observer Agreement for Categorical Data, Biometrics. 33 (1977) 159. doi:10.2307/2529310.

[21]   L.I.-K. Lin, A Concordance Correlation Coefficient to Evaluate Reproducibility, Biometrics. 45 (1989) 255. doi:10.2307/2532051.

[22]   C. Quinn, M.J. Haber, Y. Pan, Use of the concordance correlation coefficient when examining agreement in dyadic research, Nurs. Res. 58 (2009) 368–373. doi:10.1097/NNR.0b013e3181b4b93d.

[23]   A.W.W. Lim, D. Mesher, A. Gentry-Maharaj, N. Balogun, M. Widschwendter, I. Jacobs, P. Sasieni, U. Menon, Time to diagnosis of Type i or II invasive epithelial ovarian cancers: A multicentre observational study using patient questionnaire and primary care records, BJOG An Int. J. Obstet. Gynaecol. 123 (2016) 1012–1020. doi:10.1111/1471-0528.13447.

[24]   D. Weller, U. Menon, A. Zalounina Falborg, H. Jensen, A. Barisic, A.K. Knudsen, R.J. Bergin, D.H. Brewster, V. Cairnduff, A.T. Gavin, E. Grunfeld, E. Harland, M. Lambe, R.J. Law, Y. Lin, M. Malmberg, D. Turner, R.D. Neal, V. White, S. Harrison, I. Reguilon, P. Vedsted, Diagnostic routes and time intervals for patients with colorectal cancer in 10 international jurisdictions; Findings from a cross-sectional study from the International Cancer Benchmarking Partnership (ICBP), BMJ Open. 8 (2018). doi:10.1136/bmjopen-2018-023870.

[25]   A. Retzer, D. Kyte, L. Calman, A. Glaser, R. Stephens, M. Calvert, The importance of patient-reported outcomes in cancer studies, Expert Rev. Qual. Life Cancer Care. 3 (2018) 65–71. doi:10.1080/23809000.2018.1472524.

[26]   L. Barbera, F. Lee, R. Sutradhar, Use of patient-reported outcomes in regional cancer centres over time: a retrospective study, C. Open. 7 (2019) E101–E108. doi:10.9778/cmajo.20180074.

[27]   K. Tran, S. Zomer, J. Chadder, C. Earle, S. Fung, J. Liu, C. Louzado, R. Rahal, R. Shaw Moxam, E. Green, Measuring patient-reported outcomes to improve cancer care in Canada: An analysis of provincial survey data, Curr. Oncol. 25 (2018) 176–179. doi:10.3747/co.25.3995.

[28]   J. Brandt, F. Scotte, K. Jordan, Patient-reported outcomes (pros) as a routine measure for cancer inpatients: The final missing piece of the puzzle?, Ann. Oncol. 30 (2019) 167–169. doi:10.1093/annonc/mdy524.

APPENDICES

Appendix A

Table A.1. Patients included in the analyses of routes to diagnosis (top) and milestone dates (bottom) in relation to identified patients

	Analysis of routes to diagnosis				
	Identified		**Included**		**p-value**
	n	(%)	n	(%)	
Gender					
Male	16416	(32,1)	1311	(29,2)	<0.001
Female	34801	(67,9)	3191	(70,9)	
Age group					
Under 40	219	(0,4)	0	(0,0)	
40-49	3882	(7,8)	381	(8,5)	
50-59	8602	(17,3)	941	(20,9)	
60-69	14284	(28,8)	1550	(34,4)	
70-79	14119	(28,4)	1168	(25,9)	<0.001
80-89	7593	(15,3)	435	(9,7)	
90+	852	(1,7)	27	(0,6)	
Missing	114	(0,2)	0	(0,0)	
Dead at					
3 months	4083	(23,9)	0	(0,0)	
6 months	3983	(23,3)	39	(14,1)	<0.001
9 months	4203	(24,6)	115	(41,5)	
12 months	4828	(28,2)	123	(44,4)	
Tumour stage[1]					
I	13039	(29,8)	1498	(33,3)	
II	10029	(22,9)	1186	(26,3)	
III	8730	(20,0)	1114	(24,7)	<0.001
IV	8996	(20,6)	527	(11,7)	
Missing	2921	(6,7)	177	(3,9)	

