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van der Willik, K.D.; Schagen, S.B.; Ikram, M.A.

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REVIEW

WILEY

Cancer and dementia: Two sides of the same coin?

Kimberly D. van der Willik[1,2] | **Sanne B. Schagen**[1,3] | **M. Arfan Ikram**[2]

[1]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

[3]Brain and Cognition, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
M. Arfan Ikram, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.
Email: m.a.ikram@erasmusmc.nl

Abstract

Noncentral nervous system cancer and the brain share an interesting and complex relation, with an emerging body of evidence showing that cancer patients are at an increased risk of developing cognitive problems. In contrast, population-based studies consistently find an inverse link between cancer and dementia, that is patients with dementia having a lower risk of subsequently developing cancer, and cancer patients being less often diagnosed with dementia. Different biological processes such as inversely activated cell proliferation and survival pathways have been suggested to have an important role underlying this inverse association. However, the effect of methodological biases including surveillance or survival bias has not been completely ruled out, calling into question the inverse direction of the association between cancer and dementia. In fact, emerging evidence now suggests that cancer and dementia might share a positive association. This narrative review summarises the current literature on cancer, cognitive problems and dementia. Moreover, different strategies will be discussed to reduce the impact of potential methodological biases on the association between cancer and dementia, trying to reveal the true direction of this link.

KEYWORDS

Cancer, cognitive problems, dementia, epidemiology

1 | INTRODUCTION

With ageing populations worldwide, the incidence and prevalence of age-related diseases including cancer and dementia are rapidly increasing. Cancer is the second leading cause of death in the United States, and it has taken the lead in several European countries.[1,2] Early diagnosis and improvement of treatments have ensured longer survival of cancer patients, which in turn increases rates of long-term side effects, both of cancer itself and of the aggressive treatments. At the same time, prevalence rates of cognitive impairment among older individuals vary between 5% and 29%, depending on the definition used.[3] In addition, over 46 million individuals worldwide are living with dementia, which is expected to almost double every 20 years.[4]

A substantial body of literature suggests a link between cancer and dementia, that is patients with dementia have a decreased risk of subsequently being diagnosed with cancer, and cancer patients have a lower risk of dementia.[5-20] Importantly, this association is not restricted to cancer of the central nervous system (CNS) or to long-term adverse effects of cancer treatments. Indeed, there is emerging evidence suggesting a direct link between non-CNS cancer and dementia. However, the exact nature of this link as well as the mechanistic underpinnings remains largely unknown.

In this narrative review, we provide a comprehensive overview of the literature on cognitive problems in non-CNS cancer patients. We then focus on studies investigating the risk of cancer in patients with dementia, and the risk of dementia in patients with cancer in the general

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population. These studies mostly show an inverse association between these diseases. Next, an overview is given on potential biological and methodological underpinnings of this inverse link. Since methodological issues may affect the direction and magnitude of this association, we subsequently propose several strategies that will aid in reducing potential methodological biases in this research area. Finally, we discuss emerging evidence that cancer and dementia might actually share a positive association.

2 | COGNITIVE PROBLEMS IN PATIENTS WITH NON-CNS CANCER

The number of cancer survivors is growing due to ageing populations, earlier detection of cancer and advances in cancer treatments.[21] This results in a large number of persons confronted with long-term side effects of cancer and cancer treatment, such as premature menopause, congestive heart failure and cognitive problems.

The prevalence of cognitive problems during and after cancer treatment ranges between 17% and 75%, with a subgroup of non-CNS cancer survivors having long-term cognitive problems lasting up to more than 20 years after cessation of treatment.[22,23] For many years, research was primarily directed to chemotherapy as the driving force behind disturbances in the normal functioning of the brain dubbed by some cancer survivors as "chemobrain." Different mechanisms for chemotherapy-induced cognitive problems have been revealed and suggested, including toxicity to neural progenitor cells, DNA damage in postmitotic neurons and telomere shortening, deregulation of cytokines and hormonal changes.[24] However, studies examining the consequences of chemotherapy on brain functioning often were cross-sectional and therefore provided no information about the baseline cognitive function of cancer patients.[25]

