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Association of Cancer History with Alzheimer's Disease Dementia and Neuropathology

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Abstract

Background—Cancer and Alzheimer's disease (AD) are common diseases of aging and share many risk factors. Surprisingly, however, epidemiologic data from several recent independent cohort studies suggest that there may be an inverse association between these diseases.

Objective—To determine the relationship between history of cancer and odds of dementia proximate to death and neuropathological indices of AD.

Methods—Using data from two separate clinical-pathologic cohort studies of aging and AD, the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), we compared odds of AD dementia proximate to death among participants with and without a history of cancer. We then examined the relation of history of cancer with measures of AD pathology at autopsy, i.e., paired helical filament tau (PHFtau) neurofibrillary tangles and amyloid-β load.

Results—Participants reporting a history of cancer had significantly lower odds of AD (OR 0.70 [0.55–0.89], $p = 0.0040$) proximate to death as compared to participants reporting no prior history of cancer. The results remained significant after adjusting for multiple risk factors including age, sex, race, education, and presence of an *APOE* ε4 allele. At autopsy, participants with a history of cancer had significantly fewer PHFtau tangles ($p < 0.001$) than participants without a history of cancer, but similar levels of amyloid-β.

Conclusions—Cancer survivors have reduced odds of developing AD and a lower burden of neurofibrillary tangle deposition.

Keywords

Alzheimer's disease; amyloid-β; cancer; cohort study; dementia; malignancy; neurofibrillary tangles; PHFtau

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INTRODUCTION

As the global population ages, both cancer and Alzheimer's disease (AD) have become leading causes of morbidity and mortality around the world. Although the prevalence of both diseases increases with age, epidemiologic data from several independent cohorts suggest that cancer survivors have a decreased risk of AD [1–4], and that people with AD have a reduced risk of developing cancer [1–5]. A similar inverse association with cancer has been described in Parkinson's disease [6–8] and other neurodegenerative diseases as well [9]. Establishing a lower risk of neurodegenerative diseases among cancer survivors has been challenging due to the problem of selective mortality (i.e., people with cancer may die selectively before developing neurodegenerative diseases). However, prior studies that have addressed survivorship bias find that this is unlikely to explain the inverse association [3, 4].

A lower risk of AD dementia among cancer survivors is surprising given that these diseases share several common risk factors. In addition to older age, other risk factors that contribute to the incidence of both cancer and AD dementia include smoking, sedentary lifestyle, obesity, and the metabolic syndrome [10–15]. A reduced risk of AD dementia among cancer survivors is also difficult to reconcile with an accumulating body of evidence that demonstrates cognitive impairment following the administration of cytotoxic chemotherapy used in the treatment of many cancers. Longitudinal cohort studies of pediatric and adult cancer survivors who received cytotoxic chemotherapy have consistently shown marked deficits in verbal function, problem-solving, and processing speed months to years after the completion of curative cancer therapy [16–19]. These chemotherapy effects might reflect cerebral injury which would decrease cerebral reserve, and if anything, increase later clinical expression of AD.

Understanding the relationship between cancer and neuropathologic features of AD could further clarify the relationship between cancer and AD dementia. Nothing is known about the neuropathologic differences between people with a history of cancer and those without a known history of cancer. While several studies have examined the clinical outcomes of cancer survivors, we are unaware of any brain autopsy series examining the relationship of a cancer history with measures of AD or other neurodegenerative disease pathology. The purpose of this study was to investigate 1) the association between history of cancer and odds of dementia proximate to death, and 2) the association between history of cancer and expression of amyloid-β plaques and paired-helical filament tau (PHFtau) neurofibrillary tangles, the two defining pathologic lesions of AD [20], in brain autopsies from two large cohort studies of older adults.

METHODS

Study population

The data were obtained from two separate longitudinal clinical-pathologic cohort studies of aging: the Religious Orders Study (ROS) [21] and the Rush Memory and Aging Project (MAP) [22]. These studies were approved by the Institutional Review Board of Rush University Medical Center. ROS enrolls older adult Catholic clergy males and females across the US while MAP enrolls community-dwelling older adults throughout the Chicago

metropolitan area. In both studies, enrollees agree to annual detailed clinical evaluation and brain donation at the time of death. At the time of this analysis, 1,289 participants had died and had autopsy data available for evaluation. The overall follow-up rate was over 90%, and the overall autopsy rate was 86%.

