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Research Paper

Risk of dementia among older patients with lymphoma: A Danish nationwide matched cohort study

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ABSTRACT

Introduction: Treatment of lymphoma can be associated with cognitive challenges, and some patients may fear development of dementia as long-term complication. Studies report a lower risk of dementia after cancer. Some believe this difference to be a protective mechanism of cancer, others believe it to be driven by bias. The risk of developing dementia after lymphoma has not been investigated in a population-based setting. The aim of this study was to identify the risk of being diagnosed with dementia after lymphoma treatment.

Materials and Methods: This Danish nationwide matched cohort study included patients aged ≥65 years with a first-time diagnosis of a non-central nervous system lymphoma between 2005 and 2018 in complete remission after treatment with chemotherapy. Patients diagnosed with dementia or treated with dementia medication before lymphoma diagnosis were excluded. Each patient was matched 1:5 on sex, year of birth, and a modified Charlson comorbidity index. Patients and matched comparators were followed from the corresponding patient's date of complete remission. The risk of developing dementia was calculated using cause-specific hazard ratios (HR), and the cumulative risk was estimated by Aalen-Johansen with death as the competing risk.

Results: A total of 3,244 patients and 16,220 matched comparators were included in the study. There was no difference in risk of all-cause dementia among patients with lymphoma compared to matched comparators with cause-specific HR of 0.85 (95% confidence interval [CI]: 0.70;1.04). The risk of both Alzheimer's disease and non-Alzheimer's dementia was equal among patients and comparators: HR 0.89 (95% CI: 0.66;1.21) and 0.82 (95% CI: 0.63;1.07), respectively. Stratified by lymphoma subtype, age, or year of diagnosis, the risk of all-cause dementia remained equal among patients and matched comparators. The cumulative risk of all-cause dementia was significantly lower among patients with lymphoma compared to matched comparators (Gray's test $p < 0.001$), probably reflecting higher mortality in patients with lymphoma.

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Discussion: The risk of all-cause dementia, Alzheimer's disease, and non-Alzheimer's dementia was equal among older patients with lymphoma compared to matched comparators. Our data suggests that risk of developing dementia is not changed after lymphoma treatment.

1. Introduction

Many patients with lymphoma are affected by cognitive impairment and reduced memory during treatment with chemotherapy and some patients may fear that dementia could be a long-term complication. Several studies have investigated the risk of dementia after cancer and cancer treatment. Many report a lower risk of dementia among patients with a previous cancer diagnosis [1–6]. Other studies question this and point towards bias-related challenges in the investigation of the association [7–12]. Most studies include patients with various cancer diagnoses making it difficult to estimate the association between individual cancer types and dementia. Lymphoma is a cancer type with an overall five-year survival rate of approximately 70% [13]. The median age of patients with non-Hodgkin lymphoma is 67 years [14]. As patients with lymphoma have a high median age at diagnosis and a high survival rate, this type of cancer is ideal for investigating age-related diseases such as dementia. Dementia covers a group of diseases causing damage to and changes in the brain affecting cognitive and social skills. The most common is Alzheimer's disease [15]. Globally, >5–7% of people over the age of 60 years are affected by dementia, with a higher prevalence in developed countries primarily due to longer lifespan [16,17]. The risk of dementia after lymphoma is scarcely investigated and often in smaller samples of patients [3,5,9]. A single study has included approximately 26,000 patients with lymphoma. This study reported a reduced risk of Alzheimer's disease, but an increased risk of non-Alzheimer types of dementia [2]. However, the study was conducted on a cohort of US male veterans, making results non-transferable to a general population.

This study aimed to identify the risk of all-cause dementia after cancer treatment in patients ≥65 years with non-central nervous system (non-CNS) lymphoma in a nationwide population-based cohort study.

2. Materials and Methods

2.1. Study Population

Patients with lymphoma were identified in the Danish National Lymphoma Registry (LYFO) [18], which includes data on almost all patients with lymphoma in Denmark (94.9%) [19]. The registry provides information on patient characteristics at baseline as well as disease-specific and treatment-related characteristics and outcomes.

We included patients with lymphoma meeting the following inclusion criteria: (a) age 65 years or above, (b) a first-time diagnosis with a non-CNS lymphoma between January 1, 2005 and December 31, 2018 and attained complete remission (CR) (including unconfirmed CR [CRu]) within the study period, (c) no prior diagnosis with or treatment for dementia before index date, (d) living in Denmark at the time of diagnosis and index date and, (e) lymphoma treated with chemotherapy. Patients were followed from the index date, defined as the date of attaining CR. Lymphoma subtypes were grouped as presented in Supplemental Table S1.

All patients were matched with five randomly selected comparators from the general Danish population based on the birth year, sex, and comorbidity status (same level of Charlson comorbidity index 180 days prior to the date of lymphoma diagnosis). The comparators were all identified in the Danish Civil Registration System (CRS) and were free of lymphoma and dementia before the index date for the corresponding patient [20,21]. Matched comparators were assigned the same index date as the corresponding patient.

2.2. Registries and Covariates

Since 1968, all Danish citizens have been assigned a personal identification number allowing individual and complete linkage across multiple registries.

The Danish National Patient Registry (DNPR) was used to calculate burden of comorbidity 180 days before date of diagnosis (or corresponding date for matched comparators) applying a modified Charlson comorbidity index excluding lymphoma and dementia [22–24]. The DNPR provides information on all inpatient contacts since 1977 and outpatient contacts since 1995 [25,26]. All diagnoses are classified according to International Classification of Diseases, version 8 (ICD-8) until 1994 and ICD-10 thereafter. Information on dementia was also extracted from the Danish Psychiatric Central Research Register [27]. Furthermore, to ensure information on patients with diabetes treated by a general practitioner, data on medication prescribed for diabetes was also retrieved from the National Prescription Registry [28,29].

