The Danish lung cancer registry: A nationwide validation study

Gouliaev, Anja; Ali, Fatima; Jakobsen, Erik; Dalton, Susanne O.; Hilberg, Ole; Rasmussen, Torben R.; Christensen, Niels L.

Published in:
Lung Cancer

DOI (link to publication from Publisher):
10.1016/j.lungcan.2024.107527

Publication date:
2024

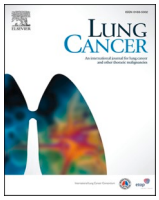
Document Version
Publisher's PDF, also known as Version of record

Lung Cancer 190 (2024) 107527

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



The Danish lung cancer registry: A nationwide validation study

Anja Gouliaev [a,b,*], Fatima Ali [c], Erik Jakobsen [d], Susanne O. Dalton [e,f], Ole Hilberg [g,h], Torben R. Rasmussen [a,b], Niels L. Christensen [a,b]

[a] Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus N, Denmark
[b] Department of Clinical Medicine, Aarhus University, Aarhus N, Denmark
[c] Department of Respiratory Diseases, Aalborg University Hospital, Aalborg, Denmark
[d] Department of Thorasic Surgery, Odense University Hospital, Odense, Denmark
[e] Survivorship & Inequality in Cancer, Danish Cancer Society Research Center, Copenhagen, Denmark
[f] Danish Research Center for Equality in Cancer (COMPAS), Department for Clinical Oncology & Palliative Care, Zealand University Hospital, Næstved, Denmark
[g] Department of Medicine, Lillebaelt Hospital, Vejle, Denmark
[h] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

ARTICLE INFO

Keywords:
Lung Cancer
Registries
Scandinavian and Nordic Countries
Epidemiology

ABSTRACT

Background: This study evaluates the validity of the information in the Danish Lung Cancer Registry (DLCR). Since 2000, the DLCR has been a tool for monitoring interventions and outcome of all Danish lung cancer patients with the intent to streamline and improve treatment and survival. The DLCR receives information from the Danish Patient Registries in addition to clinical information from the treating physicians. In the year 2022, more than 50 papers have been published using DLCR as a data source. However, the DLCR has not previously been validated.

Methods: A random sample of 1000 patients diagnosed with non-small cell lung cancer from 2014 to 2016 and recorded in the DLCR were included for validation. Medical records were reviewed and were considered as the "gold standard" to which data listed in the DLCR were compared.

Results: Information was retrieved from medical charts for all patients. Agreement on stage at diagnosis was 90.1 % (95 % CI 88.0–91.9) and on date of diagnoses was 93.8 (95 % CI 92.1–93.2). Agreement on smoking status in pack years (+/- 10 pack years) was 91.2 % (95 % CI 88.6–93.2). The positive predictive value of treatment intent was 87.4 (95 % CI 85.1–89.6).

Conclusion: The data in the DLCR are complete, detailed and accurate. The comparison of data from the DLCR with the medical records revealed overall high validity of the data in the registry.

1. Introduction

The Danish Lung Cancer Registry (DLCR) has monitored interventions and outcomes of all Danish patients diagnosed with lung cancer with a high level of completeness since its establishment in the year 2000 [1,2]. The aims of the DLCR are to evaluate treatment response and to compare and streamline treatment within the five administrative regions of Denmark, in order to improve lung cancer treatment and overall survival [3]. The DLCR was not initiated as a research tool, however, it has been utilized for clinical and epidemiological research in several studies [4]. Prospectively collected registry data are valuable for epidemiological research, as they reduce study costs and frequently enable larger study populations. As the DLCR collects data for administrative purposes unrelated to specific research questions, the risk of certain biases is reduced (e.g. recall and loss to follow-up). However, since the quality of such research depends on the robustness of the source registry data, it is essential to assess their validity [5].

The quality of a registry can be assessed in four different aspects: completeness, timeliness, comparability and validity [6,7]. Completeness is defined as the proportion of cases registered in the DLCR of all lung Danish lung cancer patient. Timeliness is defined as the time from the date of diagnosis of the cancer until it is registered in the DLCR. Comparability reflects the adherence in the DLCR to international standards such as tumor, node and metastasis classification (TNM), international classification of diseases (ICD) and pathology reporting

* Corresponding author at: Department,of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus N, Denmark.
E-mail address: a.gouliaev@rm.dk (A. Gouliaev).

https://doi.org/10.1016/j.lungcan.2024.107527
Received 7 December 2023; Received in revised form 26 February 2024; Accepted 28 February 2024
Available online 29 February 2024

standards. Validity is defined as the proportion of cases in a dataset with a given characteristic (e.g., site and age) that truly have the attribute, when comparing to medical charts as the "gold standard".

