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Routes to diagnosis and the association with the prognosis in patients with cancer – A nationwide register-based cohort study in Denmark

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ABSTRACT

Background: The prognosis of cancer is related to how the cancer is identified, and where in the healthcare system the patient presents, i.e. routes to diagnosis (RtD). We aimed to describe the RtD for patients diagnosed with cancer in Denmark by using routinely collected register-based data and to investigate the association between RtD and prognosis measured as one-year all-cause mortality.

Methods: We conducted a population-based national cohort study by linking routinely collected Danish registry data. We categorised each patient into one of eight specified RtD based on an algorithm using a stepwise logic decision process. We described the proportions of patients with cancer diagnosed by different RtD. We examined associations between RtD and one-year all-cause mortality using logistic regression models adjusting for sex, age, cancer type, year of diagnosis, region of residence, and comorbidity.

Results: We included 144,635 cancers diagnosed in 139,023 patients in 2014–2017. The most common RtD were cancer patient pathway from primary care (45.9 %), cancer patient pathway from secondary care (20.0 %), unplanned hospital admission (15.8 %), and population-based screening (7.5 %). The one-year mortality ranged from 1.4 % in screened patients to 53.0 % in patients diagnosed through unplanned hospital admission. Patients with an unplanned admission were more likely to die within the first year after diagnosis (OR = 3.38 (95 %CI: 3.24–3.52)) compared to patients diagnosed through the cancer patient pathway from primary care.

Conclusion: The majority of cancer patients were diagnosed through a cancer patient pathway. The RtD were associated with the prognosis, and the prognosis was worst in patients diagnosed through unplanned admission. The study suggests that linking routinely collected registry data could enable a national framework for RtD, which could serve to identify variations across patient-, health-, and system-related and healthcare factors. This information could be used in future research investigating markers for monitoring purposes.

1. Introduction

Cancer accounted for almost 1.2 million deaths in the European Union in 2016, making it the second most common cause of death [1]. Cancer is the leading cause of death in many countries, including Denmark, where cancer accounted for 29 % of all deaths in 2018 [2].

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Although cancer survival is generally improving, survival rates still vary markedly across countries [3]. Denmark still lags behind other comparable countries [3,4].

While tumour stage, age, and comorbidities are among the principal factors affecting prognosis, research suggests that prognosis also relates to where and how cancer is identified within the healthcare system, i.e. routes to diagnosis (RtD) [5–10]. Studies from England and the United States have shown that cancer patients diagnosed through an emergency route have a worse prognosis than cancer patients diagnosed through other routes, even when patient characteristics and stage at diagnosis are taken into account [5,6,8,10]. In contrast, patients diagnosed through routine screening programmes have better survival compared to non-screened cancer patients [5]. However, it is unknown if the same pattern applies to other healthcare systems, such as the Danish, which is based on more outpatient care.

The process by which patients are referred to diagnostic workup (e.g. specific urgent referral routes) is also related to prognosis [5,7,11–15]. Several programmes, including the English two-week wait from referral to first specialist assessment and the Danish cancer patient pathways (CPPs), have been established to facilitate early diagnosis and treatment within certain time frames and following specific clinical guidelines [16,17]. However, it remains unknown whether Danish patients referred to a CPP have a better prognosis compared to non-CPP referred patients. Previous studies were based on small cohorts, selected cancer types [11], a single-centre population [12], or concerned the CPP for non-specific symptoms and signs of cancer (NSSC-CPP) [18].

In recent years, countries like England have increasingly linked data across existing data registries to create national cohorts of cancer patients and their RtD [5,6,19]. Although Denmark is well-renowned for complete and valid national registries [20], no national data set designating RtD for individual cancer patients exists.

This study aimed to describe RtD for patients diagnosed with cancer in Denmark by using routinely collected register-based data and to investigate the association between RtD and prognosis measured by one-year all-cause mortality. We hypothesised that RtD is significantly associated with one-year all-cause mortality, that screen-detected patients display the lowest mortality followed by patients diagnosed through CPPs, and that mortality is highest among patients diagnosed through a more acute route.