Information on cohabitation status and level of education the year before the index date was found in the CRS and in the Danish Education Registries, providing data on the highest completed education [30]. Level of education was grouped according to the ISCED11 levels (ISCED 0–2, 3, 5–6 and 7–8) [31].

2.3. Dementia

The primary outcome was all-cause dementia defined as an ICD-10 code for dementia in the DNPR or the Danish Psychiatric Central Research Register or a redeemed prescription for dementia medication in the National Prescription Registry. In Denmark, patients with suspected dementia are diagnosed without cost within the secondary health system by a neurologist, a geriatrician, or a psychiatrist. Thus, all patients diagnosed with dementia in Denmark are registered with an ICD-10 code for dementia or have redeemed a prescription for dementia medication. The included ICD-10 for dementia and Anatomical Therapeutic Chemical (ATC) codes for dementia medication are shown in Supplemental Table S2. The ICD-10 codes for Alzheimer's disease, vascular dementia, frontotemporal dementia, and dementia unspecified have been validated and found to be correct in 85.8% of cases within the DNPR [32].

The date of dementia diagnosis was defined as the first date with either an ICD-10 code for dementia or a redeemed prescription for dementia medication. The ICD-10 code was used to define the type of dementia (Alzheimer's Disease [AD] or non-Alzheimer's dementia [non-AD]). If there was only a prescription date, the patient was classified as non-AD. This procedure was chosen as the included dementia medication (ATC-code N06D*) was used for treatment of both AD and non-AD (Lewy body dementia and dementia in Parkinson's disease) and information on indication is not available from the National Prescription Registry.

A sensitivity analysis with dementia defined as having at least two ICD-10 codes or redeemed prescriptions for dementia medication was performed to avoid misclassification of dementia. Patients with lymphoma and matched comparators were included and matched by the same approach as above.

2.4. Statistical Analysis

Patients and comparators were followed from index date until event (diagnosis of dementia), competing event (death), or censoring (emigration or December 31, 2018). Follow-up for matched comparators

was also terminated and treated as a competing event if they received a lymphoma diagnosis. The cumulative risk of all-cause dementia was estimated using the Aalen-Johansen estimator [33]. Gray's test was used to calculate differences in the cumulative risk [34]. When investigating the risk of specific dementia types (AD and non-AD dementia), the other dementia type was treated as a competing event.

Cause-specific hazard ratios (HR) were calculated using Cox regression. HR between patients treated with or without either anthracyclines or rituximab were reported both as crude and adjusted for sex, age (65–69, 70–74, 75–79, and ≥ 80 years), and year of diagnosis. The assumptions of proportional hazards were confirmed by visual inspection of the Schoenfeld residuals.

Median follow-up time was calculated by reverse Kaplan-Meier. Overall survival (OS) was reported as median survival time by Kaplan-Meier. Subgroup analyses were performed by using the comparators for the patients in the investigated subgroup.

Statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Gary, North Carolina, USA) and R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

2.5. Ethics Approval

The study was approved by the Danish Patient Safety Authority (3–3013-2536/1) and recorded in the research registry of the North Denmark Region (F2022–135).

3. Results

3.1. Patients and Comparators

The study included 3,244 patients and 16,220 matched comparators (Fig. 1). The median age was 72 years and 54.3% were male. The median time between diagnosis and index date was 26.9 weeks (interquartile range [IQR]: 21.6–32.7 weeks). Patients and matched comparators were followed for a median of 5.3 years. A total of 663 (20.4%) patients relapsed during follow-up. Relapse was primarily treated with chemotherapy (n = 488 [73.6%]), often in combination with immunotherapy (n = 335 [50.5%]). Baseline and clinical information is shown in Table 1. Patients fulfilling the inclusion criteria differed by age, year of diagnosis, and lymphoma subtype (Fig. 2). The use of chemotherapy was rather stable throughout the study period (Supplemental Fig. S1).

Overall survival differed between patients with lymphoma and comparators with a median survival of 8.3 years (95% confidence interval [CI]: 8.0;8.9 years) and 12.3 years (95% CI: 12.0;12.9 years), respectively. Median survival in subgroups is shown in Supplemental Table S3.

3.2. Risk of Dementia

A total of 114 (3.5%) patients with lymphoma were diagnosed with dementia (49 cases of AD) within the study period. Among comparators, 798 (4.9%) were diagnosed with dementia (330 cases of AD). The median time from index to diagnosis of dementia was 3.2 years (IQR: 1.5–6.2 years) for patients with lymphoma and 3.6 years (IQR: 1.7–6.3 years) for comparators. Time to dementia was not affected by subtype of