Completeness of the DLCR compared to the Danish Cancer Registry has previously been assessed [8]. In the current study, we present the first evaluation of the validity of data in the DLCR.

2. Materials and method

2.1. The Danish Health-Care setting

Health-care in Denmark is tax-funded and provide equal access to healthcare for all citizens regardless of social status or income. All permanent residents in Denmark have been assigned a unique personal identification number (CPR). The CPR number is used in all national registries supporting inter-registry linkage. The Danish Civil Registration System includes information on sex, date of birth, place of residence, emigration, immigration, disappearance and vital status [9]. The Danish National Patient Registry (DNPR) holds information on all hospital in- and outpatient contacts [10]. Denmark is divided in five administrative health-care regions with different medical record systems. Patients with suspicion of lung cancer are referred to the nearest pulmonary department at a university hospital or local community hospital for diagnostic procedures and evaluation. In 2022, 5043 Danish patients were diagnosed with lung cancer (47.9 % men and 52.1 % women), of whom 1259 (25.0 %) were treated surgically [11]. There are 13 departments of pulmonology involved in lung cancer evaluation, 4 departments of cardiothoracic surgery and 12 departments of oncology treating lung cancer in Denmark.

2.2. The Danish lung cancer Registry

The DLCR holds clinical information on Danish lung cancer patients since 2000. Patients are identified in the DNPR by any contact, in- or out-patient, with the diagnostic codes C34 and C33, according to the International Classification of Diseases, 10th Revision (ICD-10) [12,13]. The DLCR collects supplementary information from the Danish Pathology Register, which contains information from all Danish departments of pathology [14]. The Danish Pathology Register has previously been validated [14]. Furthermore, the entries in the DLCR are validated and provided with additional clinical information from the treating clinicians, while data on comorbidity and diagnostic procedures are obtained from the DNPR. All departments involved in the diagnostic process and/or treatment of lung cancer in Denmark report data to the DLCR, which is mandatory by law [1]. For all lung cancer patients, a general (diagnostic) form is used, and depending on treatment type additional surgical and/or oncology forms are completed. Vital status is retrieved from the Danish Civil Registration System once a month. Thus, the DLCR contains data on patient characteristics, diagnostic procedures, histology, tumor stage, lung function, performance status, comorbidity, treatment, possible treatment complications and vital status (Table 1). In addition, Denmark has a national cancer registry, The Danish Cancer Registry established in 1942, that receives information on all Danish cancer cases [15,16]. The Danish Cancer Registry does not contain clinical information, i.e. smoking status or treatment intent.

3. Method

We performed a nationwide cross-sectional validation study. We received data on all Danish lung cancer patients registered in the DLCR from January 1st 2014 until December 31th 2016 from the registry and identified patients with a diagnosis of non-small cell lung cancer (NSCLC). A random sample of 1000 NSCLC patients were obtained. Electronic medical records were retrieved on all patients. If medical record systems had been upgraded since 2014, historical records were retrieved. Information obtained from the medical records was considered as the "gold standard" to which data from the DLCR was compared. Medical records were reviewed, blinded from the data in the DLCR, with only access to the civil registration number. If data were not obtainable from the medical records, the data point would be classified as "unknown" and subsequently excluded from the analysis. Validation was performed from June 2022 through March 2023 by clinicians FA and AG. To validate the possible errors in the validation, data from 50 cases were re-abstracted from the medical records and compared to the first notations.

Table 1
Overview of the data in the DLCR.

