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FEATURED ARTICLE

Cancer and risk of Alzheimer's disease: Small association in a nationwide cohort study

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Abstract

Introduction: Small observational studies with short-term follow-up suggest that cancer patients are at reduced risk of Alzheimer's disease (AD) compared to the general population.

Methods: A nationwide cohort study using Danish population-based health registries (1980-2013) with cancer patients (n = 949,309) to identify incident diagnoses of AD. We computed absolute reductions in risk attributed to cancer and standardized incidence rate ratios (SIRs) accounting for survival time, comparing the observed to expected number of AD cases.

Results: During up to 34 years of follow-up of cancer survivors, the attributable risk reduction was 1.3 per 10,000 person-years, SIR = 0.94 (95% confidence interval 0.92-0.96). SIRs were similar after stratification by sex, age, and cancer stage, and approached that of the general population for those surviving >10 years.

Discussion: Inverse associations between cancer and AD were small and diminished over time. Incidence rates in cancer survivors approached those of the general population, suggesting limited association between cancer and AD risk.

KEYWORDS

Alzheimer's disease, dementia, epidemiology, neoplasms, risk

1 | BACKGROUND

Several observational studies have shown reductions in risk for Alzheimer's disease (AD) or dementia subsequent to a cancer diagnosis.[1-9] An intriguing explanation involves opposing pathological processes, from uncontrolled cell proliferation in malignancy to neuronal cell death in AD and dementia.[10-13] An alternative explanation for the inverse association is failure to consider the competing risk of death among cancer patients, whose mortality rates are higher compared with individuals without cancer.[14] Moreover, clinicians may be less likely to pursue a dementia diagnosis in patients with life-threatening illness and shortened life expectancy, leading to an inverse detection bias.

A recent cohort study conducted in the state Washington found mixed evidence for an association between cancer and subsequent AD (hazard ratio [HR] = 0.95 [95% confidence interval [CI]: 0.77-1.17) for prevalent cancer at study inclusion and 0.73 (95% CI: 0.55-0.96) for incident cancer diagnosed during follow-up, with similar results before and after adjustment for a variety of potentially confounding factors.[15] The investigators stratified their analyses by prevalent cancer at study entry, by incident cancer diagnosed during follow-up, and by cancer stage; power was low due to a relatively small sample (n = 4357 participants aged 65+ years).[15] Other studies have reported similar findings or even greater risk reductions but have also had parallel limitations, lacking stratification by dementia subtypes or cancer stage or including no information on relevant comorbidities.[1-7,9,15]

In this nationwide cohort study with 34 years of follow-up, we examined the risk for AD, vascular dementia (VaD), and all-cause dementia in patients with a first primary cancer diagnosis and within specific primary cancer sites and stages compared to risk within the entire Danish general population.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the relevant literature in PubMed. Evidence from small observational studies with relatively short- term follow-up suggests that cancer patients are at reduced risk of Alzheimer's disease (AD) compared to people without cancer.
2. Interpretation: We found a 6% lower relative risk for diagnosis of AD and 4% for diagnosis of all-cause dementia during 34 years of follow-up after a cancer diagnosis. Our study adds to recent studies showing that cancer patients may have decreased relative and absolute risks for AD, although the magnitude of the association was much smaller than previously reported and diminished after 10 years, approaching that of the general population.
3. Future directions: Further research should assess whether the small inverse association between cancer and AD represents shared factors that influence the initiation or progression of both disorders to a modest extent, or reflects unrecognized confounding or bias.

2 | METHODS

2.1 | Setting and data sources

The Danish health care system provides tax-supported health care to all residents. Nationwide registries track diagnoses, procedures, and vital status for the entire population. These registries can be linked accurately using the unique civil personal registration number assigned to all Danish residents at birth or upon immigration. The Civil Registration System (CRS) records emigration and vital status.[16]

The Danish Cancer Registry (DCR) maintains information on all incident cancers diagnosed in Denmark since 1943, including morphology, histology, and stage at diagnosis.[17] The Danish National Patient Registry (DNPR) has recorded all inpatient discharge diagnoses given to patients since 1977 and diagnoses made at hospital outpatient clinics since 1995.[18] The Psychiatric Central Research Registry (PCRR) has similarly recorded inpatient psychiatric diagnoses given to patients since 1969 and diagnoses made at psychiatric outpatient visits since 1995.[19] These registries coded diagnoses according to the *Eighth Revision* of the *International Classification of Diseases* (ICD-8) until 1993 and according to the ICD-10 starting in 1994.[18] The diagnostic codes used in this study are provided in Appendix Table A.

2.2 | Design and study population

We established a cohort of patients with a first incident primary cancer diagnosed during 1980-2013 recorded in the DCR. Although benign neoplasms were not regarded as cancer, benign neoplasms of the brain and meninges were included in the analysis, because these conditions may cause neurologic symptoms similar to those caused by malignancy. We excluded patients with prevalent dementia diagnosed in an inpatient or outpatient setting up to and including the date of cancer diagnosis. We first analyzed all cancer sites in aggregate. We then selected some of the most common cancer sites and those that have been associated with dementia in previous studies[2,4,7,9,15,20]—bladder, brain, breast, colon, kidney, leukemia, lung, melanoma, non-melanoma skin cancer, pancreatic cancer, and prostate cancer—for separate analysis because of varying biology and prognosis. The large size of the Danish data is a notable strength of this study because it permits analysis by cancer type. Specificity of associations with only some types of cancer might give insight into the biological phenomena underlying the association or implicate particular types of bias, but prior studies have generally been too small to provide statistically precise estimate for particular cancer types. Information on cancer stage at diagnosis was collected for solid tumors. In total 15,270 cancer patients were excluded from the study due to dementia or a diagnosis likely to represent prodromal dementia (mild cognitive impairment or amnestic syndrome) before or on the cancer diagnosis date, leaving 949,309 cancer patients for analysis.

