Alzheimer disease and cancer

Abstract—Cross-sectional studies raise the possibility of protective relationships between, or a common mechanism underlying, the development of dementia of the Alzheimer type (DAT) and cancer. Using a prospective longitudinal design, the authors found that the risk of developing cancer is less among participants with DAT vs nondemented participants ($p < 0.001$) and that the risk of developing DAT may be less for participants with a history of cancer ($p = 0.060$).

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A small number of cross-sectional and case-control studies have reported an inverse relationship between dementia of the Alzheimer type (DAT) and cancer, such that the prevalence or history of cancer among individuals with DAT is less than among nondemented participants.[1-3] These studies raise the possibility that there may be a protective relationship between DAT and cancer or that a common mechanism influences the development of both disorders. If such a relationship exists, then individuals with DAT should be less likely to develop cancer in the future compared with similar individuals without DAT, and individuals with cancer should be less likely to develop DAT than individuals without cancer.

Using a prospective longitudinal design, this study examined whether 1) the risk of developing cancer in the future is less among participants with DAT who have reached older adult age without a history of cancer compared with nondemented participants and 2) the risk of developing DAT in the future among nondemented participants is less for those with a history of cancer.

Methods. Archival data from longitudinal studies conducted by the Washington University Alzheimer's Disease Research Center were used.[4] The details of recruitment, enrollment, and assessment in these studies have been published previously.[4,5] At entry and at all subsequent assessments, each participant and his or her collateral source took part in a semistructured interview and a general physical and neurologic examination conducted by experienced clinicians. For participants who received a Clinical Dementia Rating[6] indicative of dementia, a clinical diagnosis indicating the type of dementia was assigned. We evaluated only participants with a clinical diagnosis of DAT, which is confirmed by histopathologic AD in 93% of individuals at autopsy.[4] Beginning in April 1992, participants and collateral sources were also asked at every assessment whether the participant had ever had cancer and, if so, the type of cancer and the date of cancer diagnosis. Self-reports of cancer diagnoses have been found to be accurate.[7] Given our interest in a possible relationship between DAT and cancer generally and the lack of previous research in the area, we chose to examine all cancer types.

Statistical analyses. The survival curves of time from study entry to first cancer diagnosis among participants without a history of cancer as it related to having a diagnosis of DAT vs no dementia at entry were estimated by the Kaplan–Meier product-limit method and compared by a log-rank test. Cox proportional hazard models were used to test the effect of a DAT diagnosis combined with the effect of sex, age at study entry, and education, both with each demographic variable individually and in a model containing all variables, on the rate of receiving a cancer diagnosis (race was not included because no minority participants developed cancer during follow-up). The dependent variable in the survival analyses was the time from the entry assessment session to the first cancer diagnosis. When the year, but not the month, of diagnosis was available, time from study entry to the first assessment with a recorded cancer diagnosis was used. Cancer survival time for participants not receiving a cancer diagnosis during the study were considered censored on the date of their last assessment session in the analyses.

Similar analyses were conducted to assess differences in the diagnosis rate of DAT among participants with and without a history of cancer at entry. In these survival analyses, the dependent variable was the time between study entry and the first assessment with a diagnosis of DAT. Survival time data for participants without a DAT diagnosis over the follow-up period were censored on the date of last assessment.

Results. From an original pool of 1,362 participants enrolled after collection of information on history of cancer was instituted, 882 participants with at least two assessments were eligible for study inclusion.

Rate of cancer diagnosis in the DAT group and the nondemented group. Five hundred ninety-four participants had a diagnosis of no dementia (n = 199) or DAT (n = 395) and no history of cancer at their entry assessment (table 1A). The log-rank test ($p < 0.001$) indicated that those in the DAT group had a slower rate of developing cancer (figure, A. This finding was confirmed by the results of the Cox proportional hazard models (table 2A), each of which indicated that DAT group membership was associated with a reduced risk of cancer, even when demographic factors were controlled. The hazard ratios associated with the DAT variable ranged from 0.338 to 0.391 across the

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Table 1 *Demographic characteristics of the study groups*

