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BRIEF REPORT

Is incident cancer in later life associated with lower incidence of dementia?

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ABSTRACT

Cancer has been associated with lower risk of dementia, although methodological issues raise concerns about the validity of this association. We recruited 31,080 men aged 65–85 years who were free of cancer and dementia, and followed them for up to 22 years. We used health record linkage to identify incident cases of cancer and dementia, and split time span to investigate this association. 18,693 (60.1%) and 6897 (22.2%) participants developed cancer and dementia during follow-up. The hazard ratio (HR) of dementia associated with cancer was 1.13 (95% CI = 1.07, 1.20) and dropped to 0.85 (95% CI = 0.80, 0.91) when 449 participants who developed dementia within 2 years were excluded. The diagnosis of cancer seems to facilitate the early detection of dementia cases. Older participants who survive cancer for 2 or more years have lower risk of receiving the diagnosis of dementia over time. The factors that mediate this association remain unclear.

Key words: cancer, dementia, Alzheimer's disease (AD), epidemiology

Introduction

The Alzheimer's Association and the Alzheimer's Drug Discovery Foundation examined the association between cancer and dementia, and concluded that existing evidence suggested that the risk of dementia was lower among adults with than without cancer (Snyder *et al.*, 2017). A recent systematic review and meta-analysis of 36 studies found that cancer was associated with a reduction of 11% in the risk of dementia compared with non-cancer controls, although there was inconsistency of results and marked heterogeneity across the studies (Zhang *et al.*, 2022). Publication and survivorship bias, and confounding due to exposures such as smoking, diet, and physical inactivity have been offered as possible explanations for the observed association between cancer and dementia (Ganguli, 2015), but we are not aware of previous studies having investigated how the inception cohort and approach to the analysis of the data may have affected the results of these reports.

We used data from the Health In Men Study (HIMS) to determine if incident cancer affects the risk of incident dementia (Norman *et al.*, 2009). We excluded from the cohort prevalent cases of cancer (past or current) and dementia, so as to minimize the potential bias associated with the selection of cancer survivors. This approach allowed us to investigate the contribution of novel cases of cancer to the onset of dementia over 22 years.

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Methods

Study design, setting, and participants

We used the electoral roll (voting is mandatory in Australia) to select 38,173 men who were living in the Perth metropolitan region and were aged 65–85 years in 1996. We excluded 342 participants who had received a diagnosis of dementia prior to enrollment and another 6750 who had had cancer. One other participant was excluded because he died

before the invitation date. Hence, the study sample consisted of 31,080 older participants who were followed until they received the diagnosis of dementia, died, or reached the end of the follow-up period (31 December 2018). The University of Western Australia Human Research Ethics Committee and the Ethics Committee of the Department of Health of Western Australia approved and oversaw the conduction of this study.

Outcome of interest: dementia

We used the Western Australian Data Linkage System (WADLS) to retrieve information about health contacts associated with a recorded diagnosis of dementia. WADLS brings together hospital morbidity data (inpatient and outpatient), emergency department, and mental health contacts, as well as the cancer and death registries (Holman *et al.*, 2008). The causes leading to health contacts are recorded, and the coding of diseases follows the guidelines of the International Classification of Diseases (ICD): ICD-9 from 1 January 1970 to 30 June 1999, and ICD-10 from 1 July 1999. The death registry provides information about the date and cause of death. The following ICD codes were used to ascertain the presence of dementia (all causes): 290, 294.1, 294.2, 331.0, 331.1, 331.82, and 331.2 (ICD-9), and F00, F01, F02, F03, G30, G31.0, G31.1, and G31.83 (ICD-10). The date of the first recorded diagnosis of dementia was considered the date of onset.

Cancer

The reporting of cancers is mandatory in Australia and diagnoses were retrieved using the WADLS and the following ICD codes: 140-9, 150-7, 159, 160-5, 170, 172-3, 158, 171, 176, 175, 185-9, 190-9, 200-8 and 238.0 (ICD-9), and C00-9, C10-9, C20-6, C30-9, C40-1, C43-9, C50, C60-9, C70-9, C80-9, C90-7. These codes record malignant neoplasms of the lip or oral cavity or pharynx, digestive organs, respiratory and intrathoracic organs, bone and articular cartilage, skin, mesothelial and soft tissue, breast, genital organs, urinary tract, eye of brain or other parts of the central nervous system (CNS), thyroid and other endocrine glands, ill-defined or secondary or unspecified sites, lymphoid or hematopoietic or related tissue, and independent multiple sites.