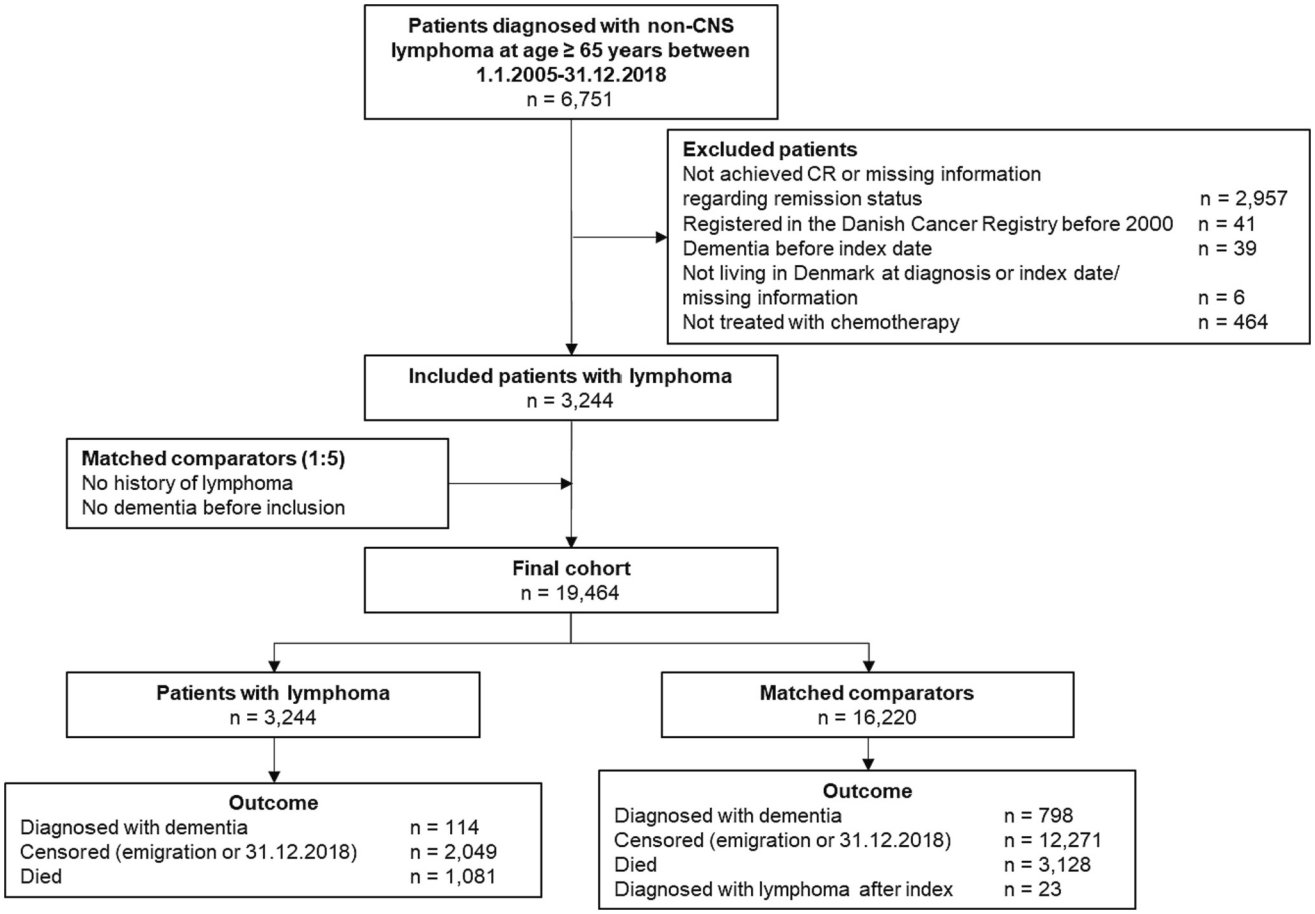

Fig. 1. Inclusion and outcome for patients and matched comparators.
Abbreviations: non-CNS, non-central nervous system.

Table 1
Baseline and clinical characteristics of patients and matched comparators.

	Lymphoma (n = 3244)	Comparators (n = 16,220)
Age, median (IQR)	72 (68–77)	72 (68–77)
Age group, n (%)		
65–69 years	1051 (32.4)	5265 (32.5)
70–74 years	1003 (30.9)	4993 (30.8)
75–79 years	649 (20.0)	3270 (20.2)
≥ 80 years	541 (16.7)	2692 (16.6)
Sex, n (%)		
Male	1763 (54.3)	8815 (54.3)
Female	1481 (45.7)	7405 (45.7)
Cohabitation status, n (%)		
Living alone	1124 (34.6)	5959 (36.7)
Living with partner	2120 (65.4)	10,206 (62.9)
Unknown	0 (0.0)	55 (0.3)
Level of education (ISCED), n (%)		
ISCED 0–2	1300 (40.1)	6494 (40.0)
ISCED 3	1233 (38.0)	6079 (37.5)
ISCED 5–6	494 (15.2)	2359 (14.5)
ISCED 7–8	148 (4.6)	766 (4.7)
Unknown	69 (2.1)	522 (3.2)
CCI prior to diagnosis, n (%)		
0	1730 (53.3)	8650 (53.3)
1	828 (25.5)	4140 (25.5)
≥ 2	686 (21.1)	3430 (21.1)
Year of diagnosis, n (%)		
2005–2008	684 (21.1)	
2009–2012	923 (28.5)	
2013–2015	847 (26.1)	
2016–2018	790 (24.4)	
Lymphoma subtype, n (%)		
Nodular lymphocyte predominant	8 (0.2)	
Classical Hodgkin lymphoma	203 (6.3)	
DLBCL	1902 (58.6)	
Intermediate lymphomas	274 (8.4)	
Indolent lymphomas	596 (18.4)	
Aggressive T-cell lymphomas	166 (5.1)	
Other aggressive B-cell lymphomas	27 (0.8)	
Other	68 (2.1)	
Ann Arbor stage, n (%)		
1–2	1015 (31.3)	
3–4	2194 (67.6)	
Unknown	35 (1.1)	
ECOG Performance status, n (%)		
0–1	2823 (87.0)	
2–4	404 (12.5)	
Unknown	17 (0.5)	
Chemotherapy, n (%)*		
CHOP-like	2263 (69.8)	
CVP	214 (6.6)	
Bendamustine	266 (8.2)	
ABVD	145 (4.5)	
Other chemotherapy	356 (11.0)	
Radiotherapy, n (%)		
No/unknown	2483 (76.5)	
Yes	761 (23.5)	
Immunotherapy, n (%)		
No	417 (12.9)	
Rituximab	2796 (86.2)	
Other	23 (0.7)	
Unknown	8 (0.2)	