2. Materials and methods

This population-based national cohort study was based on routinely collected Danish registry data.

2.1. Data sources

We used data from Danish nationwide registries and clinical databases with high completeness and validity [20]. From *the Danish Cancer Registry*, we extracted diagnosis, date of diagnosis, tumour node and metastasis (TNM) classification, region of residence, age, and sex. From *the National Patient Registry*, we extracted data on contacts with somatic hospitals, information on inpatient and outpatient visits, dates, and CPPs. From *the Register of Causes of Death*, we obtained date of death. From the database of *the Danish Breast Cancer Group*, we obtained information on screening for breast cancer. From the database of *the Danish Colorectal Cancer Group*, we obtained information on screening for rectum and colon cancer. From *the Danish Quality Database for Cervical Cancer Screening*, we obtained information on screening for cervical cancer. Data were linked at the personal level using pseudomised personal registration numbers.

2.2. Study population

All patients registered in the Danish Cancer Registry with invasive cancer, excluding non-melanoma skin cancer (ICD-10: C00-C43 & C45-C97), in 2014–2017 and aged 18+ years at the time of diagnosis were included. Men diagnosed with breast cancer were excluded as no designated diagnostic pathway exists for this patient group in Denmark (Section 1 in Supplementary material).

2.3. Defining outcome

We used one-year all-cause mortality as an indicator of prognosis. For each patient, one-year mortality was defined as death of any cause within 365 days following the date of cancer diagnosis.

2.4. Defining and designating Routes to Diagnosis (RtD)

We defined RtD as the likely series of key interactions between patients and the healthcare system during the course from presentation to cancer diagnosis, based on how patients were referred to secondary care. However, unlike stage at diagnosis on which there is established international consensus, no such universally accepted definition exists for RtD of cancer. In principle, many unique patient pathways to diagnosis could be conceptualised [5,19]. However, parallel to Elliss-Brookes et al. [5], our approach focused on major types of healthcare encounters. The categorisation of RtD was based on cancer registrations for all identified patients in the Danish Cancer Registry, which were linked to data on all hospital contacts from the National Patient Register and data on screening recorded in the clinical databases.

Eight mutually exclusive RtD were defined:

1) **Death certificate only (DCO)**: Patients registered with DCO in the Danish Cancer Registry.
2) **Screening**: Patients registered in a clinical database as detected through a national screening programme and diagnosed with breast cancer, colon cancer, or rectal cancer. Screen-detected cervical cancer implied registration with positive smear test in the Danish Quality Database for Cervical Cancer Screening at up to three months before the diagnosis.
3) **Cancer patient pathway (CPP)–primary care**: Patients referred to a CPP (including the NSSC-CPP) by a health professional in primary care (i.e. irrespective of medical specialty) within three months before the diagnosis.
4) **Cancer patient pathway (CPP)–secondary care**: Patients referred to a CPP (including the NSSC-CPP) by a health professional in secondary care (e.g. a medical specialist in a hospital) within three months before the diagnosis.
5) **Unplanned hospital admission**: Patients registered with an acute inpatient hospital admission within 30 days before the diagnosis and none of the above routes before this.
6) **Planned hospital admission for other reasons than cancer**: Patients registered with a hospital admission planned within 30 days before the diagnosis and none of the above routes before this.
7) **Outpatient**: Patients with an outpatient visit (hospital specialist clinic) within 30 days before the diagnosis and none of the above routes before this.
8) **Unknown**: All others.

We categorised patients into groups of RtD based on an algorithm using stepwise logic decision process (Section 2 in Supplementary material). First, we defined DCO and screened cases. Second, we categorised the remaining cases according to the earliest route registered. In cases with multiple routes registered on the same day, we designated the route ranking highest in the order outlined above.

2.5. Defining other variables

We categorised age at the time of diagnosis into seven categories: 18−39, 40−49, 50−59, 60−69, 70−79, 80−89, and 90 or more years. Diagnosis was categorised into 23 specific diagnosis groups based on the

topography of the cancer (Section 3 in Supplementary material). We used TNM classification (7th edition) registered in the Danish Cancer Registry [21].