	(A) Groups used in testing the development of cancer				
	Nondemented (N = 199)		DAT (N = 395)		
	n	%	n	%	*p*
Clinical Dementia Rating					
0 No dementia	199	100.0	0	0.0	NA
0.5 Very mild dementia	0	0.0	195	49.4	
1 Mild dementia	0	0.0	175	44.3	
2 Moderate dementia	0	0.0	25	6.3	
Sex					
Female	130	65.3	252	63.8	0.714*
Male	69	34.7	143	36.2	
Race					
White	186	93.5	328	83.0	<0.001†
African American	11	5.5	66	16.7	
Native American/Alaska native	2	1.0	0	0.0	
Asian	0	0.0	1	0.3	
Age at first assessment session, y					
Mean	75.9		75.5		0.589‡
SD	9.8		8.8		
Range	54–99		47–102		
Education, y					
Mean	14.5		12.9		<0.001‡
SD	3.2		3.4		
Range	4–22		4–20		
Length of follow-up, y					
Mean	4.3		3.2		<0.001‡
SD	2.4		2.2		
Range	0.7–11		0.6–11		

	(B) Groups used in testing the development of DAT				
	No cancer (N = 199)		Cancer (N = 50)		
	n	%	n	%	*p*
Sex					
Female	130	65.3	26	52.0	0.082*
Male	69	34.7	24	48.0	
Race					
White	186	93.5	50	100.0	0.063†
African American	11	5.5	0	0.0	
Native American/Alaska native	2	1.0	0	0.0	
Age at first assessment session, y					
Mean	75.9		78.1		0.163‡
SD	9.8		10.2		
Range	54–99		56–101		
Education, y					
Mean	14.5		15.0		0.315‡
SD	3.2		2.9		
Range	4–22		8–21		
Length of follow-up, y					
Mean	4.3		4.0		0.496‡
SD	2.4		2.2		
Range	0.7–11		1–9		

* Chi-square test.
† Chi-square test, white vs nonwhite.
‡ *t* Test for independent groups.

DAT = dementia of the Alzheimer type; NA = not available.

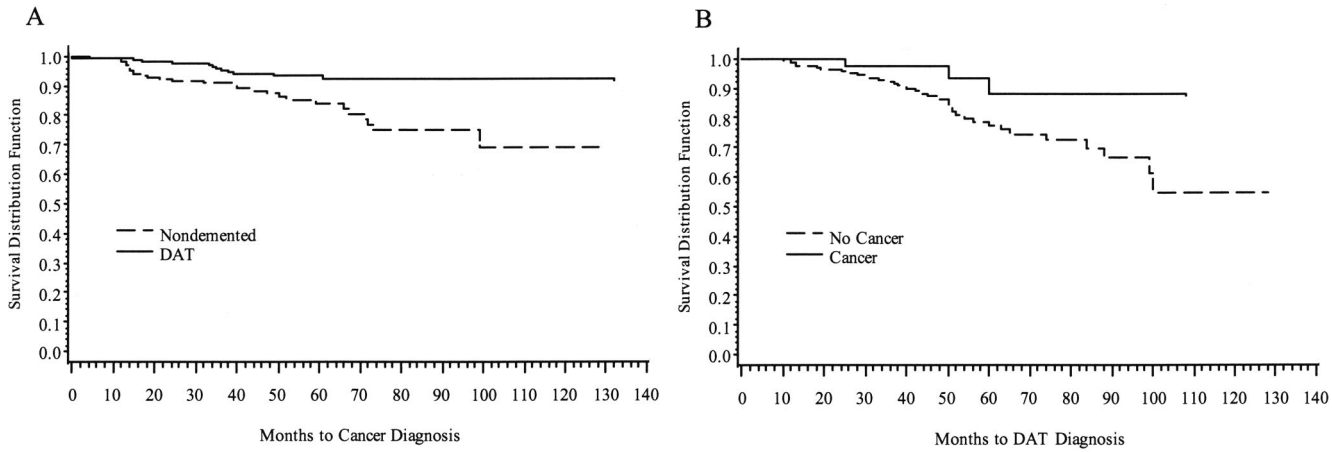

Figure. Kaplan–Meier survival curves for the study groups. (A) Time from first assessment to cancer diagnosis as a function of a diagnosis of dementia of the Alzheimer type (DAT) and no dementia at study entry (p < 0.001). (B) Time from first assessment to DAT diagnosis as a function of a history of cancer at study entry (p = 0.060).