History of cancer

A past medical history, including a history of cancer, was obtained from participants at the time of enrollment. Participants were asked, “Have you ever been told by a doctor, nurse or therapist that you had cancer, malignancy or tumor of any type?” Participants could respond, “1 =Yes,” “2 = Suspect or possible,” “3 = No, or refusal/don’t know.” This question was repeated at each annual detailed clinical evaluation. Participants were recorded as having cancer prior to baseline longitudinal study only if they responded “1 =Yes” at the time of enrollment; otherwise they were recorded as having no history of cancer prior to study baseline. Participants were recorded as having cancer proximate to death if they responded “1 =Yes” either at baseline or at any annual assessment before death.

Clinical diagnoses

A clinical diagnosis of no dementia, AD dementia, or non-AD dementia was made as previously described [21–24]. Briefly, study participants underwent annual extensive cognitive testing with 19 tests administered by trained technicians to assess multiple cognitive domains. Study participants also self-reported activities of daily living, thereby providing an assessment of their ability to independently perform basic tasks of everyday life. A neuropsychologist, blinded to demographic information other than years of formal education, reviewed the results of all of the cognitive tests to determine the presence or absence of cognitive impairment at each annual assessment.

At the time of death, an experienced clinician independently evaluated each participant and reviewed all available antemortem data to establish a final clinical diagnosis, which was used in these analyses. Participants were categorized by the physician as having AD dementia if they met the criteria established by the working group of the Department of Health and Human Services Task Force on Alzheimer’s Disease (NINCDS-ADRDA Work Group) [25], or non-AD dementia if they were diagnosed as having dementia but did not meet criteria for AD dementia. Patients who were found to have impairment by the neuropsychologist but did not meet criteria for dementia (AD or non-AD) by the physician were categorized as having mild cognitive impairment (MCI). All other participants were categorized as having normal cognitive function.

Apolipoprotein E ε4 allele (APOE ε4) genotyping

An antemortem blood sample was taken from participants during clinical evaluation or at a scheduled time for biofluid donation. Samples underwent lymphocyte separation within 24 hours of collection, and then were placed in cryopreservative. DNA was extracted and *APOE* genotyping was performed as previously described [26]. In some cases genomic DNA was extracted from postmortem frozen brain.

Neuropathology measures

All brain extractions, tissue processing, staining for PHFtau and amyloid-β, and diagnostic microscopic examinations were conducted with a standardized protocol continuously over the duration of the MAP and ROS longitudinal cohort studies, as described previously [22, 27, 28]. Briefly, after extraction and weighing, cerebral hemispheres were cut into 1 cm coronal slabs, and slabs from one hemisphere were fixed in 4% paraformaldehyde and then placed in 2% dimethylsulfoxide/2% glycerol in phosphate-buffered saline for storage. Tissue from eight CNS areas of interest were dissected, paraffin embedded, and cut into 20-μm sections for immunocytochemistry to obtain quantitative data on the two main pathologic features of AD, amyloid-β plaques and PHFtau neuronal neurofibrillary tangles. Regions included anterior cingulate cortex, dorsal lateral prefrontal cortex, superior frontal cortex, inferior temporal cortex, hippocampus (cornus ammonis subfield 1/subiculum), entorhinal cortex, angular/supramarginal gyrus, and primary visual cortex.

PHFtau was labeled with an antibody specific for phosphorylated PHFtau, AT8 (1:2000, Thermo Fisher Scientific, Rockville, IL) in 4% horse serum, and amyloid-β was labeled with one of three antibodies: 6F/3D (1:50, Dako North America Inc., Carpinteria, CA), 1–16 (10D5) (1:600, Elan Pharmaceuticals, San Francisco, CA) and 17–24 (4G8) (1:9000, Covance Labs, Madison, WI). The 10D5 antibody was initially used in the MAP cohort and the 6F/3D antibody was initially used in the ROS cohort, but we switched to the 4G8 antibody for both cohorts when the 10D5 was discontinued by the vendor. All staining was performed using identical incubation times on an automated immunohistochemical stainer. PHFtau neurofibrillary tangles were counted using computer-assisted sampling. Tangle density (/mm2) in each region was standardized and the mean of the standard scores was used as a composite measure of tangle density for statistical analysis. The percent area occupied by amyloid-β plaques was calculated using a high-throughput computer-assisted method as previously described [27] and similarly averaged across the eight regions. Neuropathologic measures were performed by operators blinded to all clinical data.