Statistical Analyses

We used the statistical software Stata 17.0 (StataCorp LLC, 2022) to manage and analyze the data, descriptive statistics to summarize categorical measures as count and proportions (%) and continuous measures as mean, range, and standard deviation of the mean (SD). We split time-span records according to the date of the recorded diagnosis of cancer, so that participants would contribute information as non-cancer cases up to the date of diagnosis of cancer. We then used Cox regression analyses according to the Breslow method to estimate the hazard ratio (HR) and respective 95% confidence interval (95% CI) of dementia associated with the diagnosis of any cancer, with age being used as the time scale. We subsequently repeated this approach to each specific cancer site. Sensitivity analyses were used to exclude participants who received a diagnosis of dementia within 1 and 2 years of the diagnosis of cancer, as more frequent contact with health services could increase the opportunity for a diagnosis of dementia to be made. Finally, a post hoc analysis examined the possibility of reverse causality, that is dementia affecting the risk of cancer. We used log-log plots to inspect the proportional hazards assumption and tested for the distribution of Schoenfeld residuals after the fitting of the regression models. Alpha was set at 5%, and all statistical tests were two-tailed.

Results

Cancer and risk of dementia

The age of participants ranged from 65.0 to 85.7 years (mean ± SD = 72.2 ± 4.5 years), and none had a recorded diagnosis of either cancer or dementia at the start of the study. They were followed for up to 22.7 years (mean = 13.2 ± 6.7 years). During follow-up, 18,693 (60.1%) men had a recorded diagnosis of cancer and 6897 (22.2%) of dementia. Of 18,693 who developed cancer during follow-up, 1930 (10.3%) received a diagnosis of dementia after the diagnosis of cancer and 1860 (10.0%) before. Among participants who had cancer and later developed dementia, the time elapsed between the two diagnoses was 5.8 ± 4.4 years. The risk of dementia was higher among older participants who developed cancer (HR = 1.13, 95% CI = 1.07, 1.20), but declined after the exclusion of those diagnosed with dementia within 1 (HR = 0.97, 95% CI = 0.91, 1.02) and 2 years (HR = 0.85, 95% CI = 0.80, 0.91) of the diagnosis of cancer (Figure 1). Table 1 shows the number of participants affected by specific types of cancer, as well as those who developed dementia.

Post hoc analyses: reverse causality

Among participants who develop cancer during follow-up, the diagnosis of dementia preceded

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Table 1. Age-adjusted hazard of dementia associated with specific types of cancer[a] and after the exclusion of 449 participants with dementia diagnosed within 2 years of the diagnosis of cancer[b]

Malignant neoplasms among 31,080 men	Affected	Dementia	Hazard ratio[a] (95% CI)	Hazard ratio[b] (95% CI)
Lip, oral cavity, and pharynx, n (%)	6072 (19.5)	1123 (3.6)	0.95 (0.68, 1.32)	0.78 (0.54, 1.14)
Digestive organs, n (%)	4580 (14.7)	671 (2.2)	1.02 (0.90, 1.15)	**0.85 (0.74, 0.97)**
Respiratory and intrathoracic organs, n (%)	10,102 (32.5)	1652 (5.3)	0.98 (0.78, 1.24)	**0.67 (0.51, 0.91)**
Bone and articular cartilage, n (%)	224 (0.7)	23 (0.1)	0.63 (0.09, 4.44)	0.66 (0.09, 4.70)
Skin, n (%)	6145 (19.8)	1353 (4.4)	**1.13 (1.05, 1.20)**	0.93 (0.86, 1.00)
Mesothelial and soft tissue, n (%)	670 (2.2)	88 (0.3)	**1.82 (1.27, 2.61)**	1.10 (0.68, 1.77)
Breast, n (%)	31 (0.1)	6 (0.0)	1.63 (0.68, 3.92)	1.73 (0.72, 4.15)
Male genital organs, n (%)	4459 (14.3)	874 (2.8)	1.02 (0.93, 1.12)	**0.88 (0.80, 0.98)**
Urinary tract, n (%)	5666 (18.2)	1542 (5.0)	**1.15 (1.01, 1.31)**	0.94 (0.82, 1.10)
Eye, brain, and other parts of the CNS, n (%)	393 (1.3)	34 (0.1)	**2.16 (1.16, 4.02)**	1.61 (0.77, 3.38)
Thyroid and other endocrine glands, n (%)	50 (0.2)	8 (0.0)	1.16 (0.52, 2.58)	1.02 (0.42, 2.45)
Ill-defined, secondary, and unspecified sites, n (%)	7296 (23.5)	1085 (3.5)	**1.38 (1.21, 1.57)**	0.98 (0.84, 1.15)
Lymphoid, hematopoietic, and related tissue, n (%)	8487 (27.3)	1375 (4.4)	0.84 (0.67, 1.05)	**0.71 (0.55, 0.91)**
Independent multiple sites, n (%)	65 (0.2)	6 (0.0)	–	–

Participants were considered to be "free of cancer" until the date of the diagnosis, after which they were counted as "exposed cases" for the calculation of the hazard ratio. Cases of dementia arising before the diagnosis of cancer were censored at the time the diagnosis of dementia was recorded. 95% CI: 95% confidence interval of the ratio. CNS: central nervous system.