For patients with the selected cancer types (n = 679,122), we also included a general population comparison cohort without any prevalent cancer diagnosis and dementia, mild cognitive impairment, or amnestic syndrome, and matched them up to 5:1 within 1 year of birth, sex, and exact index year of cancer diagnosis.

We obtained information on inpatient and outpatient hospital diagnoses of comorbidities included in the Charlson Comorbidity Index (CCI) that were diagnosed before the cancer diagnosis date and information on receipt of chemotherapy within 3 months after cancer diagnosis.[21]

2.3 | End points and follow-up

Patients and their comparators were followed from their cancer diagnosis/index date until a record of incident dementia (either AD, VaD, or all-cause dementia [including unspecified dementia, Pick disease, Creutzfeldt-Jakob disease, Huntington disease, HIV dementia, Parkinson disease dementia, Lewy body dementia, progressive supranuclear palsy, and other specified and unspecified diseases]) recorded in the DNPR or the PCRR, death, emigration from Denmark, or December 31, 2013, whichever occurred first.

2.4 | Analytic variables

Age on the index date was categorized (<50, 50-59, 60-69, 70-79, and ≥80 years) and comorbidity burden was classified using the CCI,[21] excluding malignancy and dementia. An individual's score weights were defined as total scores of 0, 1, 2-3, and ≥4, and conditions comprising the CCI were also examined individually. Cancer was analyzed as all types combined and by the predefined specific cancer sites. Stage at diagnosis for solid tumors was categorized as localized, regional, distant, and missing/unknown. Dementia was classified as AD, VaD, and all-cause dementia.

2.5 | Statistical analysis

We characterized cancer patients according to baseline characteristics. The potential reduction in dementia cases per 10,000 person-years was computed as the expected minus the observed number of cancer cases divided by the person time in days. We calculated standardized incidence rate ratios (SIRs) as a measure of relative risk by comparing observed dementia incidence among cancer patients with that expected, based on single years of age-, sex-, and single calendar-year-standardized incidence in the general population, and stratified by baseline characteristics. Associated 95% CIs were derived using Byar's approximation, assuming that the observed number of cases in a specific category followed a Poisson distribution. We used exact 95% CIs when the observed number of cancers was <10. Analyses were then stratified for cancer survivors by 0-1 year, >1-5 years, >5-10 years, >10-20 years, and >20-34 years of follow-up. To examine potential effects of chemotherapy or radiotherapy, we repeated the analysis for cancer patients diagnosed in 2004 or later receiving any chemotherapy or radiotherapy by follow-up periods.

A Cox proportional hazard regression analysis was conducted using patients with the pre-specified cancer types separately and compared with their matched general population comparators in a stratified Cox analysis within the matched factors and follow-up periods as described above.

We conducted a number of sensitivity analyses. Our initial coding classified senile dementia (ICD-8) and unspecified dementia (ICD-10) as all-cause dementia. To account for potential miscoding, we conducted sensitivity analyses that re-categorized these as AD rather than all-cause dementia, with no effect on our results. We also conducted an analysis that included only inpatient diagnoses of dementia. We then repeated the analysis including mild cognitive dementia or amnestic syndrome in the dementia outcome. Finally, for the overall estimates we calculated E-values for dementia SIRs using the formula for HRs with rare outcomes (<15%).[22] The E-value describes the strength that an unmeasured confounder or set of confounders would need to have with both the exposure and outcome (assuming these two associations were equal) to fully explain the observed-exposure-outcome association).[22]

3 | RESULTS

3.1 | Characteristics of the cancer cohort

A total of 949,309 cancer patients were included in the study (48.3% male), involving 5,242,643 person-years of observation. Median age at cancer diagnosis was 67 years (interquartile range [IQR]: 57-76 years). The median follow-up was 3.1 (IQR: 0.70-8.1) years for cancer patients with specific cancer types and 7.2 (IQR: 3.3-13.2) years for population comparisons. The majority of cancer patients had no comorbidities at diagnosis (74%) (Table 1).

3.2 | Risk of dementia after cancer

Table 2 shows the observed and expected number of dementia cases with corresponding SIRs and the absolute reduction in risk attributed to cancer per 10,000 person-years by descriptive characteristics and by follow-up period. During 34 years of follow-up, the observed to expected number was 10,048/10,725 cases of AD, 3598/3930 cases of VaD, and 28,544/29,723 cases of all-cause dementia.

After any cancer diagnosis, we observed a modestly reduced SIR for all-cause dementia (SIR: 0.96, 95% CI: 0.95-0.97). The absolute reduction in dementia risk attributed to cancer was 2.2 per 10,000 persons. Similar reductions were observed for AD and VaD and for males and females. SIRs for all-cause dementia and AD were above 1.0 for individuals with higher CCI scores and for individuals with most individual comorbid conditions, but were under 1.0 (SIR = 0.91 [95% CI: 0.84-0.99]) for AD patients with comorbidity scores of 2-3. Stratified by age group at cancer diagnosis or cancer treatment with chemotherapy or radiotherapy, the risks for all-cause dementia, AD, or VaD were reduced or near unity (Table 2). When stratified by follow-up period, the long-term (34-year) relative risk of dementia among cancer survivors approached a null association for AD and all-cause dementia, although not for VaD. The inverse associations between cancer and AD and all-cause dementia were somewhat more pronounced for a cancer diagnosis in recent years (from 1995 onward) than in earlier years (Table 2). In a sensitivity analysis including only inpatient diagnoses, the SIR for all-cause dementia was 0.94 (95% CI: 0.93-0.95), compared to 0.96 (95% CI: 0.95-0.97) in the primary analysis.