	Analysis of milestone dates				
	Identified		**Included**		**p-value**
	n	(%)	n	(%)	
Gender					
Male	16416	(32,1)	582	(25,5)	<0.001
Female	34801	(67,9)	1705	(74,6)	
Age group					
Under 40	219	(0,4)	0	(0,0)	
40-49	3882	(7,8)	235	(10,3)	
50-59	8602	(17,3)	495	(21,6)	<0.001
60-69	14284	(28,8)	806	(35,2)	

70-79	14119	(28,4)	545	(23,8)	
80-89	7593	(15,3)	193	(8,4)	
90+	852	(1,7)	13	(0,6)	
Missing	114	(0,2)	0	(0,0)	
Dead at					
3 months	4083	(23,9)	0	(0,0)	
6 months	3983	(23,3)	12	(9,6)	<0.001
9 months	4203	(24,6)	60	(38,4)	
12 months	4828	(28,2)	125	(52,0)	
Tumour stage[1]					
I	13039	(29,8)	774	(33,8)	
II	10029	(22,9)	672	(29,4)	
III	8730	(20,0)	554	(24,2)	<0.001
IV	8996	(20,6)	243	(10,6)	
Missing	2921	(6,7)	44	(1,9)	

[1] TNM classification for breast and lung cancers, TNM or Duke's classification for colorectal cancer, TNM or FIGO classification for ovarian cancer

Table A.2. Basic characteristics of patients included in the analyses of routes to diagnosis (top) and milestone dates (bottom) (n and % if nothing else stated) for each jurisdiction

Analysis of routes to diagnosis

	Wales	England	Scotland	N Ireland	Denmark	Ontario	Manitoba	Victoria
Breast cancer	(N=165)	(N=224)	(N=282)	(N=249)	(N=205)	(N=160)	(N=210)	(N=78)
Age (years), Median (IQI)	64 (53,70)	63 (55,70)	62 (54,70)	60 (51,70)	62 (54,70)	62 (55,68)	62 (53,70)	61 (52,66)
Comorbidity[1]								
None	119 (72)	168 (75)	188 (67)	189 (76)	129 (63)	106 (66)	143 (68)	56 (72)
Medium	45 (27)	54 (24)	89 (32)	56 (22)	76 (37)	47 (29)	65 (31)	22 (28)
High	1 (0.6)	1 (1)	4 (1)	3 (1)	0 (0)	0 (0)	2 (1)	0 (0)
Missing	0 (0)	1 (1)	1 (1)	1 (1)	0(0)	7 (4)	0 (0)	0 (0)
Colorectal cancer	(N=167)	(N=174)	(N=212)	(N=205)	(N=203)	(N=116)	(N=133)	(N=191)
Age (years), median (IQI)	71 (65,77)	70 (65,77)	69 (61,77)	67 (60,74)	70 (65,77)	68 (60,76)	69 (61,76)	66 (57,75)
Gender, male	103 (62)	101 (58)	122 (58)	121 (59)	118 (58)	71 (61)	71 (53)	109 (57)
Comorbidity[1]								
None	83 (50)	90 (52)	118 (56)	110 (54)	102 (50)	73 (63)	81 (61)	113 (59)
Medium	78 (47)	77 (44)	93 (44)	92 (45)	98 (47)	40 (34)	50 (38)	72 (38)
High	6 (4)	7 (4)	1 (1)	3 (1)	6 (3)	3 (3)	2 (2)	5 (3)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Lung cancer	(N=77)	(N=146)	(N=137)	(N=141)	(N=154)	(N=86)	(N=96)	(N=102)
Age (years), median (IQI)	69 (64,74)	71 (65,76)	69 (64,76)	69 (63,74)	68 (62,74)	70 (65,75)	71 (64,77)	69 (63,73)
Gender, male	41 (53)	76 (52)	80 (58)	77 (55)	76 (49)	44 (51)	43 (45)	58 (57)
Comorbidity[1]								
None	32 (42)	61 (42)	56 (41)	52 (37)	53 (34)	27 (31)	37 (39)	37 (36)
Medium	44 (57)	79 (54)	73 (53)	78 (55)	93 (60)	51 (59)	54 (56)	60 (59)
High	1 (1)	6 (4)	8 (6)	11 (8)	8 (5)	8 (9)	5 (5)	5 (5)
Ovarian cancer	(N=41)	(N=112)	(N=68)	(N=61)	(N=169)	(N=31)	(N=35)	(N=72)