More recent longitudinal studies have incorporated baseline evaluations of cognitive functioning after surgery and before initiation of systemic adjuvant therapy. These studies revealed that chemotherapy may not be the only cause of cognitive problems, as some studies found that patients already showed lower than expected cognitive functioning before start of chemotherapy.[26-29] Moreover, imaging studies show that prior to chemotherapy, patients may already have altered structural and functional brain structures, including lower white matter integrity and hyperactivation of different brain regions, in particular the frontal and parietal lobes.[30-34] Hyperactivation is often seen as a compensatory mechanism to maintain adequate levels of task performance during inadequate functioning of the brain.[35] For instance, a functional magnetic resonance imaging study conducted in breast cancer patients prior to chemotherapy showed increased frontal lobe activation during working memory performance, suggesting the need for prefrontal compensation in response to cancer.[34] Changes in brain functions were not fully explained by anxiety, depression or fatigue. However, the time of study entry may not be appropriate, as the impact of anaesthesia and side effects of surgery could also induce changes in cognitive functioning. Less is known about the cognitive functioning in cancer patients prior to surgery. Thus far, three studies have been conducted evaluating cognitive function in newly diagnosed breast cancer patients.[36-38] Interestingly, these patients also show worse neuropsychological test performance and alterations on MRI scans compared to controls that cannot be explained by the distress accompanied by cancer diagnosis, suggesting that cancer itself may induce changes in the normal functioning of the brain. Preclinical support for this observation comes from studies showing that immunodeficient mice engrafted with patient tumour tissue show molecular changes in the brain similar to those seen in neurodegeneration and brain ageing.[39,40]

Besides the role of cancer itself, cognitive problems in newly diagnosed cancer patients could also be explained by a shared pathology. For instance, genetic susceptibility, inflammation and oxidative stress are processes related to cancer and to cognitive decline.[41,42] Furthermore, shared risk factors such as ageing, smoking, lack of physical activity and a poor diet could also play a role in the development of both conditions. As yet, there are multiple candidate mechanisms for the observed cognitive problems in cancer patients after diagnosis and prior to subsequent treatment. More research is needed to determine when cognitive problems in cancer patients originates in order to distinguish the impact of cancer itself from the role of shared pathologies and risk factors.

3 | THE RISK OF CANCER IN DEMENTIA PATIENTS AND THE RISK OF DEMENTIA IN PATIENTS WITH CANCER

Literature shows intriguing findings about the association between cancer and cognitive problems, with multiple studies showing cancer patients at an increased risk of developing long-term cognitive problems. Dementia is often preceded by cognitive impairment, in which pathophysiological processes underlying dementia may already be present. Since a shared pathology between cognitive problems and cancer has been hypothesised, a logical question emerges whether cancer and cancer treatment are also associated with an increased risk of dementia.

Interestingly, multiple studies suggest an inverse association between cancer and dementia, in particular for Alzheimer disease (AD).[5-20] In 1990, Yamada et al investigated risk factors for dementia in atomic-bomb survivors and observed that the odds of having cancer prior to AD

was 70% lower in patients with AD compared to persons without AD. More than a decade later, longitudinal studies confirmed that cancer patients were at a decreased risk of developing dementia. Moreover, these studies showed also that patients with dementia were less likely to be diagnosed with cancer. These findings suggest an inverse association between cancer and dementia in both directions. This inverse association was observed for most cancer types, including nonmelanoma skin cancer, and was consistent across different studies. An overview of the individual studies investigating this association is provided in Table 1.

In addition to the role of cancer itself, few retrospective studies evaluated the effect of chemotherapy on dementia in breast cancer survivors.[43-46] All these studies used data from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. For this reason, the outcomes cannot be interpreted as independent. Nevertheless, these studies demonstrated contrasting results with only one study showing an increased incidence of dementia among patients treated with chemotherapy.[45] Comparison of the risk of dementia in cancer survivors after chemotherapy with the dementia risk among cancer-free controls showed again an inverse association.[44]