In the analysis that added mild cognitive impairment and amnestic syndrome to the definition of dementia, the number of observed all-cause dementia cases increased to 29,745 from 28,544 in our primary analysis and the association between cancer and dementia was similar to the primary analysis (SIR = 0.97; 95% CI: 0.96-0.98).

Based on SIRs for the primary analysis, we estimate E-values as 1.32 for AD, 1.39 for VaD, and 1.25 for all-cause dementia.

We found diverging results by specific cancer sites, although the stage-stratified analyses were restricted by low number of dementia cases. The SIRs were elevated for all types of dementia after brain can-

TABLE 1 Characteristics of 949,309 Danish cancer patients diagnosed between 1980 and 2013, and matched cohort of cancer patients and cancer free Danish residents

			Matched cohorts			
	All cancer patients		Patients with specific cancer types[a]		Matched population comparisons	
	N	%	N	%	N	%
Total	949,309	100	679,122	100	3,395,597	100
Sex						
Female	490,351	52	344,842	51	1,724,208	51
Male	458,958	48	334,280	49	1,671,389	49
Median age (interquartile range)	67 (57, 76)		68 (58, 76)		68 (58, 76)	
Age group, years						
0-49	134,602	14	84,021	12	420,889	12
50-59	157,616	17	111,176	16	555,402	16
60-69	255,269	27	186,794	28	934,335	28
70-79	254,144	27	187,990	28	939,871	28
80+	147,678	16	109,141	16	545,100	16
Year of diagnosis						
1980-1994	346,494	37	232,586	34	1,162,921	34
1995-2001	183,789	19	128,478	19	642,388	19
2002-2009	267,059	28	200,955	30	1,004,773	30
2010-2013	151,967	16	117,103	17	585,515	17
Charlson comorbidity index score						
None (CCI = 0)	706,123	74	501,106	74	2,628,460	77
Low (CCI = 1)	154,049	16	112,705	17	500,327	15
Moderate (CCI = 2-3)	75,150	7.9	55,192	8.1	228,482	6.7
High (CCI = 4+)	13,987	1.5	10,119	1.5	38,328	1.1
Specific comorbid condition						
Myocardial infarction	39,099	4.1	29,546	4.4	142,097	4.2
Congestive heart failure	31,901	3.4	23,559	3.5	101,655	3.0
Peripheral vascular disease	34,456	3.6	25,828	3.8	100,550	3.0
Cerebrovascular disease	57,248	6.0	42,592	6.3	200,994	5.9
Chronic pulmonary disease	61,189	6.4	46,446	6.8	173,146	5.1
Connective tissue disease	22,618	2.4	16,602	2.4	72,543	2.1
Ulcer disease	38,399	4.0	26,798	3.9	109,417	3.2
Mild liver disease	9797	1.0	6462	1.0	20,312	0.6
Diabetes I and II	38,505	4.1	27,746	4.1	123,291	3.6
Hemiplegia	1867	0.2	1309	0.2	6091	0.2
Moderate to severe renal disease	12,898	1.4	9398	1.4	32,469	1.0
Diabetes with end organ damage	14,642	1.5	10,689	1.6	49,085	1.4
Moderate to severe liver disease	2674	0.3	1795	0.3	4668	0.1
AIDS	647	0.1	232	0.0	709	0.0
Cancer stage[b]						
Localized	298,538	31	298,538	44		
Regional	69,692	7.3	69,692	10		
Distant	54,675	5.8	54,675	8.1		
Missing/unknown	526,404	56	256,217	38		
Receipt of any radiotherapy[c]			51,512	14		
Receipt of any chemotherapy[c]			76,079	21		

(Continues)

TABLE 1 (Continued)

	All cancer patients		Matched cohorts			
			Patients with specific cancer types[a]		Matched population comparisons	
	N	%	N	%	N	%
Median age at dementia diagnosis (interquartile range)			83.1 (77.9, 87.5)		83.5 (78.6, 87.7)	
Median follow-up time (interquartile range)	2.8 (0.60, 8.0)		3.1 (0.70, 8.1)		7.2 (3.3, 13.2)	

[a]Prostate cancer (n = 68,895), Lung cancer (n = 103,428), colon cancer (n = 67,315), pancreatic cancer (n = 22,114), breast cancer (n = 109,755), non-melanoma skin cancer (n = 195,899), brain cancer (n = 12,433), leukemia (n = 21,660), melanoma (n = 30,586), liver cancer (n = 7,824), kidney cancer (n = 15,728), bladder cancer (n = 23,485).
[b]Only solid cancer. Other cancer types are included in the missing/unknown category.
[c]Received within 3 months of cancer diagnosis. Restricting to patients diagnosed from 2004 onwards due to data availability.

cer; increased for all-cause dementia but null or reduced for AD and VaD after lung cancer; and reduced or similar to that of the general population for most of the remaining cancer sites (Table 3).

Results from the Cox regression analysis of the matched cohorts (ie, using both the cancer cohort and the general population comparison cohort) and stratified by years of follow-up resembled that of the SIR analysis (results not shown).

4 | DISCUSSION

In this large nationwide cohort study—which involved 34 years (5,242,643 person-years) of follow-up—we observed a 6% lower incidence rate for diagnosis of AD, and 4% for all-cause dementia associated with prior cancer diagnosis. The magnitude of the association was closer to the null than reported previously and further attenuated after 10 years, approaching that of the general population.