Statistical analysis

We first examined bivariate associations of variables of interest with a history of cancer at the time of study enrollment (baseline) or ever before death using χ^2 for categorical variables and an analysis of variance (ANOVA) for continuous variables. We then investigated whether history of cancer at baseline was associated with a diagnosis of AD dementia proximate to death using a series of logistic regression analyses. We first adjusted for age at death and sex. We then adjusted for race, education, and the presence of one or more *APOE ε4* alleles. Participants with non-AD dementia were excluded from these analyses. We then repeated these models with the inclusion of participants with non-AD dementia, using AD and non-AD dementia (i.e., any dementia) proximate to death as the primary outcome. In subgroup analyses, we repeated these logistic regression analyses for the subset of participants who were followed for at least one year.

To investigate the relationship between history of cancer and neuropathological indices of AD, we constructed a series of linear regression models with PHFtau tangles and amyloid-β plaques as the outcome variables. A reported history of cancer at baseline or at any annual

assessment before death was used for these models. Again, the basic model adjusted for age at death and sex, and the fully adjusted models added terms for race, education, and *APOE ε*4. We repeated these analyses for the subset of participants with a clinical diagnosis of AD dementia proximate to death. All statistical analyses were performed using JMP Pro 11 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and statistical significance was defined for all analyses as $p\backslash P < 0.05$.

RESULTS

Of the 1,289 participants with autopsy data available for analysis, 401 subjects (31.1%) had reported a history of cancer at the time of study enrollment. The mean age at baseline was 80.7 (SD 6.91, range 59.0–102.1) and the mean age at death was 88.6 (SD 6.7, range: 65.9–108.3). As shown in Table 1, a history of cancer was not associated with age at death, duration of longitudinal follow up, sex, race, education, or *APOE ε*4 (all $p > 0.1$). At their last clinical evaluation, 413 participants (32.0%) were cognitively normal, 319 participants (24.7%) had MCI, 522 participants (40.4%) had AD dementia, and 25 participants (1.9%) had non-AD dementia. Additional clinical-pathologic information is provided in Table 1.

The association of history of cancer with AD dementia

A lower percentage of those reporting a history of cancer at baseline developed clinical AD dementia proximate to death than those without a history of cancer: 35.5% versus 43.9% ($\chi^2 = 7.8$, $p < 0.01$). In logistic regression models, a history of cancer at baseline was associated with approximately 30% lower odds of AD dementia after adjustment for age at death and sex (Table 2, Model A, column 1), and after additional adjustment for race, education, and *APOE* genotype (Table 2, Model B, column 1). Limiting the above analyses to participants who were followed for at least one year ($n = 1158$) did not change the inverse association between cancer and AD proximate to death.

We repeated these analyses for a diagnosis of any dementia (AD or non-AD dementia) proximate to death. Again in logistic regression models, a diagnosis of cancer at baseline was inversely associated with any dementia proximate to death after adjustment for age at death and sex (Table 2, Model A, column 2), and after additional adjustment for race education, and *APOE* genotype (Table 2, Model B, column 2).

An additional 150 participants reported that they received a diagnosis of cancer during the follow up period (between baseline and death); therefore the total number of participants with a diagnosis of cancer proximate to death was 551 (42.7%). Interestingly, there were no differences in age at death for those newly reporting a history of cancer (Mean 86.2, SD 6.7) compared to those without history of cancer ever (Mean 88.7, SD 6.6, $p = 0.96$). Analyses comparing those with a history of cancer ever (at baseline or subsequent report) continued to show a lower odds of AD than those without a history of cancer ever, adjusted for age and sex (OR 0.55 [0.44 – 0.70], $p < 0.0001$), and in the fully adjusted model (OR 0.56 [0.44–0.70], $p < 0.0001$).