Age (years), median (IQI)	62 (56,72)	64 (56,71)	63 (54,72)	63 (56,70)	66 (56,73)	60 (55,70)	61 (56,70)	61 (53,68)
Comorbidity[1]								
None	25 (61)	81 (72)	50 (74)	48 (79)	110 (65)	20 (65)	21 (60)	53 (74)
Medium	16 (39)	30 (27)	16 (24)	13 (21)	59 (35)	10 (32)	13 (37)	19 (26)
High	0 (0)	1 (1)	2 (3)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)

Analysis of milestone dates

	Wales	England	Scotland	N Ireland	Denmark	Ontario	Manitoba	Victoria
Breast cancer	(N=115)	(N=158)	(N=148)	(N=189)	(N=91)	(N=45)	(N=173)	(N=89)
Age (years), median (IQI)	64 (53,72)	63 (53,70)	62 (53,73)	59 (51,68)	63 (52,69)	62 (55,69)	62 (53,68)	57 (51,67)
Comorbidity[1]								
None	81 (70)	120 (76)	99 (67)	142 (75)	56 (62)	29 (64)	119 (69)	62 (70)
Medium	32 (28)	37 (23)	45 (30)	44 (23)	34 (37)	15 (33)	53 (31)	27 (30)
High	2 (2)	0 (0)	4 (3)	2 (1)	1 (1)	0 (0)	1 (1)	0 (0)
Missing	0 (0)	1 (1)	0 (0)	1 (1)	0(0)	1 (2)	0 (0)	0 (0)
Colorectal cancer	(N=97)	(N=88)	(N=106)	(N=127)	(N=87)	(N=23)	(N=86)	(N=50)
Age (years), median (IQI)	68 (62,76)	71 (64,80)	68 (60,76)	67 (61,73)	70 (65,76)	71 (62,80)	67 (57,75)	70 (60,76)
Gender, male	56 (58)	57 (65)	66 (62)	73 (57)	52 (60)	12 (52)	53 (62)	31 (62)
Comorbidity[1]								
None	53 (55)	48 (55)	59 (56)	62 (49)	42 (48)	12 (52)	57 (66)	27 (54)
Medium	43 (44)	37 (42)	46 (43)	63 (50)	44 (51)	10 (43)	28 (33)	21 (42)
High	1 (1)	3 (3)	1 (1)	2 (2)	1 (1)	1 (4)	1 (1)	2 (4)
Lung cancer	(N=45)	(N=67)	(N=45)	(N=82)	(N=54)	(N=6)	(N=46)	(N=15)
Age (years), median (IQI)	69 (64,75)	70 (65,75)	68 (64,78)	68 (61,74)	68 (63,73)	68 (64,71)	69 (64,77)	67 (60,79)
Gender, male	29 (64)	31 (46)	27 (60)	41 (50)	28 (52)	3 (50)	15 (33)	8 (53)
Comorbidity[1]								
None	16 (36)	25 (37)	22 (49)	33 (40)	24 (44)	2 (33)	23 (50)	6 (40)
Medium	27 (60)	39 (58)	22 (49)	44 (54)	28 (52)	3 (50)	23 (50)	8 (53)
High	2 (4)	3 (4)	1 (2)	5 (6)	2 (4)	1 (17)	0 (0)	1 (7)
Ovarian cancer	(N=29)	(N=84)	(N=30)	(N=40)	(N=15)	(N=7)	(N=21)	(N=29)
Age (years), median (IQI)	61 (58,71)	63 (56,72)	63 (50,69)	65 (56,71)	69 (49,77)	63 (52,68)	64 (56,70)	61 (53,65)
Comorbidity[1]								
None	17 (59)	61 (73)	24 (80)	31 (78)	9 (60)	6 (86)	13 (62)	22 (76)
Medium	12 (41)	22 (26)	6 (20)	9 (23)	6 (40)	1 (14)	8 (38)	7 (24)
High	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[1]Comorbidity coded as none (none reported), medium (1-2 reported) and high (3+ reported)

Abbreviations: IQI: inter-quartile interval

Table A.3. Sensitivity analysis exploring the implications of including patients for whom not all data sources reported status for all types of routes to diagnosis.