During 34 years of follow-up of cancer survivors, the reduction in the number of AD cases attributed to cancer was only 1.3 AD cases per 10,000 person-years. We observed similar associations for VaD, where the primary underlying etiology is less likely to be neurodegenerative, and for dementia of any cause. The magnitude of these associations was considerably less than reported previously, as discussed below.

4.1 | Strengths and weaknesses

Strengths of this population-based cohort study include its large size and length of follow-up. Furthermore, all Danish hospitals and hospital clinics report data on diagnoses including dementia to the DNPR and the PCRR.[18,19] Data in the DCR are nearly complete and valid due to compulsory reporting, except for non-melanoma skin cancer. Most tumors are histologically confirmed since 2009.[17] Follow-up of all study participants was virtually complete, because patients were identified using comprehensive hospital-based registries in a healthcare system providing free access to health care, and patients could be tracked easily through the CRS.[16,18] The positive predictive value of the dementia diagnosis in the DNPR overall has been shown to be 89% and is higher for AD than for other dementia types.[23] Because many patients with dementia have mixed pathologies, including those of both AD and VaD,[24] any misclassification may result in a bias with an unknown direction on the study results for individual causes of dementia, but not for all-cause dementia. To account for potential inaccurate coding, we conducted sensitivity analyses that included the ICD-8 code for senile dementia and the ICD-10 code for dementia unspecified as AD, with no effect on our results. Unfortunately, we did not have information on biomarkers relevant to diagnosis of dementia types.

Several limitations should be considered. As cancer diagnostics and treatment changed over the study period, cancer survivorship may have differed by calendar year of inclusion. However, we stratified our results by calendar year of cancer diagnosis and by follow-up period without changing the results. We excluded cancer patients with a baseline diagnosis of mild cognitive impairment or amnestic syndrome to reduce inclusion of patients with prodromal dementia. Dementia and cancer are both associated with a latency and prodromal period before diagnosis.[25] For AD, the prodromal period may be as long as 25 years.[26] The temporal indeterminacy of disease onset is a concern for shorter-term associations. Although competing risk of death is a concern when comparing cumulative risk of dementia among individuals with a cancer history to cumulative risk of dementia among individuals without a cancer history, it is unlikely to explain our results because our analyses are based on incidence rates, which intrinsically correct for differences in time at risk. Residual confounding is a possible explanation and—unlike in typical studies focused on causal effects of an exposure on an outcome—would be an important explanation in this case. A confounder-based explanation of the inverse association between cancer and dementia implies that there is an unmeasured factor that increases cancer risk but decreases dementia risk (or vice-versa). This is an important possible finding, and would justify further research on what that unmeasured factor might be. Diagnostic bias is also a possible explanation for our results. Recent work in a large population-based cohort found that individuals subsequently diagnosed with cancer had slightly better memory functioning even

TABLE 2 Age, sex, and calendar-year standardized incidence rate ratios (SIRs) with 95% confidence intervals (CIs) and absolute reduction in dementia risk attributed to cancer per 10,000 person-years by descriptive characteristic for 949,309 Danish cancer patients diagnosed between 1980 and 2013

	Alzheimer´s disease				Vascular dementia				All-cause dementia			
	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolut risk reduction
All	10,048	10,725	0.94 (0.92, 0.96)	1.3	3598	3930	0.92 (0.89, 0.95)	0.6	28,544	29,723	0.96 (0.95, 0.97)	2.2
Sex												
Female	6121	6601	0.93 (0.90, 0.95)	1.6	1904	2076	0.92 (0.88, 0.96)	0.6	16,823	17,649	0.95 (0.94, 0.97)	2.7
Male	3927	4124	0.95 (0.92, 0.98)	0.9	1694	1853	0.91 (0.87, 0.96)	0.7	11,721	12,073	0.97 (0.95, 0.99)	1.6
CCI score												
None (CCI = 0)	7951	8424	0.94 (0.92, 0.96)	1.1	2441	3065	0.80 (0.77, 0.83)	1.4	21,513	23,294	0.92 (0.9, 0.94)	4.0
Low (CCI = 1)	1454	1595	0.91 (0.87, 0.96)	2.6	713	597	1.19 (1.11, 1.28)	−2.1	4668	4457	1.05 (1.02, 1.08)	−3.9
Moderate (CCI = 2-3)	573	626	0.91 (0.84, 0.99)	2.7	383	238	1.61 (1.46, 1.78)	−7.4	2068	1753	1.18 (1.13, 1.23)	−16.0
High (CCI = 4+)	70	79	0.89 (0.69, 1.12)	3.5	61	30	2.03 (1.55, 2.61)	−12.2	295	218	1.35 (1.20, 1.52)	−30.2
Age at cancer diagnosis												
0-49	117	149	0.78 (0.65, 0.94)	0.2	56	65	0.86 (0.65, 1.12)	0.1	571	527	1.08 (1.00, 1.18)	−0.3
50-59	752	725	1.04 (0.96, 1.11)	−0.2	253	298	0.85 (0.75, 0.96)	0.4	2162	2100	1.03 (0.99, 1.07)	−0.5
60-69	2353	2414	0.97 (0.94, 1.02)	0.4	975	995	0.98 (0.92, 1.04)	0.1	6812	6809	1.00 (0.98, 1.02)	0.0
70-79	4250	4485	0.95 (0.92, 0.98)	2.4	1482	1623	0.91 (0.87, 0.96)	1.4	11,433	11,904	0.96 (0.94, 0.98)	4.7
80+	2576	2953	0.87 (0.84, 0.91)	10.2	832	948	0.88 (0.82, 0.94)	3.1	7566	8382	0.90 (0.88, 0.92)	22.0
Year of cancer diagnosis												
1980-1994	5059	5076	1.00 (0.97, 1.02)	0.1	1516	1657	0.91 (0.87, 0.96)	0.6	12,786	12,958	0.99 (0.97, 1.00)	0.7
1995-2001	2124	2285	0.93 (0.89, 0.97)	1.3	1028	1093	0.94 (0.88, 1.00)	0.5	7480	7759	0.96 (0.94, 0.99)	2.3
2002-2009	2447	2832	0.86 (0.83, 0.90)	3.0	940	1033	0.91 (0.85, 0.97)	0.7	7157	7756	0.92 (0.90, 0.94)	4.7
2010-2013	418	531	0.79 (0.71, 0.87)	4.6	114	147	0.78 (0.64, 0.93)	1.3	1121	1250	0.90 (0.85, 0.95)	5.3
Year of follow-up												
0-1	1294	1348	0.96 (0.91, 1.01)	0.7	405	453	0.89 (0.81, 0.99)	0.6	3446	3346	1.03 (1.00, 1.07)	−1.3
>1-5	2964	3517	0.84 (0.81, 0.87)	2.9	1080	1219	0.89 (0.83, 0.94)	0.7	8102	9137	0.89 (0.87, 0.91)	5.5
>5-10	2495	2602	0.96 (0.92, 1.00)	0.8	898	963	0.93 (0.87, 1.00)	0.5	7033	7308	0.96 (0.94, 0.99)	2.1
>10-20	2446	2406	1.02 (0.98, 1.06)	−0.4	994	1004	0.99 (0.93, 1.05)	0.1	7648	7572	1.01 (0.99, 1.03)	−0.7
>20-34	849	852	1.00 (0.93, 1.07)	0.1	221	291	0.76 (0.66, 0.87)	2.8	2315	2361	0.98 (0.94, 1.02)	1.8