Form	Variable
Diagnosis	WHO Performance status
	MDT conference decision (since 2021) (yes/no)
	Diagnostic work-up procedures performed
	Diagnosis incl histology
	TMN classification
Surgery	Date of referral and date of admission
	Neo adjuvant treatment
	Surgery delayed (yes/no)
	Risk factors (COPD, heart disease, others)
	Alcohol intake
	Date of surgery and discharge
	Surgical approach
	Treatment intent (curative/palliative)
	Surgery radical (yes/no)
	Pathology
	Post-operative complications
	Intensive care admission
	Lymph node malignancy
	TNM classification
Oncology	Date of referral
	Treatment delayed (yes/no)
	WHO Performance status
	Date of treatment
	Treatment type (chemo therapy, radiation, other)
	Treatment intent (curative, neo adjuvant, palliative)
	Reason for radiation

3.1. Statistical methods

Completeness was calculated as the number of correctly registered patients divided by the number of patients with information regarding the variable in the medical record. We used Wilsońs score methods to calculate 95 % confidence intervals (CIs). We calculated proportion of agreement for variables with several outcomes. In addition, we constructed 2 × 2 tables and computed positive predictive values (PPVs) and negative predictive values (NPVs) for each dichotomous variable.

3.2. Ethics

Registration in the DLCR was approved by the National Board of Health and the Danish Data Protection Agency. The present study was approved by the Danish Data Protection Agency (registration no. 1–45–70-80–21).

4. Results

The DLCR contained information on 14,216 patients in the study period 2014–2016 of whom 11,575 were diagnosed with NSCLC. Of the 1000 patient in the random sample, 16 were duplicates (Fig. 1). We were able to retrieve all of the 984 remaining medical records. Three patients were lost to follow-up due to emigration after being diagnosed with NSCLC. Six patients (0.6 %) were misclassified as NSCLC, when in fact their pathologic diagnosis was small cell lung cancer (SCLC), mesothelioma, breast cancer, colon cancer or nasal cancer (Fig. 1). One patient was diagnosed with NSCLC later than the study period, but had been surveilled for a lung nodulus since 2014. 974 cases remained for further

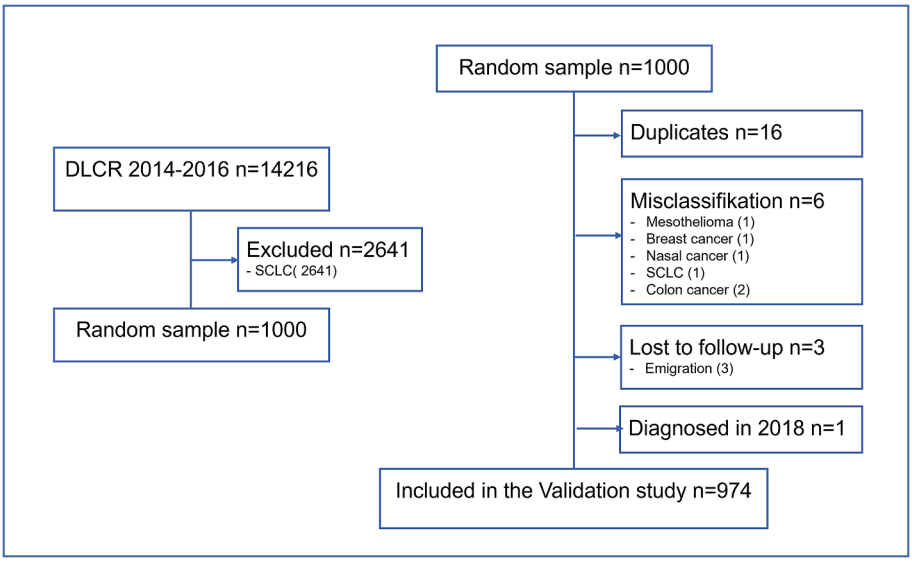


Fig. 1. Flow chart of patients. DLCR = Danish Lung Cancer Registry, SCLC = small cell lung cancer.

analysis.

Table 2 shows completeness and agreement of data in the DLCR compared to the medical charts. There was a concordance within 3 months on the date of diagnosis in 912 of the 972 patients (93.8 %) (two had missing data in the medical record) between the DLCR and the medical records. Agreement on stage at diagnosis was 90.1 %, treatment with curative intent was 92.3 %, performance status was 62.3 % and pack-years plus/minus 10 pack-years was 91.2 %.

Table 3 displays sensitivity, specificity and PPV of variables in the DLCR compared to the medical records. PPV values were generally high with exception of alcohol use and surgical complications.

The results of the small re-abstraction study can be found in the supplementary material. When comparing the two abstractions, there is a high concordance within treatment intent, treatment type, stage, but less agreement for pack years and performance status. The results display the difficulties in finding the "gold standard" for smoking history, as patients describe the use differently and pack years are noted differently in the chart. Similarly, performance status can be noted as "1–2" or different from the first statement at following medical consultation. The gold standard would be the performance status and smoking history noted in the multidisciplinary team meeting, where treatment options are discussed. In some charts, however, the information was not in the chart note from that meeting.