We used the Charlson Comorbidity Index (CCI) to assess the burden of comorbidity [22]. We calculated CCI score based on diagnoses (including previous cancers) registered in the National Patient Registry within the 10 years preceding the cancer diagnosis. Total CCI scores were grouped into: "low" (CCI score: 0), "moderate" (CCI score: 1–2), or "high" (CCI score: ≥ 3). Region of residence was categorised according to the five Danish administrative regions.

2.6. Statistical analyses

The study comprised a descriptive analysis of the RtD distribution and an analysis of the association between the patients' RtD and prognosis.

The descriptive analysis investigated the number and percentages of patients identified through the various RtD tabulated by sex, age, and diagnosis.

Logistic regression models were used to estimate associations between RtD and prognosis measured as all-cause mortality within one year of diagnosis. The regression analyses were performed both unadjusted and adjusted for sex, age, year of diagnosis, diagnosis, region of residence, and comorbidity. Standard errors were clustered at the individual patients. We excluded DCOs and patients emigrating from Denmark within one year after diagnosis (n = 133). CPP from primary care was used as reference category.

To test the robustness of the regression models, we performed sensitivity analyses. First, we reran the analyses using an alternative categorisation of the RtDs in which unplanned admissions took priority over all other routes, except for screening and DCO if they occurred on the same date. Second, we used tumour stage as an alternative indicator of prognosis with advanced tumour stage defined as TNM stage III and IV; this was only done for solid tumours (i.e. haematological cancers were excluded). Third, we reran the analyses, restricting the sample to first-time cancers only, i.e. excluding secondary primary cancers.

3. Results

We included 139,015 patients diagnosed in 2014–2017. A total of 144,635 cancers were identified; 96.1 % of patients had only one cancer during the inclusion period. Women constituted 48.8 % (70,568 cancers in 68,203 individuals) and men constituted 51.2 % (74,067 cancers in 70,812 individuals). The mean age was 67.2 years (standard deviation (SD): 13.1), and 22.8 % died within the first year after diagnosis (Table 1).

3.1. Distribution of routes to diagnosis

The majority of cancers were identified through a CPP from primary care (45.9 %) or secondary care (20.0 %) (Table 2). Screening detected 7.5 % of cancers, whereas 0.4 % were detected based on a DCO. Unplanned hospital admission accounted for 15.8 % of the cases. Finally, 3.1 % of the cases could not be assigned to a specific RtD (i.e. 'unknown' RtD).

RtD varied across age groups (Fig. 1); e.g. unplanned hospital admission ranged from 9% among patients aged 18−39 and 29 % among patients aged 90 or more. Screening allowed only for detection of cancers in women under the age of 80 and in men aged 50–79 by definition.

RtD also varied across cancer sites (Fig. 1). For instance, cancers diagnosed by a CPP through referral from primary care ranged from 19 % (eye, brain and central nervous system (CNS)) to 79 % (malignant melanoma), while cancers diagnosed by unplanned hospital admission ranged from 2% (malignant melanoma) to 37 % (pancreas). The percentages of screen-detected cancers were 29 % for breast, 21 % for colon, 19 % for rectal, and 35 % for cervical cancers.

Table 1
Characteristics of the included cancer patients aged ≥18 years stratified by sex (and total).