Multiple biological mechanisms have been proposed supporting this inverse association between cancer and dementia in both directions. Promotion of genetic pathways involved in cell proliferation and survival could result in an increased cancer risk, while dementia is associated with increased cell death. For instance, the expression of the tumour suppressor protein p53 is often decreased in cancer, while elevated in AD brains.[47] Furthermore, the enzyme pin1 is involved in protein folding and cell cycle regulation, and is often overexpressed in tumours whereas it is depleted in AD. Other candidate processes are opposite disturbances of the epigenome and ultraviolet radiation exposure.[17,48]

Despite consistent results and suggested biological mechanisms, several methodological issues driving this inverse association have not completely been ruled out. Therefore, careful interpretation and critical evaluation of the observed link are needed. Cancer and dementia are accompanied by multiple symptoms, which can mask symptoms of other, yet undiagnosed diseases. Additionally, physicians could be less willing to refer diseased patients, resulting in surveillance bias. Furthermore, studying diseases in the older population may be subject to survival bias. Since it is important to understand the potential methodological limitations to critically review the inverse association between cancer and dementia, the two types of biases will be discussed in more detail.

3.1 | Surveillance bias

Surveillance bias arises when patients with a certain disease undergo increased or decreased screening, resulting in a respectively higher or lower probability to be diagnosed with the studied outcome.[49] For instance, patients with urinary tract stones seem to have an increased risk of cancer, whereas there is no evident biological relation between these conditions.[50] The diagnosed tumours are more often in situ carcinomas and are smaller compared to tumours in patients without urinary tract stones, suggesting that these cancers are identified during the diagnostic work-up of urinary tract stones. Without the diagnostic process of the urinary tract stones, patients would have been diagnosed with cancer in a more advanced stage or not at all. Therefore, part of the association between urinary tract stones and cancer seems to be the result of surveillance bias.

Surveillance bias due to decreased screening could be introduced in the investigation of the association between cancer and dementia, since patients with these diseases may be less likely to be screened and diagnosed with other diseases. Several observations support this conception.

First, patients with dementia are not always able to communicate symptoms.[51] It has been observed that dementia patients often use less pain medication for comorbid conditions compared to healthy controls, which may be due to disturbances in communication or as a result of decreased pain experience due to neurodegeneration.[52,53] This is supported by the finding that cancer in dementia patients is often diagnosed in a more advanced stage compared to persons without dementia, since pain is an important symptom of a variety of cancers.[54] In turn, symptoms of comorbid diseases in cancer patients may be attributed to cancer by patients and their physicians, leaving the other underlying disease unrecognised.[55]

Moreover, when a patient has a serious illness with a limited life expectancy, physicians may be less prepared to start a diagnostic work-up for new symptoms. In the case of dementia, patients undergo less often screening for cancer.[56,57] It can be difficult for these patients to understand the risks and benefits of screening.[58] Additionally, the benefits of cancer screening may not outweigh the harm due to the risk of overdiagnosis and overtreatment. A study under elderly care physicians in nursing homes showed that end stage dementia was the primary reason to not refer patients with suspected breast cancer.[59] In cancer patients, cognitive problems remain often unrecognised since cognitive assessment is not standard practice.[60] For this reason, a diagnosis of cognitive impairment or dementia could remain unrecognised in cancer patients.

Lastly, when a dementia patient is suspected to have cancer, pathological confirmation through biopsies is often omitted since it does not have therapeutic consequences.[61] Several studies demonstrated that patients with dementia and cancer often do not receive cancer treatment.[54] Since many cancer registries only register pathological confirmed tumours, these tumours will remain unnoticed.[62]

TABLE 1 Overview of studies investigating the association between cancer and dementia