Table 2
Completeness and agreement of data registered in the DLCR compared to medical records. ECOG PS = Eastern Cooporative Oncology Group Performance Status.

Variable	Definition	n (correct/ observations)	Agreement, % (95 % CI)
Date of diagnosis	Date +/- 3 months	912/972	93.8 (92.1–95.2)
Stage at diagnosis	I, II, III, IV, unknown	846/939	90.1 (88.0–91.9)
Health Region	Capital Region of Denmark, Central Denmark Region, North Denmark Region, Region Zealand, Region of Southern Denmark	969/974	99.4 (98.6–99.7)
ECOG PS	0,1,2,3,4, unknown	555/891	62.3 (59.1–65.4)
Pack year	Correct +/- 10	540/592	91.2 (88.6–93.2)
Treated with curative intent		325/352	92.3 (89.0–94.7)
Treated with chemotherapy		382/417	91.6 (88.5–93.9)
Treated with radiation		323/406	79.6 (75.3–83.2)

5. Discussion

This is the first study to examine the validity of data in the DLCR. In this study, we evaluated the quality of the data by extensive review of nearly one thousand medical charts and found overall high data validity. Completeness of the DLCR has previously been accessed [8]. In 2013 and 2014, 9,111 lung cancer patients were identified in the Danish Cancer Registry (DCR) and 9,316 patients in the DLCR, of whom 87 % were in agreement. When they disregarded the study period the agreement increased to 95 %. The main discrepancies between registrations in the DCR and the DLCR were due to the different capture algorithms, different definitions of the dates of diagnosis or the use of slightly different data sources [8].

Other large population-based registries with data on lung cancer patients used for epidemiologic studies exist worldwide. One example is The US Surveillance, Epidemiology, and End Results (SEER) cancer registry, covers information on 48 % of the population. However, this registry has several limitations including lack of validation of the diagnosis and limited clinical data such as smoking and performance status, and to our knowledge, data in lung cancer patient registries have never been validated [17]. Another example is the association of the Nordic cancer registries (NORDCAN), an online platform with data on all cancers covering patients from all Nordic countries [18]. As with SEER, there are no clinical information in NORDCAN. Denmark is the only Nordic country with a separate clinical lung cancer registry, where other Nordic countries have national cancer registries with data on lung cancer patients [19].

Other Danish cancer registries have previously been validated by comparison to clinical charts. Arboe et al found PPV of 87–100 % and completeness of 92–100 % in the Danish National Lymphoma Registry, slightly better than the results of the validation of the DLCR [20]. A study validating the Danish Acute Leukemia Database found comparable low proportion of misclassification of diagnosis (0.4 %) [21]. However, only few centers in the country enter data to these registries compared to the much larger lung cancer setup.

This study found high PPV and completeness in the DLCR with exceptions of alcohol use, performance status and surgical complications.

Table 3
Sensitivity, Specificity and Predictive Values for variables in the DLCR. ECOG PS = Eastern Cooporative Oncology Group Performance Status. FEV1 = forced expiratory volume in the first second. DLCO = diffusing capacity of the lungs for carbon monoxide. VAT = video-assisted thoracic surgery.