Abbreviations: IQR, interquartile range; ISCED, International Standard Classification of Education; CCI, Charlson Comorbidity Index; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

* Chemotherapy is listed as the most potent regimen. CHOP-like includes CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP/EPOCH (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), MAXICHOP and CHOP with HD-ARAC. Other chemotherapy includes other regimens and single treatments not mentioned above.

dementia.

Patients diagnosed with lymphoma had a lower cumulative risk of all-cause dementia compared to the matched comparators (Fig. 3A); however, the crude cause-specific HR showed no difference between the two groups, HR 0.85 (95% CI: 0.70;1.04).

There was no difference in the cumulative risk of AD between patients with lymphoma and matched comparators, but the cumulative risk of non-AD was lower in patients (Fig. 3B-3C). The corresponding cause-specific HR was 0.89 (95% CI: 0.66;1.21) for AD and 0.82 (95% CI: 0.63;1.07) for non-AD.

3.3. Stratified Risk of Dementia

When stratified by age group, the cumulative risk of all-cause dementia was significantly lower for patients with lymphoma aged 70–74 and 75–79 years compared to matched comparators (Fig. 4). The cause-specific HR showed, however, no difference between patients and comparators in all age groups (Table 2).

Stratified by year of diagnosis, the cumulative incidence showed a lower risk of all-cause dementia for patients diagnosed in the period 2005–2008, but not in the period 2009–2018 (Fig. 5). However, the cause-specific HR was not different between patients and matched comparators for any of the time periods (Table 2).

Stratified by type of lymphoma or Ann Arbor stage, patients did not have a higher incidence of all-cause dementia than their matched comparators regardless of subgroup (Table 2).

Type of treatment had no impact on risk of dementia. Hence, we found no significant difference in the risk of all-cause dementia for patients treated with or without anthracyclines; crude and adjusted HR of 0.94 (95% CI: 0.60;1.48) and 1.11 (95% CI: 0.71;1.76). Similarly, there was no difference between patients treated with or without rituximab; crude and adjusted HR of 0.74 (95% CI: 0.46;1.18) and 0.74 (95% CI: 0.46;1.19).

When changing the definition of dementia to a minimum of two diagnoses in the sensitivity analysis, the cause-specific HR of all-cause dementia, AD, and non-AD showed no difference between patients and matched comparators (data not shown).

4. Discussion

This study reported the risk of a dementia diagnosis in a national cohort of patients ≥65 years diagnosed with non-CNS lymphoma and treated with chemotherapy. Overall, there was no difference in the risk of all-cause dementia among patients with lymphoma compared to matched comparators from the general population with a crude cause-specific HR of 0.85 (95% CI: 0.70;1.04).

Other studies have investigated the association between cancer and dementia. Many studies have found a lower risk of dementia in cancer survivors [1–7,9,11,12]. Some believe this to be a result of a protective mechanism in cancer survivors, while others believe it to be driven by study design and bias. Freedman et al. examined the risk of AD in 742,809 patients with cancer and found a reduced risk with of HR 0.87 (95% CI: 0.84–0.90) compared to a cancer-free population [7]. However, they attribute the difference to bias. Another large study by Ording et al. found a reduced risk with a standardized incidence rate ratio of 0.94 (95% CI: 0.92;0.96) [11]. They found that the risk approximated the risk of the general population over time. They concluded that due to the small difference between patients with cancer and the cancer-free population, the association was not clinically relevant. Hanson et al. studied the influence of mortality on the association between cancer and dementia [12]. They concluded that the protective association between cancer and dementia is driven by a higher rate of overall mortality among patients with cancer.

Frain et al. have examined the risk of dementia after lymphoma [2]. They identified a reduced risk of AD (HR 0.86 [95% CI: 0.73;0.99]), but an increased risk of non-AD (HR 1.11 [95% CI: 1.03;1.19]). The authors