The association of history of cancer with PHFtau tangle density and amyloid-β load

As compared to subjects with no history of cancer prior to death, those with a history of cancer had significantly lower densities of PHFtau tangles at autopsy ($F = 15.5$, $p < 0.0001$). In linear regression analyses, a history of cancer was associated with fewer PHFtau tangles after adjustment for age at death, sex, race (Model A, column 1), and after full covariate adjustment in Model B (Table 3, column 1). Within the subgroup of participants with a clinical diagnosis of AD dementia proximate to death, those with a history of cancer had fewer PHFtau tangles than participants with no history of cancer ($F = 7.4$, $p = 0.007$).

By contrast, there were no differences in amyloid-β plaques between participants with and without a history of cancer proximate to death in bivariate analyses ($F = 0.28$, $p = 0.60$). In linear regression analyses, there were no significant differences in amyloid-β plaques between participants with and without a history of cancer after adjustment for age at death, sex, and race (Model A, column 2), and after full covariate adjustment in Model B (Table 3, column 2).

DISCUSSION

In this study of older adults from two longitudinal clinical-pathological cohorts, we observed a lower likelihood of AD dementia proximate to death among participants reporting a history of cancer. Furthermore, we newly demonstrate that a history of cancer proximate to death is associated with a lower density of brain PHFtau neurofibrillary tangles, but not amyloid-β plaque load, on postmortem examination. We and others have shown that the accumulation of PHFtau tangles correlates with cognitive impairment and dementia severity more so than amyloid-β plaques and may mediate the relationship of amyloid-β to AD dementia [27, 29]. Therefore, a lower burden of PHFtau pathology among cancer survivors may be a mechanism through which cancer is associated with a lowered risk for AD dementia.

Our results build upon prior epidemiologic studies reporting that cancer survivors are at a reduced risk of AD dementia [1–5]. However, several issues must be overcome before concluding that a real association exists. Persons with neurodegenerative disease (or preclinical disease) may be less likely to undergo cancer screening and workup. Thus, it is possible that some subjects in our cohort had antecedent cognitive impairment that resulted in reduced cancer screening and diagnosis. Furthermore, history of cancer was self-reported in this study, and those with early cognitive impairment may be less likely to report having received a diagnosis of cancer. Another challenge with our approach is competing risks of mortality for these two diseases, and the possibility of survivorship bias. The possibility of survivorship bias was alleviated somewhat in a recent nested case-control analysis of dementia and cancer from the Framingham Heart Study [4]. In this study, the inverse association between cancer and AD dementia was not seen using an alternative diagnosis as the outcome, and also did not change after excluding participants who died, suggesting that the association is not caused by selective mortality in cancer survivors. Furthermore, our sample showed no differences in age at death among those reporting a history of cancer. Our neuropathological findings provide additional support for a real association between cancer

and a reduced risk of AD, as they demonstrate a biological inverse association between cancer and AD.

We hypothesize a number of pathways by which surviving cancer may affect PHFtau accumulation in the brain and subsequent expression of AD dementia. As both cancer and AD have been hypothesized to represent failures of the immune system [30, 31], it is possible that immune function could mediate enhanced survival from cancer and resilience in AD. Alternatively, cancer survivors may make healthy lifestyle choices in response to learning about their diagnosis, such as increased exercise and better nutrition, that result in healthier brain aging. Another possibility is that therapies used to treat cancer could impact the brain and reduce PHFtau tangle levels and incidence of AD. Microtubules are a target of several widely used chemotherapeutic agents: the taxanes [32] (paclitaxel, docetaxel, cabazitaxel) are microtubule stabilizers, whereas the vinca alkaloids [33] (vinblastine, vincristine, vindesine, vinorelbine) are microtubule inhibitors. It is therefore notable that tau protein, which becomes hyperphopshorylated and misfolds to form the neurofibrillary tangles that are a pathological hallmark of AD, is a microtubule-stabilizing protein and may be impacted by these chemotherapeutic agents. Paclitaxel and other microtubule-stabilizing agents have been investigated as a treatment for AD, and have demonstrated reduced PHFtau pathology in preclinical models [34, 35].