Study	Study design		Cancer type	Dementia type	Study participants	Age at inclusion	Mean follow-up (years)	Effect estimate (95% CI)	Controlling for bias	Conclusion
Studies investigating the risk of dementia in patients with cancer/cancer survivors										
Yamada et al[19]	Prevalence study in atomic-bomb survivor cohort	Cross-sectional	Any cancer type	AD	Total N = 2222 (28.7% men). 230 participants had (a history of) cancer. 74 participants had AD. Unknown how many AD patients had a history of cancer	≥60	NA	OR 0.3 (0.05-0.98)	None	Decreased risk of AD in cancer patients/ survivors
Realmuto et al[13]	Case-control study	Cross-sectional	Any cancer type	AD	Total N = 378 (28.6% men). 84 participants had (a history of) cancer. 126 participants had AD, of whom 23 with a history of cancer (18.3%)	No criterion	NA	OR 0.6 (0.4-1.1)	Different cancer types	Decreased risk of AD in cancer patients/ survivors
White et al[18]	Population-based cohort study	Longitudinal	NMSC	AD	Total N = 1102 (39.3% men). 141 participants had (a history of) NMSC. 100 participants developed AD, of whom 6 with prevalent NMSC (6.0%)	≥70	3.7	HR 0.47 (0.21-1.09)	None	Decreased risk of AD in NMSC patients/ survivors
Nudelman et al[11]	Case-control study	Cross-sectional	Any cancer type	AD	Total N = 1609 (51.3% men). 503 participants had (a history of) cancer. 446 participants had AD, of whom 83 with a history of cancer (18.6%)	≥50	NA	OR 1.5 (1.3-1.8)[a]	Different cancer types	Decreased risk of AD in cancer patients/ survivors, driven by NMSC
Frain et al[8]	Retrospective cohort study of US veterans	Longitudinal	Exclusion of NMSC	AD	Total N = 3499 378 (98.0% men). 771 285 participants had (a history of) cancer. 82 998 participants developed AD. Unknown how many AD patients had a history of cancer	≥65	5.7	HR 1.00 (0.97-1.03)	Risk over four time intervals following cancer diagnosis Negative control diseases Different cancer types	Decreased risk of AD in some cancer type patients/ survivors, but not for all cancer types together

(Continues)

TABLE 1 (Continued)

Study	Study design		Cancer type	Dementia type	Study participants	Age at inclusion	Mean follow-up (years)	Effect estimate (95% CI)	Controlling for bias	Conclusion
Bowles et al[6]	Prospective population-based cohort study	Longitudinal	Exclusion of NMSC	AD	Total N = 4357 (41.3% men). 756 participants had prevalent cancer. 583 participants developed incident cancer. 877 participants developed AD, of whom 126 with prevalent cancer (14.4%) and 73 with (a history of) incident cancer (8.3%)	≥65	6.4 (median)	Prevalent cancer: HR 0.95 (0.77-1.17) Incident cancer: HR 0.73 (0.55-0.96)	Risk of dementia per cancer stage Analysis in participants who survived at least to age 80 Different cancer types	Only a decreased risk of AD in incident cancer patients/ survivors, not in prevalent cancer patients/ survivors
Studies investigating the risk of cancer in patients with dementia										
Attner et al[5]	Case-control study	Cross-sectional	18 different cancer types	Any	Total N = 167 080 (unknown % men). 2985 participants had a history of AD. 19 756 had cancer, of whom 253 with a history of AD (1.3%)	No criterion	NA	RR 0.60 (0.52-0.69)	Different cancer types	Decreased risk of cancer in dementia patients
Ou et al[12]	Retrospective population-based cohort study	Longitudinal	Any cancer type	AD	Total N = 6960 (39.7% men). All 6960 participants had AD. 405 of these participants developed cancer (5.8%)	≥40	4.25	SIR 0.88 (0.80-0.97)	Stratified analysis by duration of AD diagnosis Different cancer types	Decreased risk of cancer in AD patients
Romero et al[16]	Prospective population-based cohort study	Longitudinal	Any cancer type (only cancer specific mortality)	AD	Total N = 4197 (42.0% men). 467 participants had AD. 441 participants died of cancer, of whom 16 had AD (3.6%)	≥65	10.1	HR 0.50 (0.27-0.93)	None	Decreased risk of cancer specific mortality in AD patients
Van der Willik et al[20]	Prospective population-based cohort study	Longitudinal	Exclusion of NMSC	AD	Total N = 13 207 (41.9% men). 1404 participants had AD. 2316 participants developed cancer, of whom 63 with AD (2.7%)	≥45	9.4	HR 0.53 (0.41-0.68)	Analyses in a preclinical stage of dementia (MCI)	Decreased risk of cancer in AD patients

(Continues)

TABLE 1 (Continued)