Agreement between different data sources as to whether a cancer case was presented through screening, symptomatic or other route for each type of cancer.

Route to diagnosis	Data sources	Overall agreement (%)	Kappa (95%CI)	AC1 (95%CI)
Breast cancer				
	Patient vs GP (n=1766)	93	0.85(0.83-0.88)	0.86(0.84-0.88)
Screening	Registry vs Patient (n=2046)	93	0.85(0.83-0.88)	0.85(0.83-0.88)
	Registry vs GP (n=1449)	94	0.89(0.86-0.91)	0.89(0.87-0.92)
Symptomatic	Patient vs GP (n=1766)	93	0.87(0.85-0.89)	0.87(0.85-0.89)
Other	Patient vs GP (n=1766)	91	0.16(0.08-0.24)	0.91(0.89-0.92)
Colorectal cancer				
	Patient vs GP (n=1287)	90	0.71(0.66-0.75)	0.85(0.82-0.87)
Screening	Registry vs Patient (n=1031)	91	0.78(0.74-0.82)	0.86(0.83-0.89)
	Registry vs GP (n=910)	95	0.86(0.82-0.90)	0.93(0.91-0.95)
Symptomatic	Patient vs GP (n=1420)	84	0.61(0.56-0.66)	0.75(0.72-0.78)
Other	Patient vs GP (n=1420)	82	0.09(0.03-0.15)	0.78(0.75-0.81)
Lung cancer				
Symptomatic	Patient vs GP (n=940)	80	0.11(0.04-0.19)	0.74(0.70-0.78)
Other	Patient vs GP (n=939)	74	0.09(0.02-0.16)	0.65(0.60-0.69)
Ovarian cancer				
Symptomatic	Patient vs GP (n=589)	86	0.11(0.00-0.22)	0.84(0.80-0.88)
Other	Patient vs GP (n=589)	80	0.06(-0.03-0.15)	0.75(0.70-0.80)

Abbreviations: CI: confidence interval, GP=general practitioner

Table A.4. Sensitivity analysis exploring the implications of including patients for whom not all data sources reported status for all types of dates.

Mean difference (in days), proportions of agreement and concordance correlation coefficient (CCC) for dates of first visit to primary care, diagnosis and treatment shown for each type of cancer and all types combined.

Type of date	Data sources	Mean difference in days	Fully agree (%)	Agree within 1 week (%)	Agree above 1 week (%)	CCC (95% CI)
Breast cancer						
First visit to PC*	GP vs Patient (n=928)	-5.9	44	24	32	0.90 (0.89, 0.91)
	GP vs Patient (n=1790)	1.4	24	35	41	0.94 (0.93, 0.94)
	Registry and Patient (n=2645)	-5.9	15	38	47	0.98 (0.98, 0.98)
Diagnosis	Registry and GP (n=1822)	-5.7	27	39	34	0.97 (0.97, 0.97)
	SP and Registry (n=1001)	-4.9	17	61	23	0.99 (0.98, 0.99)
	SP and Patient (n=989)	-1.0	16	49	35	0.93 (0.93, 0.94)