Alternatively, cancer and AD may represent terminal events of opposite aging pathways, driven by molecular processes that are deregulated in opposite directions. Such an explanation would explain not only why cancer survivors are at reduced risk for AD, but also why people with AD may be at a reduced risk for cancer [1–5]. One molecular candidate that could explain this bidirectional inverse association between cancer and AD is the peptidyl–prolyl cis/trans isomerase (PPIase) Pin1 [36–39]. This regulatory enzyme has multiple known cell functions including regulating cell-cycle control, cell proliferation, and apoptosis. Pin1 expression is increased in many human cancers [40], and is inversely correlated with neuronal degeneration, neurofibrillary tangles, and AD dementia [41, 42]. Differences in Pin1 expression could be responsible for the inverse association between cancer and expression of tau hyperphosphorylation and clinical AD described in our study and warrants further study.

Strengths of this investigation included the use of large longitudinal cohorts of older adults without known dementia at baseline and the use of quantitative pathological markers of AD. However, our analysis also had several limitations. A history of cancer was self-reported, and we were unable to investigate the relationship between specific cancers or cancer treatments and subsequent AD, due to insufficient power to investigate any particular malignancy and because this information was not obtained prospectively from participants. Further investigation of the relationship between cancer and AD using Medicare records of patients who enrolled in these longitudinal cohorts, instead of self-reported cancer history, is ongoing. As noted previously, it is also not possible to know if people who died from cancer at a younger age would have had a similar risk of AD and similar levels of PHFtau pathology as the cancer survivors who lived longer and were included in our cohort. Finally, the makeup of our cohort with a high proportion of white, non-Hispanic participants may limit the generalizability of our findings. In conclusion, an inverse association between

cancer and AD dementia has now been consistently reported in multiple cohort studies [1–5] and in the aggregate strongly supports the notion of a true inverse association. Our finding of lowered neuropathological burden of AD in cancer survivors provides additional support to this notion and a mechanistic clue for its understanding. Further investigation into the mechanisms underlying this association may lead to novel therapies for both AD and cancer.

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Table 1

Characteristics of the study participants

	No History of Cancer at Baseline	History of Cancer at Baseline	*p* value *p* value
No.	888	401	
Age at death [mean (SD)], y	88.7 (6.6)	88.6 (6.7)	$p = 0.79$
Duration of longitudinal follow up [mean (SD)], y	6.9 (4.7)	6.7 (4.6)	$p = 0.59$
Sex [No. (%)]			$p = 0.99$
Female	580 (65.3%)	262 (65.3%)	
Male	308 (34.7%)	139 (34.5%)	
Years of formal education [mean (SD)], y	16.3 (3.8)	16.5 (3.5)	$p = 0.27$
Race [No. (%)]			$p = 0.09$
Non-Hispanic, White	857 (96.5%)	394 (98.3%)	
Non-white or unknown	31 (3.5%)	7 (1.8%)	
≥1 ApoE4 allele	237 (26.9%)	100 (25.3%)	$p = 0.55$
AD dementia proximate to death	383 (43.9%)	139 (35.5%)	$*p = 0.0053$

Table 2

Cancer survivors have a reduced risk of AD dementia and any dementia. Numbers in brackets represent standard deviations

	AD dementia among participants with a history of cancer at baseline*	Any dementia among participants with a history of cancer at baseline
Unadjusted analysis	OR 0.71 [0.55–0.90], $p = 0.0040$	OR 0.73 [0.57–0.93], $p = 0.0097$
Model A		
+Age and sex	OR 0.70 [0.54–0.90], $p = 0.0047$	OR 0.72 [0.57–0.93], $p = 0.0097$
Model B		
+education, race, and ApoE4	OR 0.73 [0.56–0.94], $p = 0.015$	OR 0.75 [0.58–0.97], $p = 0.023$

* Participants with non-AD dementia ($n = 25$) were removed from analyses with AD dementia as outcome.

Table 3

At brain autopsy, participants with a history of cancer had decreased expression neurofibrillary tangles, but similar rates of amyloid-β. as participants with no history of cancer

	PHFtau tangles	Amyloid-β plaques
Unadjusted analysis	Est = 0.88, StdEr = 0.22, $p < 0.0001$	Est = 0.07, StdEr = 0.12, $p = 0.60$
Model A		
+Age, sex	Est = 0.87, StdEr = 0.22, $p < 0.0001$	Est = 0.06, StdEr = 0.12, $p = 0.65$
Model B		
+education, race, and ApoE4	Est = 0.82, StdEr = 0.22, $p = 0.0002$	Est=0.01, StdEr = 0.12, $p = 0.91$