Study	Study design		Cancer type	Dementia type	Study participants	Age at inclusion	Mean follow-up (years)	Effect estimate (95% CI)	Controlling for bias	Conclusion
Studies investigating both the risk of dementia in patients with cancer/cancer survivors and the risk of cancer in patients with dementia										
Roe et al[14]	Prospective cohort study	Longitudinal	Any cancer type	AD	Total N = 594 (35.7% men). 50 participants had (a history of) cancer. It is unknown how many participants developed AD	≥47	4.0 in patients with cancer	HR 0.34 (0.10-1.12)	None	Decreased risk of AD in cancer patients/survivors
	Prospective cohort study	Longitudinal	Any cancer type	AD	Total N = 249 (37.3% men). 395 participants had AD. 45 participants developed cancer. Unknown how many cancer patients had AD	≥47	3.2 in patients with AD	HR 0.34 (0.18-0.62)	None	Decreased risk of cancer in AD patients
Roe et al[15]	Prospective cohort study	Longitudinal	Any cancer type	AD	Total N = 2151 (unknown % men). 390 participants had (a history of) cancer. It is unknown how many participants developed AD	≥65	5.4	HR 0.72 (0.52-1.00)	None	Decreased risk of AD in cancer patients/survivors
	Prospective cohort study	Longitudinal	Any cancer type (only cancer specific hospitalisation)	AD	Total N = 2225 (unknown % men). 118 participants had AD. Unknown how many participants had cancer hospitalisations	≥65	8.3	HR 0.41 (0.20-0.84)	None	Decreased risk of cancer in AD patients
Driver et al[7]	Prospective population-based cohort study	Longitudinal	Exclusion of NMSC	AD	Total N = 1278 (38.8% men). 423 participants had (a history of) cancer. 256 participants developed AD. Unknown how many AD patients had a history of cancer	≥65	10	HR 0.81 (0.59-1.11)	Different cancer types Analysis in participants who survived at least to age 80 Negative control disease	Decreased risk of AD in cancer patients/survivors
	Case-control study	Cross-sectional	Exclusion of NMSC	AD	Total N = 1980 (unknown % men). 376 participants had AD. 252 participants developed cancer. Unknown how many cancer patients had AD	≥65	NA	HR 0.38 (0.25-0.56)	Different cancer types	Decreased risk of cancer in AD patients

(Continues)

TABLE 1 (Continued)

Study	Study design		Cancer type	Dementia type	Study participants	Age at inclusion	Mean follow-up (years)	Effect estimate (95% CI)	Controlling for bias	Conclusion
Musicco et al[10]	Prospective/ retrospective historical cohort study	Longitudinal	Any cancer type	AD	Total N = 21 451 (57.0% men). All of these participants had (a history of) cancer. 161 participants developed AD of whom 68 with (a history of) cancer (42.2%)	≥60	101 317.9 person years	RR 0.64 (0.50-0.81)	Retrospective and prospective follow-up Separate analyses for persons surviving or dying during follow-up Different cancer types	Decreased risk of AD in cancer patients/survivors
	Prospective/ retrospective historical cohort study	Longitudinal	Any cancer type	AD	Total N = 2832 (33.4% men). All of these participants had AD. 161 participants developed cancer, of whom 93 with AD (57.8%)	≥60	15 063.0 person years	RR 0.79 (0.64-0.97)	Retrospective and prospective follow-up Separate analyses for persons surviving or dying during follow-up Different cancer types	Decreased risk of cancer in AD patients
Freedman et al[9]	Prospective cohort study in Medicare population	Longitudinal	Any cancer type	AD	Total N = 1163 327 (50.4% men). 742 809 participants had (a history of) cancer. 21 526 developed AD of whom 11 812 with (a history of) cancer (54.9%)	≥66	1.9 in patients with cancer	HR 0.87 (0.84-0.90)	Negative control disease Different cancer types	Decreased risk of AD in cancer patients/survivors
	Case-control study	Cross-sectional	Any cancer type	AD	Total N = 979 816 (54.8% men). 7321 participants had AD. 836 947 participants had cancer, of whom 5961 with AD (0.7%)	≥66	NA	OR 0.86 (0.81-0.92)	Negative control disease Different cancer types	Decreased risk of cancer in AD patients

AD, Alzheimer dementia; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; NA, not applicable; NMSC, nonmelanoma skin cancer; OR, odds ratio; RR, risk ratio; SIR, standardised incidence ratio.
[a]Cancer history positive is used as reference.