Treatment	SP and Patient (n=984)	2.4	62	15	23	0.89 (0.88, 0.90)
Colorectal cancer						
First visit to PC*	GP vs Patient (n=865)	-3.2	24	20	56	0.89 (0.88, 0.91)
	GP vs Patient (n=1462)	1.7	16	30	55	0.95 (0.94,0.95)
	Registry and Patient (n=2133)	-4.5	20	27	53	0.96 (0.96,0.96)
Diagnosis	Registry and GP (n=1517)	-5.0	28	28	44	0.96 (0.96,0.97)
	SP and Registry (n=835)	-5.1	19	51	30	0.96 (0.96,0.97)
	SP and Patient (n=813)	-0.6	9	42	49	0.94 (0.93,0.95)
Treatment	SP and Patient (n=785)	3.2	55	19	26	0.91 (0.90, 0.92)
Lung cancer						
First visit to PC	GP vs Patient (n=669)	0.03	18	19	64	0.90 (0.88, 0.91)
	GP vs Patient (n=1024)	11.9	8	22	69	0.93 (0.92, 0.94)
Diagnosis	Registry and Patient (n=1449)	4.0	4	21	74	0.96 (0.96,0.97)
	Registry and GP (n=868)	-9.9	23	25	53	0.96 (0.96,0.97)
	SP and Registry (n=452)	-10.7	24	32	44	0.97 (0.96,0.97)
	SP and Patient (n=575)	7.7	5	30	65	0.93 (0.92,0.94)
Treatment	SP and Patient (n=509)	2.4	45	24	31	0.94 (0.93,0.95)
Ovarian cancer						
First visit to PC	GP vs Patient (n=533)	5.0	36	20	44	0.91 (0.89, 0.92)
	GP vs Patient (n=653)	4,9	9	26	65	0.92 (0.91,0.93)
Diagnosis	Registry and Patient (n=959)	7.0	7	23	70	0.95 (0.95,0.96)
	Registry and GP (n=658)	-2.2	20	24	56	0.95 (0.94,0.96)
	SP and Registry (n=332)	-10.0	28	25	47	0.98 (0.97,0.98)
	SP and Patient (n=329)	5.3	7	30	63	0.96 (0.95,0.97)
Treatment	SP and Patient (n=317)	7.2	53	18	29	0.90 (0.88,0.92)
All cancers						
First visit to PC	GP vs Patient (n=2995)	-1.9	31	21	48	0.90 (0.90,0.91)
	GP vs Patient (n=4929)	4.1	16	29	54	0.94 (0.94,0.94)
Diagnosis	Registry and Patient (n=7186)	-1.8	13	29	57	0.97 (0.97,0.97)
	Registry and GP (n=4865)	-5.7	26	31	43	0.97 (0.96,0.97)
	SP and Registry (n=2620)	-6.6	20	48	32	0.97 (0.97,0.98)
	SP and Patient (n=2706)	1.7	11	40	49	0.94 (0.94,0.94)
Treatment	SP and Patient (n=2595)	3.2	56	18	26	0.91 (0.90,0.92)

*only for symptomatic patients

Abbreviations: CI: confidence interval, GP: general practitioner, PC: primary care, SP: cancer specialist

Table A.5. Basic characteristics of patients excluded and included in the analyses of routes to diagnosis (top) and milestone dates (bottom) (n and % if nothing else stated)

	Analysis of routes to diagnosis		
	Excluded (if at least one diagnostic route was missing) **(N=3,431)**	**Included** **(N=4,502)**	**p-value**
Age (years), Median (IQI)	67 (58,75)	66 (58,74)	0.018[1]
Gender, Male, among colorectal and lung cancer patients	956 (54)	1,311 (56)	0.179[2]
Comorbidity[3]			<0.001[2]
None	2,193 (64)	2,630 (58)	
Medium	1,055 (31)	1,761 (39)	
High	46 (1)	99 (2)	
Missing	137 (4)	12 (1)	

	Analysis of milestone dates		
	Excluded (if at least one date was missing) **(N=5,390)**	**Included** **(N=2,287)**	**p-value**
Age (years), Median (IQI)	67 (59,75)	65 (57,73)	<0.001[1]
Gender, Male, among colorectal and lung cancer patients	1609 (55)	582 (57)	0.247[2]
Comorbidity[3]			0.358[2]
None	3277 (61)	1402 (61)	
Medium	1868 (35)	844 (37)	
High	105 (2)	38 (2)	
Missing	140 (3)	3 (1)	

[1] Mann-Whitney U test
[2] Pearson's Chi[2] test
[1]Comorbidity coded as none (none reported), medium (1-2 reported) and high (3+ reported)
Abbreviations: IQI: inter-quartile interval

Appendix B

THE ICBP MODULE 4 WORKING GROUP

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