Table 2 *Cox proportional hazard regression results*

Model	Variable	95% CI			
		Hazard ratio	Lower limit	Upper limit	Two-tailed probability
(A) Models testing the development of cancer in the DAT and nondemented groups					
1	DAT diagnosis	0.338	0.183	0.624	<0.001
	Male	2.133	1.187	3.833	0.011
2	DAT diagnosis	0.371	0.200	0.688	0.002
	Age at first assessment	1.047	1.014	1.081	0.006
3	DAT diagnosis	0.364	0.193	0.685	0.002
	Years of Education	1.026	0.935	1.125	0.589
4	DAT diagnosis	0.391	0.207	0.739	0.004
	Male	2.326	1.279	4.229	0.006
	Age at first assessment	1.055	1.020	1.092	0.002
	Education	1.026	0.941	1.120	0.561
(B) Models testing the development of DAT in the cancer and no cancer groups					
1	Cancer diagnosis	0.341	0.104	1.115	0.075
	Male	0.987	0.509	1.914	0.002
2	Cancer diagnosis	0.395	0.120	1.297	0.126
	White	0.202	0.084	0.491	<0.001
3	Cancer diagnosis	0.351	0.108	1.143	0.082
	Age at first assessment	1.053	1.018	1.086	0.003
4	Cancer diagnosis	0.348	0.107	1.132	0.079
	Education	0.942	0.849	1.045	0.261
5	Cancer diagnosis	0.400	0.122	1.132	0.132
	Male	1.330	0.663	2.668	0.422
	White	0.185	0.072	0.472	<0.001
	Age at first assessment	1.054	1.018	1.092	0.003
	Education	0.991	0.895	1.097	0.862

DAT = dementia of the Alzheimer type.

four models, and the effect of the DAT group was significant in each model (all p values <0.005). To ensure that the difference in the rate of cancer diagnosis was not associated with the differential racial makeup of the groups, the analyses were repeated using only white participants and yielded similar results (data not shown). Forty-five participants developed one or more cancers during the follow-up period. Twenty-six of these 45 reported at least one skin cancer. Rates of developing cancer were faster for males and for older participants (all p values <0.05).

Rate of DAT diagnosis in the cancer and no cancer groups. Fifty of the 249 participants with a diagnosis of no dementia at entry also had a history of cancer at that assessment (table 1B). One-half of those with cancer at entry reported skin cancer (n = 25) as the first type of cancer experienced. Although the Kaplan–Meier survival curves (figure, B) and the hazard ratios associated with the variable representing a cancer diagnosis in the Cox proportional hazards models (range 0.341 to 0.400) suggest that the rate of developing DAT is slower among participants with a history of cancer, the difference between the groups did not reach significance at an α level of 0.05 in the log-rank test ($p = 0.060$) or in the proportional hazard models (table 2B; p value range 0.072 to 0.132). Rates of DAT diagnosis were faster for older ($p = 0.003$) and slower for white ($p < 0.001$) participants when the effect of cancer history together with all demographic variables was tested (table 2B, p values <0.005).

Discussion. Among participants who have reached older adult age without a history of cancer, the rate of developing cancer in the future is slower for those with a preexisting diagnosis of DAT. Conversely, older adults with a history of cancer may develop DAT at a slower rate than participants without cancer, although this result was not significant at the 0.05 level, possibly due to the relatively low power.

Our finding of a reduced risk of cancer among DAT participants is congruent with previous cross-sectional and case-control studies that suggested that the prevalence of cancer is less among participants with DAT,[1-3] and the types and frequencies of cancer reported in our participants were similar to those reported nationally.[8] Differential survival bias could have accounted for the inverse relationship between the prevalence of DAT and cancer in cross-sectional research but should be of less concern in the present longitudinal study. We found that the rate of developing DAT was slower for whites,[9] the rate of developing cancer was faster for males,[8] and the rate of developing both disorders increased with age, as previously reported.[8,9]

The temporal relationship shown here between DAT and cancer should be replicated in population-based longitudinal samples and should examine the extent to which this relationship is specific to particular cancer types. The finding of a temporal association between DAT and cancer suggests that further efforts should be made to investigate whether a protective relationship exists between, or a common mechanism underlies, this intriguing relationship. For example, excessive apoptosis has been associated with DAT, whereas too little apoptosis may be associated with cancer. Thus, the two conditions may be linked through a common biological mechanism, such as one that influences the susceptibility of cells to undergo apoptosis.

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