[a]All participants were free of cancer and dementia at study entry.
[b]Excludes 449 participants who developed dementia during the first 2 years following the diagnosis of cancer.
Bold print used to highlight associations that were statistically significant ($p < 0.05$).

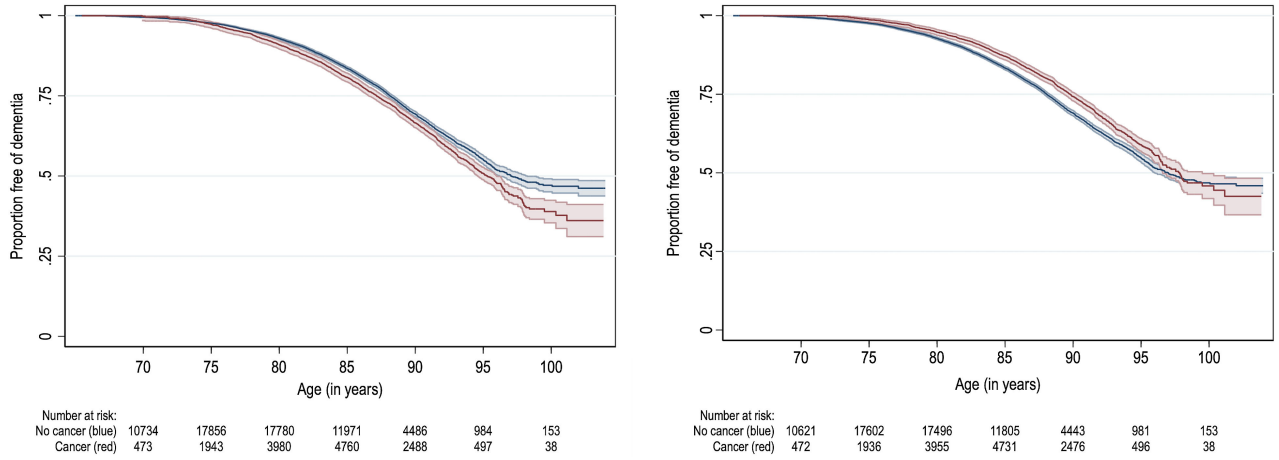

Figure 1. Age-adjusted proportion of men with and without diagnosis of cancer who remained free of dementia during follow-up. The shady bands represent the 95% confidence interval (95% CI) of the proportion. The left panel shows data for the entire sample of 31,080 participants: the hazard ratio (HR) of dementia-associated cancer was 1.13 (95% CI = 1.07, 1.20). The right panel excludes 449 participants who developed dementia within the first 2 years after the diagnosis of cancer: the HR of dementia associated with cancer was 0.85 (95% CI = 0.80, 0.91).

that of cancer in 1860 (9.9%). The diagnosis of dementia increased the age-adjusted risk of incident of cancer (HR = 2.32, 95% CI = 2.20, 2.44), but this association was no longer significant when 1200 men who developed cancer within 2 years of a diagnosis of dementia were dropped from the analyses (HR = 0.96, 95% CI = 0.89, 1.04). During follow-up, 24,931 (80.2%) participants died, and of these, 11,849 (47.5%) died of cancer. Among the men who died of cancer, 2248 (19.0%) had a recorded diagnosis of dementia.

Discussion

The design of this study sought to minimize inception bias and bias associated with frequent health contacts triggered by the diagnosis of cancer. We

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found that the direction of the association between cancer and dementia varied according to the approach used to analyze the data: increased hazard when we used time-to-event analyses and decreased hazard when participants who developed dementia within 2 years of the diagnosis of cancer were excluded from the analyses.