(Continues)

TABLE 2 (Continued)

	Alzheimer´s disease				Vascular dementia				All-cause dementia			
	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolut risk reduction
Specific comorbidcondition												
Myocardial infarction	358	411	0.87 (0.78, 0.97)	4.4	201	167	1.20 (1.04, 1.38)	−2.8	1142	1182	0.97 (0.91, 1.02)	3.3
Congestive heart failure	231	288	0.80 (0.70, 0.91)	8.4	136	107	1.27 (1.07, 1.50)	−4.3	832	820	1.01 (0.95, 1.09)	−1.8
Peripheral vascular disease	250	281	0.89 (0.78, 1.01)	3.6	140	107	1.30 (1.10, 1.54)	−3.8	859	779	1.10 (1.03, 1.18)	−9.2
Cerebrovascular disease	560	599	0.93 (0.86, 1.02)	2.4	532	223	2.39 (2.19, 2.60)	−18.9	2250	1686	1.33 (1.28, 1.39)	−34.5
Chronic pulmonary disease	385	461	0.83 (0.75, 0.92)	4.5	153	171	0.89 (0.76, 1.05)	1.1	1247	1251	1.00 (0.94, 1.05)	0.2
Connective tissue disease	220	250	0.88 (0.77, 1.00)	3.7	103	88	1.16 (0.95, 1.41)	−1.8	691	692	1.00 (0.93, 1.08)	0.2
Ulcer disease	384	365	1.05 (0.95, 1.16)	−1.6	177	142	1.24 (1.07, 1.44)	−2.8	1220	1051	1.16 (1.10, 1.23)	−13.7
Mild liver disease	34	35	0.98 (0.68, 1.37)	0.3	20	13	1.49 (0.91, 2.29)	−2.7	165	97	1.70 (1.45, 1.98)	−28.1
Diabetes I and II	314	310	1.01 (0.91, 1.13)	−0.4	192	110	1.74 (1.50, 2.01)	−7.4	1085	822	1.32 (1.24, 1.40)	−23.8
Hemiplegia	5	13	0.40 (0.13, 0.93)	13.8	<5	4	NA	0.5	29	33	0.88 (0.59, 1.27)	7.0
Moderate to severe renal disease	81	92	0.88 (0.70, 1.09)	2.9	51	35	1.46 (1.09, 1.92)	−4.3	285	256	1.11 (0.99, 1.25)	−7.6
Diabetes with end organ	101	105	0.96 (0.79, 1.17)	1.0	87	40	2.19 (1.76, 2.71)	−12.6	397	287	1.38 (1.25, 1.52)	−29.2
Moderate to severe liver disease	<5	7	NA	NA	<5	3	NA	NA	26	20	1.29 (0.84, 1.90)	−10.7
AIDS	<5	1	NA	NA	<5	0	NA	NA	5	2	2.57 (0.83, 5.98)	−14.3
Cancer stage[a]												
Localized	733	824	0.89 (0.83, 0.96)	2.8	253	272	0.93 (0.82, 1.05)	0.6	1910	2156	0.89 (0.85, 0.93)	7.5
Regional	6912	7195	0.96 (0.94, 0.98)	0.8	2452	2670	0.92 (0.88, 0.96)	0.6	19,503	20,192	0.97 (0.95, 0.98)	1.9
Distant	585	691	0.85 (0.78, 0.92)	2.7	176	243	0.73 (0.62, 0.84)	1.7	1677	1812	0.93 (0.88, 0.97)	3.4
Missing	1818	2014	0.90 (0.86, 0.94)	2.1	717	745	0.96 (0.89, 1.04)	0.3	5454	5562	0.98 (0.95, 1.01)	1.2

(Continues)

TABLE 2 (Continued)