	Women		Men		Total	
Total, n (%)	70,568	(48.8)	74,067	(51.2)	144,635	(100.0)
Age at diagnosis, mean (SD)	66.2	(14.1)	68.1	(12.0)	67.2	(13.1)
Diagnosis group, n (%)						
Head & neck	1,193	(1.7)	2,716	(3.7)	3,909	(2.7)
Oesophagus	593	(0.8)	1,563	(2.1)	2,156	(1.5)
Stomach	857	(0.2)	1,664	(2.2)	2,521	(1.7)
Colon	7,259	(10.3)	7,708	(10.4)	14,967	(10.3)
Rectum	2,643	(3.7)	4,206	(5.7)	6,849	(4.7)
Liver	516	(0.7)	1,263	(1.7)	1,779	(1.2)
Pancreas	1,899	(2.7)	2,055	(2.8)	3,954	(2.7)
Lung	9,381	(13.3)	9,533	(12.9)	18,914	(13.1)
Melanoma	5,177	(7.3)	4,584	(6.2)	9,761	(6.7)
Breast	19,389	(27.5)	n/a		19,389	(13.4)
Uterus	3,286	(4.7)	n/a		3,286	(2.3)
Ovary	2,133	(3.0)	n/a		2,133	(1.5)
Female genitals	2,112	(3.0)	n/a		2,112	(1.5)
Prostate	n/a		18,184	(24.6)	18,184	(12.6)
Male genitals excl. prostate	n/a		1,469	(2.0)	1,469	(1.0)
Kidney	1,472	(2.1)	2,713	(3.7)	4,185	(2.9)
Bladder	976	(0.4)	2,724	(3.7)	3,700	(2.6)
Eye	1,041	(1.5)	1,372	(1.9)	2,413	(1.7)
Endocrine glands	1,119	(1.6)	471	(0.6)	1,590	(1.1)
Lymphoma	2,345	(3.3)	2,954	(4.0)	5,299	(3.7)
Multiple myeloma	843	(0.2)	1,095	(1.5)	1,938	(1.3)
Leukaemia	1,509	(2.1)	2,283	(3.1)	3,792	(2.6)
Other	4,825	(6.8)	5,510	(7.4)	10,335	((7.1)
Year of diagnosis, n (%)						
2014	17,481	(24.8)	18,430	(24.9)	35,911	(24.8)
2015	17,698	(25.1)	18,492	(25.0)	36,190	(25.0)
2016	17,633	(25.0)	18,529	(25.0)	36,162	(25.0)
2017	17,756	(25.2)	18,616	(25.1)	36,372	(25.1)
Cancer stage I-IV (TNM, version 7), n (%)						
I	15,381	(21.8)	7,381	(10.0)	22,762	(15.7)
II	9,272	(13.1)	5,451	(7.4)	14,723	(10.2)
III	5,834	(8.3)	6,033	(8.1)	11,867	(8.2)
IV	11,746	(16.6)	14,686	(19.8)	26,432	(18.3)
Missing or n/a	28,335	(40.2)	40,516	(54.7)	68,851	(47.6)
Charlson Comorbidity Index score, n (%)						
Low (CCI [a] = 0)	39,923	(56.6)	36,044	(48.7)	75,967	(52.5)
Moderate (CCI [a] = 1-2)	21,076	(29.9)	23,856	(32.2)	44,932	(31.1)
High (CCI [a] ≥3)	9,569	(13.6)	14,167	(19.1)	23,736	(16.4)
1-year all-cause mortality, n (%)						
Alive after 1 year	55,669	(78.9)	55925	(75.5)	111,594	(77.2)
Dead after 1 year	14,899	(21.1)	18,142	(24.5)	33,041	(22.8)

Abbreviations: n: number, SD: standard deviation, TNM: tumour, node, metastasis, CCI: Charlson Comorbidity Index, n/a: not applicable.

Table 2
Proportions of cancer cases by routes to diagnosis (RtD) shown as percentages with 95 % confidence intervals (CIs).

	Women n = 70,568		Men n=74,067		Total[a] N=144,635	
Routes to diagnosis (RtD)	%	(95% CI)	%	(95% CI)	%	(95% CI)
DCO	0.5	(0.4;0.5)	0.4	(0.4;0.5)	0.4	(0.4;0.5)
Screening	11.5	(11.3;11.7)	3.6	(3.5;3.7)	7.5	(7.3;7.6)
CPP – primary care	42.6	(42.3;43.0)	49.0	(48.7;49.4)	45.9	(45.7;46.2)
CPP – secondary care	21.6	(21.3;21.9)	18.5	(18.2;18.8)	20.0	(19.8;20.2)
Unplanned admission	14.9	(14.6;15.2)	16.7	(16.4;17.0)	15.8	(15.6;16.0)
Planned admission - other	1.0	(0.9;1.0)	1.1	(1.0;1.2)	1.0	(1.0;1.1)
Outpatient - other	5.1	(4.9;5.2)	7.4	(7.2;7.6)	6.3	(6.1;6.4)
Unknown	2.9	(2.7;3.0)	3.3	(3.1;3.4)	3.1	(3.0;3.2)

[a] Displayed numbers may not total 100.0 % due to rounding. Abbreviations: CPP: cancer patient pathway, DCO: death certificate only.