Strengths of the study include the use of a large community-representative sample of older men, access to health record linkage, long duration of follow-up that allowed for the accrual of thousands of cases of cancer and dementia, and an analytical approach that minimized the risk of bias (the association between cancer and decreased risk of dementia has been reported by others, but the approach we used to examine this association represents a novel contribution, as does the reporting of the association between different types of cancer and dementia). This study also generated data about specific cancer groups and showed that the association between cancer and dementia is not specific to one type of cancer (except for skin cancer). Limitations include the non-availability of women in the sample, confounding associated with unmeasured factors, residual confounding, and the absence of detailed clinical information to confirm the diagnosis of dementia, although recent evidence suggests that the use of health administrative data can provide robust information about the rates of dementia in the community (Flicker *et al.*, 2022). Survivorship bias could have also affected the results by maintaining in the sample cancer survivors who are at lower risk of dementia than those who die early. Moreover, we cannot be certain about the time lag between the onset of the disease and the diagnosis of cancer, so that delayed diagnosis could conceivably bias the results by mislabeling "cases" as "non-cases" during part of the follow-up period. Our sensitivity analyses should have contributed to circumvent, at least in part, this limitation. Nonetheless, it is possible that the diagnosis of cancer may have contributed to decrease the focus on the need for dementia screening in later life (or vice versa), in which case the inverse association between cancer and dementia could have arisen as a result of bias. Again, the results of our sensitivity analyses suggest this is an unlikely explanation for our findings, particularly if one accepts that cognitive screening is more likely to be neglected during the acute phase following the diagnosis of cancer. Finally, we acknowledge that the observed effect size of the association between cancer and dementia was small and most likely of limited clinical significance to an older person with cancer. However, these results imply that a physiological mechanism mediating such an association exists and, once unveiled, could potentially lead to the development of novel and clinically meaningful approaches to reducing the risk of dementia in the population.

A recent neuropathological study has confirmed that cancer is associated with lower burden of Alzheimer's disease pathology (Karanth *et al.*, 2022), although the mechanisms mediating this association remain unclear (Ganguli, 2015; Snyder *et al.*, 2017). Future studies should seek to clarify if the inverse relationship between cancer and dementia is a consequence of current cancer treatments, or is due to environmental or genetic factors. For example, shorter telomeres have been associated with increased risk of dementia (Honig *et al.*, 2012), whereas longer telomeres seem to increase the risk of cancer (Telomeres Mendelian Randomization Collaboration, 2017). The systematic evaluation of the relationship between cancer and dementia may generate valuable information to address the health needs of an aging population (Ahmad and Anderson, 2021).

Data availability

The data reported in this study are available to other researchers upon request to Prof. Leon Flicker (leon.flicker@uwa.edu.au).

Conflict of interest

None.

Description of authors' roles

Obtaining funding for the study: all investigators.
Data collection: all investigators.
Supervision of research staff: LF.
Data Analysis: OPA.
Drafting of paper: OPA.
Critical review of paper for important intellectual content: all investigators.
Consent of submission for publication: all investigators.

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References

Ahmad, F. B. and Anderson, R. N. (2021). The leading causes of death in the US for 2020. *Journal of the American Medical Association*, 325, 1829–1830.

Flicker, L. *et al.* (2022). Differing methodologies are required to estimate prevalence of dementia: single study types are no longer reliable. *Journal of Alzheimers Disease*, 88, 943–948.

Ganguli, M. (2015). Cancer and dementia: it's complicated. *Alzheimer Disease and Associated Disorders*, 29, 177–182.

Holman, C. D. *et al.* (2008). A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. *Australian Health Review*, 32, 766–777.

Honig, L. S., Kang, M. S., Schupf, N., Lee, J. H. and Mayeux, R. (2012). Association of shorter leukocyte telomere repeat length with dementia and mortality. *Archives of Neurology*, 69, 1332–1339.

Karanth, S. D. *et al.* (2022). Cancer diagnosis is associated with a lower burden of dementia and less Alzheimer's-type neuropathology. *Brain*, 145, 2518–2527.

Norman, P. E., Flicker, L., Almeida, O. P., Hankey, G. J., Hyde, Z. and Jamrozik, K. (2009). Cohort profile: the Health In Men Study (HIMS). *Internaltional Journal of Epidemiology*, 38, 48–52.

Snyder, H. M. *et al.* (2017). Exploring the nexus of Alzheimer's disease and related dementias with cancer and cancer therapies: a convening of the Alzheimer's Association & Alzheimer's Drug Discovery Foundation. *Alzheimers and Dementia*, 13, 267–273.

Telomeres Mendelian Randomization Collaboration (2017). Association between telomere length and risk of cancer and non-neoplastic diseases: a mendelian randomization study. *JAMA Oncology*, 3, 636–651.

Zhang, D. D. *et al.* (2022). Risk of dementia in cancer survivors: a meta-analysis of population-based cohort studies. *Journal of Alzheimers Disease*, 89, 367–380.

https://doi.org/10.1017/S1041610222001119