3.2 | Survival bias

Survival bias is considered as a special case of selection bias and may occur when the studied exposure is associated with survival.[63] When the exposure negatively influences survival, those exposed individuals who will survive are likely to have some other, protective characteristics helping them to survive. This results in a lower frequency of the exposure among the survivors, which can be observed as an inverse association between the exposure and outcome.

A nice illustration is the observed association between smoking and dementia. It has repeatedly been shown that smoking increases the risk of dementia among younger persons, while it seems to be protective for dementia in older persons. This lower risk of dementia in older smokers is most likely due to selection bias. Most smokers who are susceptible for developing dementia will develop dementia due to their smoking habits before a certain age. The group of smokers who survive beyond this age is depleted by those smokers who were susceptible for developing dementia, resulting in a distorted low risk of dementia among smokers in the older population. Therefore, smoking may be falsely interpreted as protective for dementia among the older population. Survival bias can especially affect the results when studying the older population, since death rates are higher among older persons, and death is often affected by the exposure.[64]

Both cancer and dementia are potentially fatal diseases and affect survival. For dementia, the median overall survival depends on the age of the patient and ranges between 6.0 years for persons aged ≤75 and 3.5 years for those aged ≥85 years.[65] Survival rates for patients with cancer differ per cancer type and depend on the stage at diagnosis.[1] Importantly, patients who developed both cancer and dementia have a higher overall mortality and disease-specific mortality compared to the patients with only one of these conditions.[66] This suggests that survival bias could affect estimates of the association between cancer and dementia, resulting in lower exposure rates among the diseased (ie lower numbers of prevalent cancer diagnosis in patients with dementia, and less diagnoses of dementia before cancer development).

3.3 | Strategies to deal with surveillance and survival bias

Few studies investigating the inverse association between cancer and dementia have tried to overcome potential biases. Two studies restricted the analyses to persons who survived at least to age 80 years, trying to account for selective mortality resulting in survival bias.[6,7] The first study by Driver et al investigated the risk of AD in 995 participants from the longitudinal community-based Framingham Heart Study who survived at least to age 80 years. They proposed that if the inverse effect is mainly due to death of cancer survivors, this effect would be diminished after exclusion of the nonsurvivors. The effect estimates hardly changed in these sensitivity analyses (hazard ratio (HR) among all participants = 0.81, 95% confidence interval (CI) 0.59-1.11, and among cancer survivors aged at least 80 years = 0.81, 95% CI 0.46-1.46)[7]. Bowles et al[6] performed the same analysis among 2787 participants from the prospective community-based Adult Changes in Thought cohort study and found a HR of 0.69, 95% CI 0.51-0.92 among the survivors, compared to a HR of 0.73, 95% CI 0.55-0.96 in the total study population. Related to this approach, one study compared the effect estimates in persons who died to the effect estimates in those who survived during follow-up.[10] They reported that the inverse association between cancer and dementia was more pronounced in the survivors (risk ratio (RR) for cancer in AD patients in survivors 0.42, 95% CI 0.33-0.53; in nonsurvivors 0.86, 95% CI 0.68-1.06; RR for AD in cancer patients in survivors 0.58, 95% CI 0.46-0.72; in nonsurvivors 0.75, 95% CI 0.60-0.93). These findings indicate that the impact of survival bias on the association between cancer and dementia is limited. However, there are some caveats when limiting the analyses to survivors as used in the two abovementioned methods. First, cancer and dementia patients who survived may be healthier than those who died at younger ages. Moreover, cancer patients diagnosed with dementia, and dementia patients with cancer, have a shorter life expectancy than those patients with only one of these diseases. Therefore, restricting analyses to survivors can result in selection bias and may not be the most suitable approach to deal with survival bias.