Variable	N	Sensitivity, % (95 % CI)	PPV, % (95 % CI)	Specificity, % (95 % CI)	NPV, % (95 % CI)
Stage I-IIIA/IIIB-V	939	97.3 (96.2–98.3)	94.1 (92.5–95.6)	90.5 (88.6–92.4)	95.6 (94.3–96.9)
EGOC PS 0–1/2–4	848	78.7 (75.9–81.6)	74.8 (71.7–77.8)	91.7 (89.8–93.6)	93.2 (91.5–95.0)
Alcohol use (Surgical patients only)	144	45.0 (37.4–52.6)	47.4 (39.8–55.0)	93.1 (89.2–97.0)	92.5 (88.4–96.5)
FEV1 performed	644	100	100	100	100
DLCO performed	148	100	100	100	100
Curative intent (yes/no)	836	92.3 (90.5–94.1)	87.4 (85.1–89.6)	90.3 (88.3–92.3)	94.2 (92.6–95.8)
Chemo therapy (yes/no)	735	92.5 (91.1–94.8)	77.2 (74.1–80.2)	65.1 (61.7–68.5)	87.9 (85.6–90.3)
Radiation (yes/no)	735	80.8 (77.9–83.6)	72.9 (69.7–76.1)	64.2 (60.7–67.7)	73.6 (70.4–76.8)
Surgery (yes/no)	967	98.8 (98.1–99.4)	99.1 (98.5–99.7)	96.2 (95.1–97.4)	94.7 (93.3–96.1)
Surgical approach (VAT/thoracotomy)	151	87.4 (82.4–92.4)	100	100	71.4 (64.6–78.3)
Neo adjuvant treatment	135	98.4 (96.6–100)	78.3 (72.1–84.4)	20.5 (14.4–26.5)	81.8 (76.1–87.6)
Surgical complications (yes/no)	178	75.7 (69.5–82.1)	47.2 (39.8–54.5)	80.7 (74.9–86.5)	93.6 (90.0–97.2)

Performance status is occasionally stated differently throughout the medical record and not noted in the description from the MDT conference. Thus; it can be difficult to extract the "correct" performance status from records. In the supplementary data the same researcher only noted the same performance status in 37 out of 50 records when cross checking. In the DLCR, alcohol consumption is only registered for surgically treated patients, leading to a possible bias of the registry, as there is more information on patients treated surgically than oncological.

The perspective of a validation study as the current is partly to act as a reference for other studies using data from DLCR and partly to pinpoint where to improve on the data quality in the register. One example from the current study would be to make a note on performance status in the record of the MDT-meeting mandatory. Currently there is no registration of recurrence of lung cancer in the DLCR. However, a registration of recurrence through extraction of information from the DNPR and the Pathology Register is planned. Such registrations would also require validation based on the medical records.

The strength of this study is the extensive review of medical records from the entire country, in which all medical charts of the sample were reviewed. In total, our validation represents about seven percent of the patients in the database in the study period. We validated a high number of variables that are regarded as important covariates for the study of lung cancer prognosis. Medical records were chosen as the gold standard, because these data are accessible to clinicians when patients are recorded in the DLCR. A weakness of this study is that each medical record was reviewed by not two, but only one medical doctor (AG or FA). In addition, certain variables lend themselves more readily to validation, such as TNM stage and FEV1. In contrast, performance status poses a greater challenge for validation due to its inherently subjective nature. The DLCR included the variable "MDT conference decision" in 2021, after the present study period, therefore this variable was not validated in the present paper.

6. Conclusion

Population-based databases like the Danish Lung Cancer Registry (DLCR) are powerful research tools, provided that data in the database are valid: data are readily available at a low cost and with limited bias. With this validation study, we found that data from the DLCR compared to the medical records revealed overall high validity. Thus, the large amount of validated clinical and research-relevant data recorded for lung cancer patients in the DLCR makes it a valuable tool for research of lung cancer. Additional parameters of interest (e.g., socioeconomic position, comorbidity) can also be linked to the DLCR from other Danish registries.

Funding

The present study was funded by the Danish Cancer Society (grant no. R321-A17579) and supported by The Danish National Research Center for Lung Cancer, Danish Cancer Society (grant no. R198-A14299).

CRediT authorship contribution statement

Anja Gouliaev: Writing – original draft, Visualization, Validation, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fatima Ali:** Writing – review & editing, Data curation. **Erik Jakobsen:** Writing – review & editing, Supervision, Conceptualization. **Susanne O. Dalton:** . **Ole Hilberg:** Writing – review & editing, Supervision. **Torben R. Rasmussen:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Niels L. Christensen:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The study was funded by the Danish Cancer Society. Thank you to all departments that provided data to the study and to the Danish Research Center for Lung Cancer for support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107527.

References

[1] E. Jakobsen, T. Rasmussen, The Danish lung cancer registry, Clin. Epidemiol. 8 (2016) 537–541, https://doi.org/10.2147/CLEP.S99458.

[2] E. Jakobsen, T.R. Rasmussen, A. Green, Mortality and survival of lung cancer in Denmark: results from the danish lung cancer group 2000–2012, Acta Oncol. 55 (sup2) (2016) 2–9, https://doi.org/10.3109/0284186X.2016.1150608.