	Alzheimer´s disease				Vascular dementia				All-cause dementia			
	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolut risk reduction
Radiotherapy by follow-up period[b]												
>3 months-10 years	165	220	0.75 (0.64, 0.87)	4.1	55	70	0.79 (0.60, 1.03)	1.1	494	545	0.91 (0.83, 0.99)	3.8
>3 months-1 year	23	42	0.55 (0.35, 0.82)	6.5	12	15	0.80 (0.41, 1.39)	1.1	98	111	0.88 (0.72, 1.08)	4.5
>1-5 years	95	129	0.74 (0.60, 0.90)	4.1	38	41	0.92 (0.65, 1.26)	0.4	293	322	0.91 (0.81, 1.02)	3.6
>5-10 years	47	49	0.96 (0.70, 1.27)	0.9	5	13	0.38 (0.12, 0.89)	3.4	103	113	0.91 (0.75, 1.11)	4.0
Chemotherapy by follow-up period[b]												
>3 months-10 years	130	170	0.76 (0.64, 0.91)	2.2	30	55	0.55 (0.37,0.78)	1.4	342	425	0.80 (0.72, 0.89)	4.6
>3 months-1 year	18	41	0.44 (0.26, 0.70)	5.2	<10	15	0.20 (0.04,0.60)	2.7	70	107	0.65 (0.51, 0.83)	8.4
>1-5 years	75	98	0.77 (0.60, 0.96)	2.1	20	32	0.63 (0.38, 0.97)	1.1	197	245	0.80 (0.70, 0.92)	4.5
>5-10 years	37	32	1.16 (0.82, 1.60)	−1.8	<10	9	0.82 (0.33, 1.68)	0.6	75	73	1.02 (0.81, 1.28)	-0.6

CCI, Charlson comorbidity index.
[a]Only solid tumors.
[b]Treatment received within 3 months of cancer diagnosis, starting follow-up at this date. Restricting to patients diagnosed from 2004 onwards due to data availability.

prior to cancer diagnosis.[27] This would imply that the diagnostic bias, if relevant, results from individuals with higher cognitive function having increased chance of cancer diagnosis. We consider this most plausible for cancers that are often undiagnosed or diagnosed upon screening, such as prostate and breast cancer.

4.2 | Previous literature

Most studies that assessed the risk for AD or dementia after cancer were conducted in the United States, were limited to study populations aged 65+ years, and were not population based.[1-7,9,15] The reported inverse associations between cancer and dementia is stronger for AD than for other dementia types. For example, Roe et al. reported that cancer was associated with a reduced risk for AD (HR = 0.57, 95% CI: 0.36-0.90) after adjustment for a number of factors, including *APOE* genotype, over a median of 5.4 years of follow-up. No association was found between cancer and VaD.[4] Driver et al. found a reduced risk of probable AD (HR = 0.67, 95% CI: 0.47-0.97) following a cancer diagnosis, particularly for survivors of lung cancer and other smoking-related cancer (HR = 0.26, 95% CI 0.08-0.82).[2] Freedman et al. similarly reported a decreased risk for AD within 10 years of follow-up after diagnosis of cancer at different sites.[7] In a study with 21 years of follow-up, Bowles et al. reported a HR for AD of 0.95 (95% CI: 0.77-1.17) for patients with prevalent cancer and 0.73 (95% CI: 0.55-0.96) for patients with incident cancer.[15] Findings from Frain et al. based on data from the U.S. Veteran Healthcare System including patients age 65+ years, support previous studies of an inverse association between some cancer types and subsequent AD.[9] A study conducted in Italy reported similar findings in a population aged 60+ years.[3] However, a study based on data from the Utah Population Database argue that such associations arise from bias due to the competing risk of dying.[14] Both for AD and for VaD, we found a lower relative risk associated with some smoking- and alcohol-related cancers such as those of the lung and colon, but not for other smoking or alcohol-related cancers (bladder, breast, kidney, pancreatic cancer), and not for long-term cancer survivors.

4.3 | Potential Mechanisms

Neurodegenerative diseases and carcinogenesis may share several molecular signaling pathways and factors involved in cell cycle dysfunction.[8,13,28-33] Although still controversial, chemotherapeutic agents may affect cognition, ranging from maintaining cognitive function through suppressed inflammation and blocked cell cycles, on the one hand,[8] to potential peripheral neurotoxic effects, on the other hand.[12] As well, specific comorbidities may lead to differing diagnostic procedures and treatment choices.[8,34,35] We found inverse associations between cancer and AD across all comorbidity levels, but increased risk for VaD and all-cause dementia among cancer patients with increasing CCI scores.

TABLE 3 Standardized incidence rate ratios (SIRs) with 95% confidence intervals (CIs) and absolute reduction in dementia risk attributed to cancer per 10,000 person-years for dementia, in 679,122 Danish cancer patients with specific cancer sites diagnosed between 1980 and 2013, by stage