Few studies investigated the relation of cancer with other diseases including stroke, automobile injuries, osteoarthritis and macular degeneration, which were used as negative control diseases.[7-9] In case of survival bias, cancer patients would also have a decreased risk of these diseases. The risk of stroke, osteoarthritis and macular degeneration after cancer was found to be increased, while there was no relation with automobile injuries. Interestingly, the risk of cancer following automobile injuries was decreased. For this reason, the authors suggested that the ascertainment of cancer after serious medical conditions is limited. However, it is questionable whether these diseases are suitable negative controls. Stroke and automobile injuries are characterised by acute symptoms, making the association with cancer less sensitive to surveillance bias. Moreover, there seems to be a biological mechanism underlying the frequently found positive relation between cancer and stroke.[67,68] Lastly, cancer shares risk factors with osteoarthritis and macular degeneration such as obesity and

inflammation.[69,70] Therefore, the results of the association of cancer with these negative control diseases should be interpreted carefully.

Furthermore, several studies investigated the risk of dementia in relation to different cancer sites or stages.[5,6,8-12] Tumours originated deep in the body may progress over a longer time until they become clinically manifest, compared to tumours located at the body surface. For instance, it would be less complicated to detect breast or skin cancer, compared to tumours originated in the pancreas or lung. Identifying these tumours could be easier, as well as performing diagnostic work-up such as obtaining tissue material for pathology. Although some results suggest that the inverse association is more pronounced for deep located tumours, risk estimates per cancer site differ across studies. A meta-analysis found that the decreased risk was mostly pronounced in head and neck, and colorectal cancer, while the risk of prostate cancer was increased in patients with dementia.[71] Due to nonreferral of suspected cancer patients, the risk of specific cancer types in dementia could still be underestimated.

At last, two studies stratified follow-up time to detect bias. In case of bias, the decreased risk of cancer or dementia is expected to be more pronounced in a longer period after the diagnosis has been made. Ou et al[12] found that the risk of cancer in patients with AD within the first year after AD diagnosis was comparable to the cancer risk in the general population, whereas the risk was lower thereafter (standardised incidence ratio (SIR) 0.98, 95% CI 0.76-0.95 and 0.85, 95% CI 0.76-0.95, respectively). In addition, Frain et al[8] determined the risk of AD during four time periods after cancer diagnosis for different cancer types, which was relatively constant over time depending on cancer type.

Despite the discussed applied strategies, potential effects of surveillance and survival bias have not been satisfactory ruled out. Studies with a different methodology, for example autopsy studies, studies using genetic information, or investigation of cancer in preclinical stages of the disease could shed additional light on the link between cancer and dementia.

3.4 | Autopsy studies

Searching for undiagnosed malignancies during autopsy in patients with dementia could account for surveillance bias. Autopsy studies show different results with respect to the prevalence of neoplasms in patients with AD, with some studies finding higher cancer rates in patients compared to controls, while others finding lower a prevalence than expected.[72-74] It should be noted that autopsied dementia patients may differ from nonautopsied dementia patients, which could result in selection bias.[75] Autopsied patients are more likely to be Caucasian, educated beyond high school, married and tend to have a lower Mini-Mental State Examination score. At present, no studies reporting on the prevalence of AD pathology in autopsied cancer patients have been published.

3.5 | Genetics

Evaluation of the genetic overlap between dementia and cancer could reveal the true direction of the association between cancer and dementia. One study used genomewide association study summary statistics showed a positive genetic correlation between these diseases, implying that cancer and dementia share some genetic background.[76] Shared genetic variants could modulate the risk of cancer and dementia in the same direction, thereby pointing towards pleiotropic effects. The strongest positive genetic correlations were found in regions representing enhancer marks on the genome, indicating a possible role of gene expression regulation in the pathogenesis of both diseases.

3.6 | Preclinical stages

Identifying persons with an increased risk of developing cancer or dementia could be another strategy to deal with surveillance or survival bias. For instance, persons with an increased genetic risk or a preclinical stage of the disease could provide more insight in the association between cancer and dementia, since their life expectancy will be longer compared to persons who already developed the disease. Carcinoma in situ can be seen as a preclinical stage of cancer. However, not all cancer types are preceded with this noninvasive stage and it can be hard to identify these patients. It could be less complicated to identify patients with an early stage of dementia.