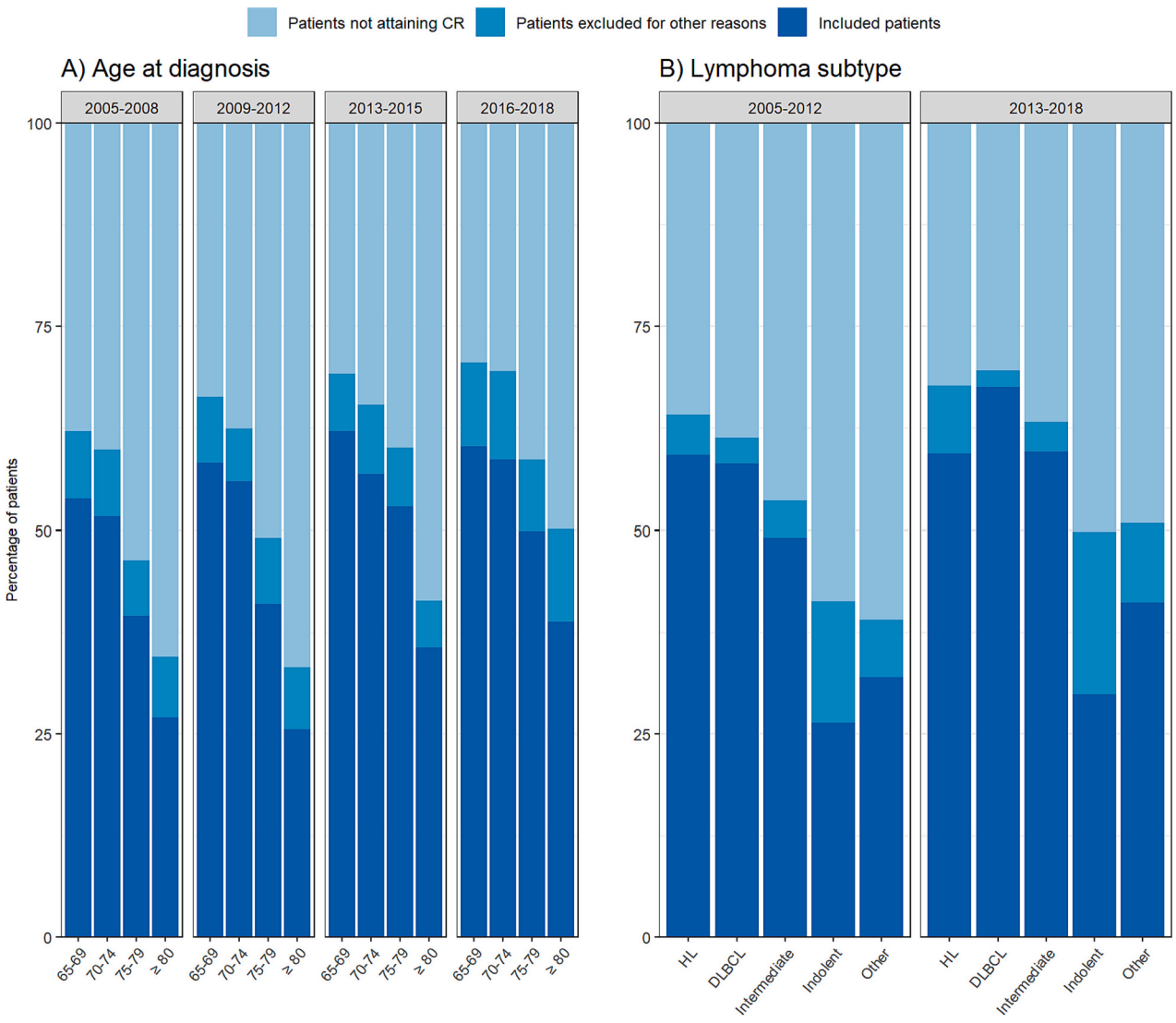

Fig. 2. Inclusion and exclusion of patients stratified by (A) age at diagnosis (65–69, 70–74, 75–79, and ≥ 80 years) and year of diagnosis (2005–2008, 2009–2012, 2013–2015, and 2016–2018) and by (B) lymphoma subtype (Hodgkin lymphoma [HL], diffuse large B-cell lymphoma [DLBCL], intermediate lymphoma, indolent lymphoma, and other [including aggressive T- and B-cell lymphoma]) and year of diagnosis (2005–2012 and 2013–2018). Patients with missing information on remission status are not included.
Abbreviations: HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

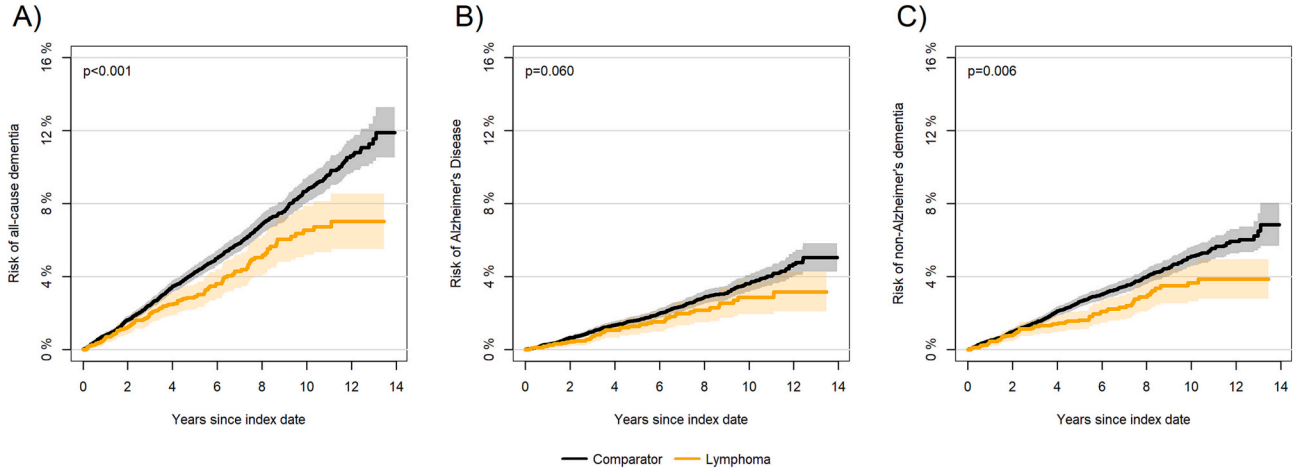

Fig. 3. Cumulative risk of (A) all-cause dementia, (B) Alzheimer's' disease, and (C) non-Alzheimer's dementia for patients with lymphoma and matched comparators.