3.2. Route to diagnosis and prognosis

The proportion of patients who died within the first year after diagnosis varied by RtD, ranging from 1.4 % for screening to 53.0 % for unplanned hospital admission (Table 3). Across covariates, one-year mortality was highest in patients diagnosed through unplanned hospital admission, ranging from 18.1 % in patients aged 18−39 to 77.0 % in patients aged 90 or more (Table 3).

After adjustments for co-variates, patients with screen-diagnosed cancers displayed the lowest one-year mortality (odds ratio (OR) = 0.20 (95%CI: 0.17;0.24)), whereas patients diagnosed through unplanned hospital admissions displayed the highest one-year mortality (OR = 3.38 (95%CI: 3.24;3.52)), both compared to diagnosis through CPP referral from primary care (Table 4). Patients diagnosed through CPP referral from secondary care were also slightly more likely to die within the first year compared to patients diagnosed through CPP referral from primary care (OR = 1.09 (95%CI: 1.04;1.14)), while patients diagnosed through planned admission and the outpatient RtD displayed lower one-year mortality compared to patients diagnosed through CPP referral from primary care (OR = 0.78 (95%CI: 0.67;0.91) and OR = 0.93 (95%CI: 0.87;0.99), respectively).

3.3. Sensitivity analyses

Using alternative criteria to designate RtDs resulted in an additional 2.7 percentage point (18.5 %) of the cancers being categorised as unplanned admissions. The association between RtD and one-year all-cause mortality was largely similar when this alternative categorisation was used aside from CPP referral from secondary care displaying slightly lower 1-year mortality compared to CPP referral from primary care with this alternative hierarchy (OR = 0.95 (95%CI: 0.91;1.00)) (Section 4 in Supplementary material).

Analyses using TNM stage (instead of mortality) as an indicator of prognosis displayed overall parallel results, though here – contrary to the analyses with mortality – CPP referral from secondary care displayed slightly better prognosis (i.e. better stage) compared to CPP referral from primary care (OR = 0.85 (95%CI: 0.82;0.89)). Note, however, that TNM stage was missing or not applicable for a large share of the sample (43.3 %) (Section 5 in Supplementary material).

Analyses restricted to first-time cancers only (i.e. excluding patients with previous cancers (ICD-10: C00-C43 & C45-C97)), gave similar results, except for patients with "unknown" RtD, who displayed similar one-year mortality as patients diagnosed after "unplanned admission" (Section 6 in Supplementary material).

4. Discussion

This register-based nationwide study of 144,635 cancers demonstrated that two out of three cancer patients in Denmark were diagnosed through a CPP; more than two-thirds of these patients were referred from primary care. Three other main RtD were identified: unplanned admission (16 %), screening (8%), and outpatient admission (6%). The proportion of patients who died from any cause within the first year after diagnosis ranged from 1.4 % for screening to 53.0 % for unplanned hospital admission. Additionally, when we accounted for case mix and