The pathophysiological process underlying AD begins years before the clinical diagnosis has been made.[77] Mild cognitive impairment (MCI) has the same pathological underpinnings as AD and can be seen as a preclinical stage of AD. Despite the fact that not every person with MCI will eventually develop AD, over half of these persons will progress to AD within a period of 5 years.[78] In case of a suspected tumour, it is more likely that patients with MCI will be referred to a physician compared to AD patients. These persons also have a longer life expectancy compared to patients with AD. For these reasons, the relation between cancer and AD could be explored with less influence of biases using MCI as a proxy for dementia. In a first attempt to do so, we investigated the risk of cancer in persons with MCI and compared this with the risk of cancer in dementia patients in a population-based prospective cohort study.[20] In this study, we showed that persons with MCI tended to have an increased risk of developing cancer

(HR 1.24, 95% CI 0.99-1.58), which is in contrast with the decreased cancer risk among patients with dementia (HR 0.59, 95% CI 0.41-0.68). Although the risk of MCI in cancer patients has yet to be investigated, these findings suggest that the inverse association between cancer and dementia might be based on methodological bias.

4 | EXPLORING THE CONCEPT OF A POSITIVE ASSOCIATION BETWEEN CANCER AND DEMENTIA

The association between cancer and dementia remains complicated, since a substantial amount of bias may influence the direction of the association. Based on the high prevalence of cognitive problems among cancer patients, shared genetic traits and the increased risk of cancer in persons with MCI, the existence of a true inverse link between cancer and dementia can be questioned; in fact, it is reasonable to explore the existence of a positive association which may be more plausible from a mechanistic point of view.

Support for a positive association between cancer and dementia is found in the notion that various processes are involved in the pathogenesis of cancer and dementia, such as inflammation, oxidative stress and angiogenesis. Increased inflammatory biomarkers such as fibrinogen and interleukin-6 are associated with lower cognitive performance and cognitive decline. Different proteins are involved in this process, including the amyloid beta (Aβ) peptide. Aβ is the product of amyloid precursor protein (APP) proteolysis and can be measured in blood, cerebrospinal fluid and by imaging. Accumulation of plaques containing Aβ is one of the hallmark features of AD and is currently the earliest detectable pathological change in the preclinical stage of AD.[77] It has been suggested that Aβ is also involved in cancer, since APP is overexpressed in several tumours and is associated with cell proliferation, migration and invasion.[79] Moreover, the BRCA1 protein, an important tumour suppressor protein, has recently been linked to AD. Overactivation of BRCA1 can indirectly result in Aβ pathology and can promote neuronal cell death.[80] Furthermore, plasma levels of Aβ-40 and Aβ-42 are increased in patients with different cancer types.[81]

DNA damage caused by oxidative stress and deficient DNA repair mechanisms are also important in the pathogenesis of cancer and dementia. Genetic polymorphisms associated with a decreased capacity to repair damaged DNA can be related to an increased risk of cancer and cognitive impairment. Furthermore, syndromes such as xeroderma pigmentosum and ataxia telangiectasia are caused by genetic defects in DNA damage repair mechanisms and are characterised by an increased risk of cancer and cognitive problems, indicating a shared pathology.[24]

5 | CONCLUSION

The relation between non-CNS cancer and the brain is complex. Whereas an emerging body of research has shown that cancer patients often experience cognitive problems, the risk of developing dementia in cancer survivors is still unclear. Methodological issues such as surveillance and survival bias complicate the investigation of the association between cancer and dementia in both directions. Although multiple attempts have been made to deal with these biases, this is still insufficiently taken care of, and consensus is lacking about the driving force behind the inverse association. Understanding the contrasting but also the overlapping mechanisms underlying cancer and dementia can provide insight into prevention and therapeutic strategies for both diseases. Therefore, it is necessary to reveal the true nature of the association, for instance by focussing more on the preclinical stages of cancer and dementia.

CONFLICT OF INTEREST

The authors report no disclosures relevant to the manuscript.

ORCID

Kimberly D. van der Willik http://orcid.org/0000-0002-4479-2914

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