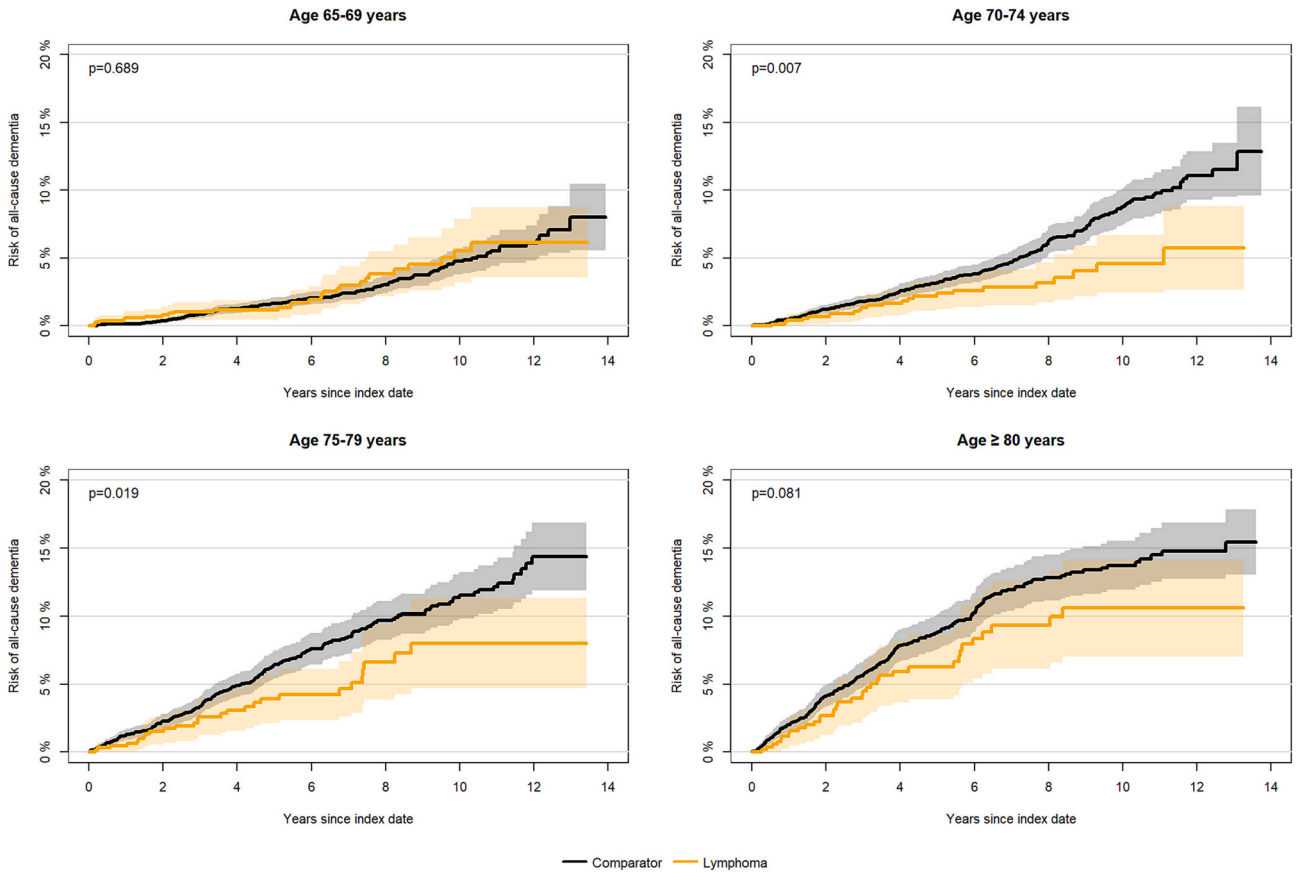

Fig. 4. Cumulative risk of all-cause dementia for patients with lymphoma and matched comparators grouped by age: 65–69 years, 70–74 years, 75–79 years, ≥80 years.

Table 2
Crude cause-specific hazard ratio (HR) in stratified risk of all-cause dementia in patients vs. matched comparators.

	HR (95% CI)	*P* value
All patients	0.85 (0.70;1.04)	0.11
Age group		
65–69 years	1.31 (0.87;1.98)	0.19
70–74 years	0.68 (0.45;1.04)	0.08
75–79 years	0.74 (0.50;1.11)	0.15
≥ 80 years	0.86 (0.60;1.23)	0.41
Year of diagnosis		
2005–2008	0.84 (0.62;1.14)	0.27
2009–2012	0.92 (0.66;1.28)	0.62
2013–2015	0.82 (0.52;1.29)	0.39
2016–2018	0.64 (0.25;1.62)	0.35
Lymphoma subtype		
Hodgkin lymphoma	1.14 (0.58;2.24)	0.70
DLBCL	0.89 (0.69;1.15)	0.36
Intermediate lymphomas	0.93 (0.48;1.80)	0.82
Indolent lymphomas	0.70 (0.44;1.11)	0.13
Aggressive T-cell lymphomas	1.11 (0.47;2.62)	0.81
Other aggressive B-cell lymphomas	NA	NA
Other	NA	NA
Ann Arbor stage		
1–2	0.95 (0.69;1.30)	0.74
3–4	0.80 (0.62;1.03)	0.09

Abbreviations: NA, Not Available; DLBCL, diffuse large B-cell lymphoma.

stated that this difference argues against the belief that the difference between persons with and without cancer is driven by a competing risk of death. The strength of the study by Frain et al. is the large cohort including 25,949 patients with lymphoma. However, all patients with lymphoma were male war veterans, thus the results are not transferable to a general population. Contrary to Frain et al., the present study found no difference in the risk of AD or non-AD for patients with lymphoma compared to matched comparators.