[3] E. Jakobsen, A. Green, K. Oesterlind, T.R. Rasmussen, M. Iachina, T. Palshof, Nationwide quality improvement in lung cancer care: the role of the danish lung cancer group and registry, J. Thorac. Oncol. 8 (10) (2013) 1238–1247, https://doi.org/10.1097/JTO.0b013e3182a4070f.

[4] The Danish Lung Cancer registry; [cited 2023 August 16]. Available from: https://www.lungecancer.dk/forskning-og-udtraek/publikationer/.

[5] V. Ehrenstein, S. Antonsen, L. Pedersen, Existing data sources for clinical epidemiology: Aarhus University prescription database, Clin Epidemiol. 2 (2010) 273–279, https://doi.org/10.2147/CLEP.S13458.

[6] D.M. Parkin, F. Bray, Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness, Eur. J. Cancer 45 (5) (2009) 756–764, https://doi.org/10.1016/j.ejca.2008.11.033.

[7] Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer. 2009 Mar;45 (5):747-55. doi: 10.1016/j.ejca.2008.11.032. Epub 2008 Dec 29. PMID: 19117750.

[8] J. Christensen, A. Mette, T. Kejs, L. Kristine, H. Schmidt, J. Søgaard, M.C. Rasted, O. Andersen, E. Jakobsen, D. Med, Agreement between the danish cancer registry and the danish lung cancer registry, Original Article Dan Med. J. 67 (8) (2020).

[9] C.B. Pedersen, The danish civil registration system, Scand J. Public Health. 39 (7 Suppl) (2011) 22–25.

[10] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical Epidemiology*. Published online November 2015:449. doi:10.2147/CLEP.S91125.

[11] The Danish Cancer registry; [cited 2023 August 18]. Available from: https://www.esundhed.dk/Registre/Cancerregisteret.

[12] E. Lynge, J.L. Sandegaard, M. Rebolj, The Danish National Patient Register, Scand. J. Public Health 39 (7_suppl) (2011) 30–33, https://doi.org/10.1177/1403494811401482.

[13] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H. T. Sørensen, The danish National Patient Registry: a review of content, data quality, and research potential, Clin Epidemiol. 7 (2015) 449–490, https://doi.org/10.2147/CLEP.S91125.

[14] B. Bjerregaard, O.B. Larsen, The danish pathology register, Scand. J. Public Health 39 (7_suppl) (2011) 72–74, https://doi.org/10.1177/1403494810393563.

[15] M.L. Gjerstorff, The danish cancer registry, Scand. J. Public Health 39 (7_suppl) (2011) 42–45, https://doi.org/10.1177/1403494810393562.

[16] H.H. Storm, E.V. Michelsen, I.H. Clemmensen, J. Phil, The danish cancer registry – history, content, quality and use, Dan. Med. Bull. 44 (5) (1997) 535–539.

[17] SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Jun 8; cited 2023 Aug 16]. Available from: https://seer.cancer.gov/statistics-network/explorer/.

[18] NORDCAN. Association of the Nordic Cancer Registries; [cited2023 August 16]. Available from: https://nordcan.airc.fr/.

[19] A. Gouliaev, T.R. Rasmussen, N. Malila, L. Fjellbirkeland, L. Löfling, E. Jakobsen, S. O. Dalton, N.L. Christensen, Lung cancer registries in Denmark, Finland, Norway and Sweden: a comparison and proposal for harmonization, Acta Oncol. 62 (1) (2023) 1–7, https://doi.org/10.1080/0284186X.2023.2172687. Epub 2023 Jan 30 PMID: 36718556.

[20] B. Arboe, T.C. El-Galaly, M.R. Clausen, P.S. Munksgaard, D. Stoltenberg, M. K. Nygaard, T.W. Klausen, J.H. Christensen, J.S. Gørløv, P.N. Brown, The danish National Lymphoma Registry: coverage and data quality, PMID: 27336800; PMCID: PMC4919044, PLoS One 11 (6) (2016) e0157999.

[21] L.S.G. Østgård, J.M. Nørgaard, M.T. Severinsen, H. Sengeløv, L. Friis, M.K. Jensen, O.J. Nielsen, M. Nørgaard, Data quality in the danish National Acute Leukemia Registry: a hematological data resource, Clin. Epidemiol. 5 (1) (2013) 335–344, https://doi.org/10.2147/CLEP.S48411.