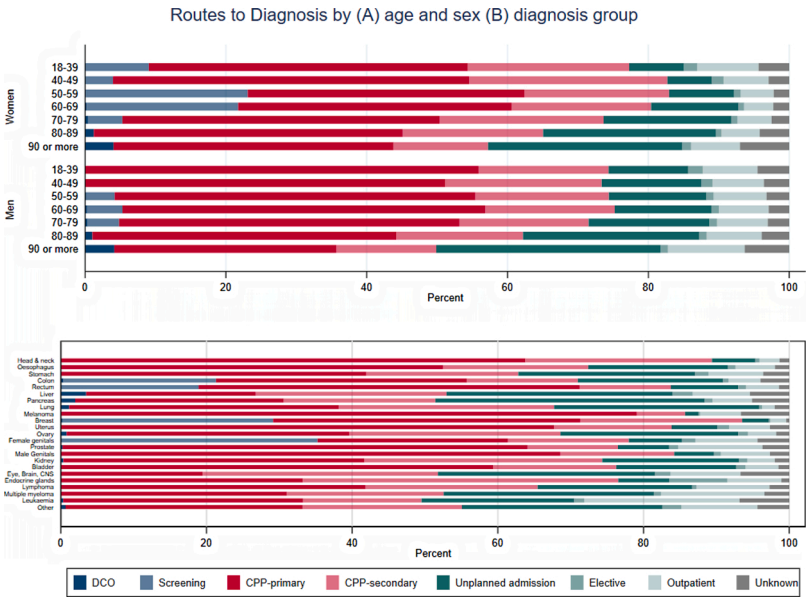

Fig. 1. Distribution (%) of RtD by sex and age group (top) and diagnosis (bottom).
Abbreviations: CPP: cancer patient pathway, DCO: death certificate only. RtD: routes to diagnosis. Note: An RtD with less than five cases in any subgroup was excluded to ensure personal confidentiality.

Table 3
One year all-cause mortality by route to diagnosis across covariates, expressed as percentages of individuals who died within the first year after diagnosis.

	Route to diagnosis							
	DCO	Screening	CPP – Primary care	CPP - Secondary care	Unplanned admission	Planned admission - other	Outpatient - other	Unknown
Total deaths (%)	100	1.4	15.6	22.6	53.0	16.8	16.0	33.7
Sex								
Women	100	0.8	14.9	19.1	53.0	15.7	17.8	38.3
Men	100	3.4	16.1	26.5	53.1	17.7	14.8	30.0
Age groups, years								
18–39	–	–	1.9	4.4	18.1	–	3.5	5.2
40–49	–	–	4.0	7.1	29.1	–	5.0	12.5
50–59	100	0.5	9.71	15.3	41.9	12.8	10.0	18.7
60–69	100	1.2	13.9	21.2	48.2	14.5	11.3	28.4
70–79	100	3.5	17.8	25.5	54.2	19.5	16.7	33.6
80–89	100	–	27.0	37.8	64.3	33.5	31.0	56.8
≥90	100	–	38.7	49.2	77.0	55.8	47.9	72.9
Comorbidity								
Low (CCI: 0)	100	0.9	12.3	17.7	46.1	10.9	10.2	27.0
Moderate (CCI: 1-2)	100	1.9	18.1	24.5	54.5	17.4	19.7	36.7
High (CCI: ≥3)	100	4.8	24.9	31.3	60.0	26.8	28.1	47.9
Year of diagnosis								
2014	100	1.4	15.6	22.9	54.5	16.8	17.0	36.5
2015	100	1.7	15.2	23.3	53.5	16.8	15.6	35.4
2016	100	1.5	15.5	21.9	51.8	15.4	14.7	33.4
2017	100	1.1	15.9	22.2	52.3	18.0	16.5	29.5
Region of residence								
North Denmark	100	1.1	14.0	28.2	54.3	18.6	14.8	32.9
Central Denmark	100	1.7	16.6	19.9	52.5	9.9	17.0	33.5
Southern Denmark	100	1.3	15.3	25.2	51.5	13.6	15.0	33.1
Capital	100	1.2	14.3	20.4	53.0	16.4	14.6	32.2
Zealand	100	1.6	17.4	22.3	55.0	27.6	20.5	39.3

Abbreviations: CCI: Charlson Comorbidity Index score, CPP: cancer patient pathway, DCO: death certificate only.
Note: "–" indicates suppressed numbers (less than five patients) to ensure personal confidentiality.

Table 4
Odds ratios (OR) for death of all causes within the first year after a cancer diagnosis according to the patient's route to diagnosis in Denmark.