Among others, Hanson and Frain argued for and against the influence of survival bias when studying the association between cancer and dementia. Within the present study, we found median OS to be significantly lower among patients with lymphoma within all stratified analysis indicating potential survival bias (Supplemental table S3). This might be explained by increased mortality caused by the lymphoma alone. Furthermore, patients with lymphoma and cognitive impairment or undiagnosed dementia are less likely to be treated with chemotherapy [35], which increases their mortality. The same may apply to patients experiencing relapse, which could increase the mortality among patients. This higher mortality may mean that some patients do not live long enough to developed dementia. The latter may be the reason for the discrepancy between cumulative risk and cause-specific HR for all-cause dementia and non-AD found within this study. As cumulative risk is lowered with higher mortality, this might be the explanation for the significantly lower cumulative risk found in all-cause dementia and non-AD. The cause-specific HR is less influenced by competing events and is therefore a more appropriate effect measure in this study, where survival bias is inescapable due to the life-threatening nature of lymphoma. However, the cumulative risks are still useful for assessing the incidence of dementia in the current treatment era.

This study only included patients treated with chemotherapy who attained CR. It could be argued that these patients are more fit and less comorbid as their physical condition allows them to receive chemotherapy. Furthermore, there is a risk that patients with cognitive impairment before lymphoma diagnosis are not treated with chemotherapy. Both situations will introduce selection bias. However, we tried to reduce this by matching patients and comparators on level of

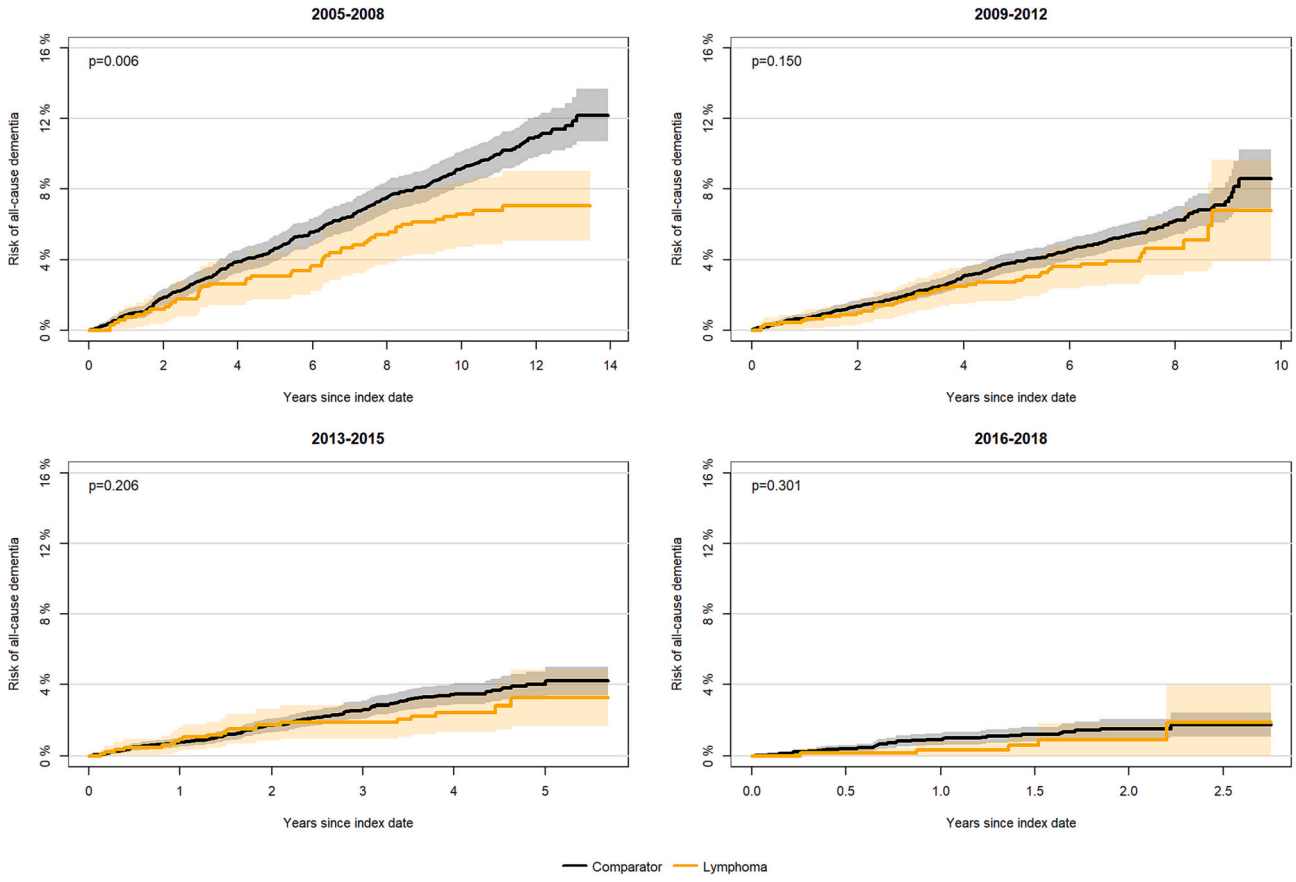

Fig. 5. Cumulative risk of all-cause dementia for patients with lymphoma and matched comparators grouped by year of diagnosis: 2005–2008, 2009–2012, 2013–2015, and 2016–2018. Please note different time axes.

comorbidity. We found the exclusion of patients not to be equally distributed between subgroups (Fig. 2). The exclusion of patients, primarily due to not attaining CR, was higher among the oldest patients but decreased for all ages during the study period. However, we did not find any difference in the risk of all-cause dementia in the stratified analysis, pointing towards a low impact of selection bias within this study.