	Alzheimer's disease				Vascular dementia				All-cause dementia			
	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction
Bladder cancer	227	242	0.94 (0.82, 1.07)	1.6	98	97	1.01 (0.82, 1.23)	−0.1	640	662	0.97 (0.89, 1.04)	2.3
Localized	135	148	0.91 (0.77, 1.08)	2.1	59	60	0.99 (0.75, 1.28)	0.1	385	403	0.96 (0.86, 1.06)	3.0
Regional	28	23	1.23 (0.81, 1.77)	−5.2	17	9	1.90 (1.11, 3.05)	−8.1	67	60	1.11 (0.86, 1.41)	−6.8
Distant	<5	3	NA	12.9	<5	1	NA	7.6	8	7	1.08 (0.47, 2.13)	−3.9
Missing/unknown	63	69	0.92 (0.70, 1.17)	2.5	22	28	0.79 (0.50, 1.20)	2.5	180	192	0.94 (0.81, 1.09)	5.0
Brain cancer	13	8	1.62 (0.86, 2.77)	−1.6	10	3	2.90 (1.39, 5.33)	−2.1	91	24	3.77 (3.03, 4.63)	−21.1
Breast cancer	1495	1569	0.95 (0.91, 1.00)	0.8	486	492	0.99 (0.90, 1.08)	0.1	4129	4132	1.00 (0.97, 1.03)	0.0
Localized	899	901	1.00 (0.93, 1.07)	0.0	276	285	0.97 (0.86, 1.09)	0.2	2403	2385	1.01 (0.97, 1.05)	−0.4
Regional	419	471	0.89 (0.81, 0.98)	1.7	148	147	1.01 (0.85, 1.18)	0.0	1176	1214	0.97 (0.91, 1.03)	1.2
Distant	30	38	0.79 (0.53, 1.12)	4.3	10	11	0.90 (0.43, 1.66)	0.6	94	95	0.99 (0.80, 1.21)	0.4
Missing/unknown	147	158	0.93 (0.78, 1.09)	1.9	52	50	1.05 (0.78, 1.37)	−0.4	456	438	1.04 (0.95, 1.14)	−3.0
Colon cancer	833	944	0.88 (0.82, 0.94)	3.6	279	337	0.83 (0.73, 0.93)	1.9	2343	2598	0.90 (0.87, 0.94)	8.4
Localized	207	253	0.82 (0.71, 0.94)	6.0	71	86	0.83 (0.64, 1.04)	1.9	585	668	0.88 (0.81, 0.95)	10.8
Regional	93	104	0.90 (0.73, 1.10)	3.0	22	34	0.64 (0.40, 0.98)	3.4	231	266	0.87 (0.76, 0.99)	9.9
Distant	20	27	0.75 (0.46, 1.16)	5.8	<5	8	NA	4.8	54	64	0.85 (0.64, 1.11)	8.3
Missing/unknown	513	561	0.91 (0.84, 1.00)	2.6	183	208	0.88 (0.76, 1.02)	1.4	1473	1601	0.92 (0.87, 0.97)	7.0
Kidney cancer	86	110	0.78 (0.62, 0.96)	3.7	53	42	1.25 (0.94, 1.63)	−1.6	286	303	0.95 (0.84, 1.06)	2.5
Localized	62	74	0.84 (0.65, 1.08)	2.6	43	29	1.48 (1.07, 2.00)	−3.1	204	206	0.99 (0.86, 1.14)	0.4
Regional	5	9	0.56 (0.18, 1.30)	8.1	<5	3	NA	NA	17	24	0.72 (0.42, 1.15)	13.4
Distant	6	7	0.86 (0.31, 1.86)	2.0	<5	3	NA	NA	16	18	0.88 (0.50, 1.43)	4.2
Missing/unknown	13	21	0.63 (0.33, 1.08)	7.6	8	8	1.06 (0.46, 2.08)	−0.4	49	55	0.89 (0.66, 1.18)	6.0
Leukemia	150	162	0.93 (0.78, 1.09)	1.2	51	60	0.85 (0.63, 1.11)	0.9	395	440	0.90 (0.81, 0.99)	4.5
Lung cancer	174	207	0.84 (0.72, 0.97)	2.5	65	81	0.80 (0.62, 1.02)	1.2	613	546	1.12 (1.04, 1.22)	−5.1
Localized	83	101	0.82 (0.66, 1.02)	2.9	38	41	0.93 (0.66, 1.28)	0.5	291	272	1.07 (0.95, 1.20)	−3.0
Regional	32	43	0.75 (0.51, 1.06)	3.2	12	18	0.68 (0.35, 1.19)	1.7	124	115	1.07 (0.89, 1.28)	−2.6
Distant	25	38	0.67 (0.43, 0.98)	5.4	8	14	0.58 (0.25, 1.14)	2.5	110	97	1.14 (0.93, 1.37)	−5.6
Missing/unknown	34	26	1.31 (0.91, 1.83)	−6.5	7	9	0.82 (0.33, 1.68)	1.3	88	61	1.43 (1.15, 1.76)	−21.6

(Continues)

TABLE 3 (Continued)