	Adjusted[a] – case mix		Adjusted[b] – comorbidity	
Routes to diagnosis (RtD)	OR	(95%CI)	OR	(95%CI)
Screening	0.20	(0.17;0.24)	0.20	(0.17;0.24)
CPP – primary Care	1.00	Reference	1.00	Reference
CPP – secondary Care	1.12	(1.08;1.17)	1.09	(1.04;1.14)
Unplanned admission	3.54	(3.39;3.68)	3.38	(3.24;3.52)
Planned admission - other	0.82	(0.71;0.96)	0.78	(0.67;0.91)
Outpatient - other	0.95	(0.89;1.02)	0.93	(0.87;0.99)
Unknown	2.53	(2.34;2.73)	2.48	(2.29;2.68)

All cases diagnosed by a death certificate only were excluded.
[a] Adjusted for sex, age, diagnosis, year of diagnosis, and region of residence.
[b] Adjusted for sex, age, diagnosis, year of diagnosis, region of residence, and comorbidity. Abbreviations: RtD: Routes to Diagnosis, CPP: cancer patient pathway.

comorbidity, patients diagnosed through screening had the lowest likelihood of dying within the first year after diagnosis, whereas cancer patients diagnosed through an unplanned admission had the highest likelihood of dying.

4.1. Comparison with other literature

4.1.1. Route to diagnosis

The fact that CPP was the most common route (46 %) in our study mirrors the fact that the (analogous) two-week-wait route is also the most common in England (39 %) [5,23].

Our study suggests that a smaller proportion of Danish cancer patients were diagnosed by an acute route compared to an emergency route among English cancer patients (15.8 % in our study vs. 19 %–24 % in England) [5,6,23]. This is likely to be a result of differences in the organisation of the healthcare system in the two countries. The diagnostic workup and all appointments until potential surgical treatment are conducted as outpatient services for patients referred to a CPP in Denmark [16]. This implies that a smaller proportion of patients will be registered with unplanned admissions, especially among cases referred to more than one CPP in succession [24].

Only 7.5 % of all cancer cases were detected through screening, which concords with prior studies [5]. Yet, the proportion of cancers detected through a national population-based screening program is in line with the detection rates within each cancer type in Denmark [25].

Consistent with previous studies, RtD varied greatly by cancer site [5]. Differences across cancer sites are likely to reflect differences in symptoms, presentation, and specificity, thus also the degree to how easy or difficult the underlying cancer is suspected [26]. For instance, symptoms related to pancreatic and liver cancers are often non-specific compared to e.g. breast cancer and melanoma. As a consequence, liver and pancreatic cancers are more likely to be discovered incidentally at an early stage during an unplanned or elective hospital admission for other conditions, or the patients may not be diagnosed before being hospitalised with severe complications arising from the cancer itself when the neoplastic process has advanced. Other factors could be the extent to which the disease is likely to co-occur with other morbidities, which may weaken the clincal suspicion of an underlying cancer [27].

4.1.2. RtD and prognosis

The prognosis associated with the RtD in the present study is similar to findings in other populations. Patients diagnosed through screening display the best one-year survival, whereas patients diagnosed through more acute or unplanned routes have the worst one-year survival rate [5,6,23]. Screening often detects cancers prior to symptom presentation or when symptoms are prodromal. In contrast, unplanned admission occurs because the cancer is so advanced that it causes severe complications, or because of other acute or serious conditions that are likely to negatively affect the prognosis while masking the underlying cancer [19,28,29].

While patients diagnosed through a CPP referral from secondary care had a slightly worse prognosis compared to that observed in patients diagnosed CPP referral from primary care, the prognosis was somewhat better among patient diagnosed through planned hospital admission or outpatient admission. This contrasts previous findings from small-scale studies, which showed better survival among CPP patients in Denmark [11,12]. This discrepancy is likely to occur because these previous studies did not include a separate category for unplanned admission, which implies that these patients – who have a worse prognosis – were instead categorised as non-urgently referred patients.

The analysis using TNM stage, instead of one-year mortality, as an alternative marker of prognosis displayed parallel results [30]. However, the stage analysis should be evaluated in light of the missing data on disease stage that were missing for 48 % of the population. Yet, to the extent that the TNM stage analysis is still considered useful, it supports the conclusions regarding RtD and one-year survival.