Finally, when studying the association between cancer and dementia, there is a risk of surveillance bias as patients and comparators may be unequally monitored for symptoms or diseases. This may be the situation when patients receiving chemotherapy develop cognitive problems perceived to be cancer-related cognitive impairment (CRCI), which may persist for years and affects up to 70% of patients. This condition involving changed cognition, awareness, impaired executive functions, processing speed, and memory [36–38] can mimic dementia, possibly resulting in a lower rate of dementia diagnosis in patients with lymphoma. Furthermore, as lymphoma is a life-threatening disease, there is a risk that diagnostics of dementia in patients with cognitive impairment is not relevant due to the disease burden of the lymphoma or short life expectancy. Finally, patients with lymphoma are monitored extensively with blood tests, blood pressure assessments, and electrocardiography, enabling treatment and lifestyle changes that may decrease vascular risk factors known to affect the risk of both AD and vascular dementia [39]. On the other hands, patients with lymphoma have more regular contact with health care providers, increasing the likelihood of detecting cognitive changes, and thus early diagnosis of dementia.

Previous studies have examined biological associations between dementia and cancer. One explanation could be an association between inflammation and AD [40]. It is suggested that immunomodulating treatment of patients with cancer could contribute to the reduced risk of dementia. Our study did not find a significant difference in risk of all-cause dementia between patients treated with and without the anti-CD20 antibody rituximab. This was similar to a study investigating the risk of AD after rheumatoid arthritis treated with rituximab [41]. Other studies point towards a neuroprotective effect of chemotherapy, e.g., tyrosine kinase inhibitors [40] and anthracyclines [42], the latter being able to reduce tau tangles. The present study did not find a difference in risk of dementia between patients treated with and without anthracyclines, nor in the risk of AD.

Besides the low influence of selection bias, a strength of this study is the inclusion of essentially all patients diagnosed with lymphoma in Denmark from 2005 to 2018. Furthermore, the study is strengthened by the ability to conduct complete follow-up across registries. However, the study may be limited by surveillance bias. Furthermore, we cannot rule out that survival bias might have influenced the result even though we have tried to avoid it by only including patients in CR. The median follow-up time was 5.3 years, and even though this is acceptable for a cohort with a median age of 72 years, there is a risk that it might have limited the results, as dementia is a slowly developing disease. Finally, when using register-based data there is a risk of inaccuracy affecting the risk of dementia among both patients and matched comparators. There is a risk that patients without the relevant diagnostic work-out may be diagnosed with dementia based on symptoms reported by relatives or clinical presentation. This is supported by a study by Phung et al. that conducted a medical chart review and patient interviews and found dementia diagnosed in 2003 to be correct in the DNPR in 85.8% of the cases [32]. In the remaining cases, data was insufficient in 9.1% and dementia was ruled out in 5.1%. Second, there is a risk that doctors do not register a patient with a dementia diagnosis code when another disease is more relevant since it is common practice only to apply one diagnosis per encounter. The latter may be more present among patients

with lymphoma than matched comparators.

In conclusion, this national cohort study found no difference in the risk of developing dementia among older patients with lymphoma treated with chemotherapy compared to matched comparators. Therefore, our study suggests that dementia is neither to be considered as a late effect after lymphoma treatment nor is lymphoma per se a protective factor against dementia.

To further elucidate the association between cancer and dementia, more research is needed and may be addressed by investigating younger patients with cancer treated with modern therapy and with high survival rate to minimize bias.

Author Contributions

Conception and design: Eva Futtrup Maksten, Lasse Hjort Jakobsen, Boris Modrau, Hilde Jensvoll, Kristian Hay Kragholm, Tarec El-Galaly, Marianne Tang Severinsen.

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Analysis and interpretation of data: Data analysis was done by Eva Futtrup Maksten and Lasse Hjort Jakobsen. All authors participated in data interpretation.

Manuscript writing: Draft was written by Eva Futtrup Maksten, but all authors contributed to the writing and editing of the final manuscript.

Approval of final article: All authors.

Accountable for all aspects of the work: All authors.

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Declaration of Competing Interest

E.F.M., L.H.J., B.M., H.J., K.H.K., R.S.P., A.D-A., C.B.P., A.O.G., T.C. *E*-G., and M.T.S.: has nothing to declare.

J.M.J.: Advisory board/consultancy: Roche, Giled/KITE, Novartis, Celgene/BMS, Abbvie, SOBI, Incyte, and Orion.

M.R.C.: Consultancy: Gilead, AstraZeneca, AbbVie, Janssen, and Incyte. Travel Expenses: AbbVie, Genmab, and Roche. Speaker fee: Genmab.

T.S.L.: Advisory Board: Roche, Gilead, Novartis, and BMS.

P.B.: Advisory board/consultancy: Roche, Gilead and Swedish Orphar (SOBI).

Data Availability

All data used for this article is located at a server at Statistics Denmark in pseudo anonymized form. Data is only extractable as figures and tables, and therefore, no data sharing is possible.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101672.

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