	Alzheimer's disease				Vascular dementia				All-cause dementia			
	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction	Observed number	Expected number	SIR (95% CI)	Absolute risk reduction
Melanoma skin cancer	284	325	0.87 (0.78, 0.98)	1.5	92	124	0.74 (0.60, 0.91)	1.2	805	929	0.87 (0.81, 0.93)	4.5
Localized	253	285	0.89 (0.78, 1.00)	1.3	82	110	0.75 (0.59, 0.93)	1.1	715	820	0.87 (0.81, 0.94)	4.2
Regional	9	10	0.94 (0.43, 1.78)	0.7	<5	4	NA	NA	27	27	1.01 (0.66, 1.47)	−0.3
Distant	<5	2.8	NA	NA	<5	1	NA	NA	<5	7	NA	NA
Missing/unknown	20	27	0.73 (0.44, 1.12)	3.9	9	10	0.91 (0.42, 1.74)	0.4	59	76	0.78 (0.59, 1.00)	8.9
Non-melanoma skin cancer	3876	4005	0.97 (0.94, 1.00)	0.8	1366	1505	0.91 (0.86, 0.96)	0.9	10805	11479	0.94 (0.92, 0.96)	4.3
Localized	3316	3384	0.98 (0.95, 1.01)	0.5	1171	1277	0.92 (0.87, 0.97)	0.8	9251	9725	0.95 (0.93, 0.97)	3.6
Regional	16	11	1.50 (0.86, 2.43)	−15.3	<5	4	NA	NA	36	31	1.17 (0.82, 1.63)	−15.3
Distant	5	2	2.48 (0.80, 5.77)	−35.6	<5	1	NA	NA	9	6	1.60 (0.74, 3.05)	−40.5
Missing/unknown	539	608	0.89 (0.81, 0.96)	2.8	190	223	0.85 (0.74, 0.98)	1.3	1509	1718	0.88 (0.83, 0.92)	8.5
Pancreatic cancer	19	26	0.72 (0.43, 1.13)	5.2	4	9	0.45 (0.12, 1.15)	3.5	59	66	0.90 (0.69, 1.16)	4.7
Localized	8	7	1.19 (0.51, 2.34)	−3.4	<5	2	NA	NA	17	17	1.00 (0.58, 1.60)	0.1
Regional	<5	6	NA	NA	<5	2	NA	NA	10	14	0.70 (0.34, 1.29)	10.8
Distant	<5	5	NA	NA	<5	2	NA	NA	14	11	1.22 (0.67, 2.05)	−8.3
Missing/unknown	6	9	0.67 (0.25, 1.46)	9.0	2	3	0.66 (0.08, 2.39)	3.2	18	23	0.79 (0.47, 1.25)	14.9
Prostate cancer	779	813	0.96 (0.89, 1.03)	1.2	325	340	0.96 (0.85, 1.07)	0.5	2175	2237	0.97 (0.93, 1.01)	2.2
Localized	387	399	0.97 (0.88, 1.07)	0.8	162	164	0.99 (0.84, 1.15)	0.1	1080	1077	1.00 (0.94, 1.06)	−0.2
Regional	29	27	1.09 (0.73, 1.57)	−2.1	10	11	0.91 (0.43, 1.67)	0.9	69	70	0.98 (0.76, 1.24)	1.2
Distant	84	94	0.90 (0.72, 1.11)	3.1	22	40	0.55 (0.35, 0.83)	5.7	217	258	0.84 (0.73, 0.96)	13.0
Missing/unknown	279	294	0.95 (0.84, 1.07)	1.8	131	125	1.05 (0.88, 1.24)	−0.7	809	831	0.97 (0.91, 1.04)	2.5

We also found an initial inverse association between some smoking- and alcohol-related cancers and AD and VaD, which diminished during follow-up for cancer survivors. Patients with disseminated cancer are likely to have died from their disease in the first decade after diagnosis, leaving disease-free cancer patients for the long-term analysis. Misclassification of mild AD or mild dementia as no-dementia in patients with cancer also could explain the small, early inverse association. We found an increased risk of dementia after diagnosis of both benign and malignant brain tumor, consistent with the well-known increase in dementia and cognitive dysfunction associated with all types of brain tumors.

Our overall results for AD and VaD, which are largely similar, contrast with evidence that separated AD from other types of dementia, such as the results of Roe,[4] Driver[2] and Freedman,[7] although other studies have reported a decreased risk for all-cause dementia after cancer.[1,6] It is possible that neurodegeneration among cancer patients with comorbid cardiovascular conditions tended to be classified as VaD rather than AD, especially since the dementia diagnoses were not supported by brain imaging for the majority of our registry-defined cohort. Therefore, some patients classified as having VaD may have had Alzheimer´s pathology or a combination of vascular and AD pathologies.[36] When we stratified results by cancer stage, we also found largely similar results by stage category within each dementia subtype. This suggests that dementia is not underdiagnosed in patients with metastatic cancer who have poorer survival prospects than the general population.

5 | CONCLUSIONS AND IMPLICATIONS

The evidence presented here augments recent reports showing that cancer patients may have decreased relative and absolute risks for AD after standardization to the general population. However, the magnitude of the association was much less than previously reported and diminished after 10 years, approaching that found in the general population. This study does not indicate a clinically relevant association between cancer and risk of AD, VaD, or all-cause dementia. Interest in the association is largely because it suggests the possibility of a physiologic process or risk factor that increases cancer risk but decreases dementia risk, that is, a potential confounder with biological relevance; identifying such a potential confounder might provide novel insight into the mechanisms of dementia. When interpreting the strength of the observed inverse association, it is therefore valuable to assess how strong the effects of such a potential confounder or set of confounders would have to be in order to account for the association. The E-value provides such an estimate: Under the assumption that the confounder has equally strong (but inverse) associations with cancer and dementia, the confounder or set of confounders would need to increase dementia risk by roughly 32% to account for the observed inverse association. The modest effect estimates are not as large as for single major risk factors such as APOE ε4 allele but are in line with estimates related to some cardiovascular risk factors, for example. Such small effects may be of biological interest if they relate to pathological cascade that culminate in dementia, but could also plausibly be explained by detection bias. We also note that the major advantages of our use of administrative records, which provides a much larger sample size than ever previously evaluated, also introduces potential biases that may underestimate the association between cancer and dementia, for example, due to non-differential misdiagnoses.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ETHICS COMMITTEE APPROVAL

No ethical committee approval was needed.

DATA PERMISSION

The study was approved by the Danish Data Protection Agency (record number 2007-58-0010).

DATA SHARING

Not allowed.

PATIENT INVOLVEMENT

No patient involvement.

AUTHOR CONTRIBUTIONS

HTS conceived the study idea and designed the study together with AGO and VWH. EHP and KV carried out the analyses. AGO organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. AGO is the guarantor.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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