Altogether, the identified associations between RtD and prognosis correspond to our theoretical expectations, and these findings increases the confidence in the categorisation of RtD. The findings also replicate the patterns from studies in the UK [5,6,30], although the survival reduction related to unplanned admission is larger in Denmark.

4.2. Methodological considerations

A major strength of the study is the high quality of data covering the entire population of patients with cancer in Denmark. Danish national registers are known to be reliable and to have high completeness [20,31]. The minor exclusions made to facilitate the analyses are unlikely to have affected the results substantially. Moreover, although registration errors do happen occasionally, they are unlikely to have systematically skewed the results. The results were similar in sensitivity analyses, which indicates that the method used was robust.

While the quality of the Danish registers is high, two principal limitations relate to the data. First, data on cancer stage were missing for nearly half the population. Second, patients might have died from other causes than cancer as the study used all-cause mortality [32]. However, for non-cancer mortality to cause bias in the observed variation in the mortality by diagnostic route, it would have to be markedly different. This seems unlikely as the asscoiation between prognosis and RtD remained practically unaltered after adjustment for comorbidity. Another limitation relates to our categorisation of RtD through the use of all hospital contacts during the last months preceding a cancer diagnosis [5,19]. Although not all hospital contacts within these preceding months are related to cancer, the assumption seems reasonable because cancer patients do have increased hospital contacts prior to a cancer diagnosis [5,33–35]. On this background, RtD were defined contextually, as opposed to a clinically definition relating to the patient's medical condition, in line with most related studies [30]. In spite of the contextual definition, our findings of high adverse prognosis among cases categorised as unplanned admissions support the validity of RtD as a marker of clinical severity.

4.3. Implications

Our study has three main implications. First, the findings support the feasibility of linking routinely collected Danish registry data and thereby enabling a national framework for categorising the routes by which cancer patients are diagnosed in Denmark. Second, by establishing a categorisation for RtD through existing Danish data, the study constitutes a stepping stone for further research aiming to explore associations between RtD and patient-, health- or system-related factors. Third, the categorisation of RtD can be used for monitoring purposes as a means to identify e.g. regional variation or developments related to specific cancer sites that may warrant further investigation or special attention.

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Ethical considerations

The study is part of the "Cancer in the Elderly" project, which is registered in the record of processing activities at the Research Unit for General Practice (RUGP) in accordance with Danish guidelines and the general data protection regulation (GDPR) of the European Union. The Danish Clinical Registries provided permission to receive and use data from the database of the Danish Breast Cancer Group (DBCG), the database of the Danish Colorectal Cancer Group (DCCG), and the Danish Quality Database for Cervical Cancer Screening (DKLS). According to Danish law, approval by the Committee on Health Research Ethics in the Central Denmark Region was not required as no biomedical intervention was performed.

Data availability

The data supporting the findings of this study are stored and maintained electronically at Statistics Denmark. The data are not publicly available due to the Danish legislation on data privacy.

Author contributions

BD and HJ conceived the study. All authors were involved in the development and design of the study. BD and HJ performed the statistical analyses and drafted the manuscript. All authors provided critical input to the intellectual content of the manuscript. All authors have read and approved the final version of the manuscript.

CRediT authorship contribution statement

Bolette Danckert: Project administration, Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Alina Zalounina Falborg:** Methodology, Data curation, Formal analysis, Writing - review & editing. **Niels Lyhne Christensen:** Methodology, Writing - review & editing. **Henrik Frederiksen:** Conceptualization, Methodology, Writing - review & editing. **Georgios Lyratzopoulos:** Conceptualization, Methodology, Writing - review & editing. **Sean McPhail:** Conceptualization, Methodology, Writing - review & editing. **Jesper Ryg:** Conceptualization, Methodology, Writing - review & editing. **Peter Vedsted:** Conceptualization, Methodology, Writing - review & editing. **Linda Aagaard Thomsen:** Writing - review & editing. **Henry Jensen:** Project administration, Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Henrik Frederiksen has received project grants from Novartis,Alexion, andGileadfor studies unrelated to this studies, and honoraria from Sanofi and Alexion for lectures on ttp and tma. All other authors declare to have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2021.101983.

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