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Chapter 9

Inverse Association between Cancer and Dementia of the Alzheimer's Type

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Abstract

With increasing life expectancy there is also a concomitant increase in the prevalence of age-related disorders, including neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and various cancers. Here we report findings suggesting that there is an inverse relationship between development of dementia of the Alzheimer type and a history of cancer. The inverse relationship was found when all cancer types were analyzed and also when skin cancers (both benign and melanomas) were analyzed separately. We discuss possible explanations for this inverse relationship, among them, the possibility that a common biological mechanism might be regulated in opposite directions in neurodegenerative diseases and cancer.

Introduction

Life expectancy is increasing worldwide, and with it, the prevalence of age related disorders. Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and several others are among these age-related disorders. They are characterized by the gradual and progressive loss of neuronal cells or synapses and many

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of them are accompanied by dementia. AD is rare before age 65 years, but increases almost exponentially thereafter reaching levels between 30-50% in persons over 85 years of age (Skoog et al, 1993, Kukull & Ganguli, 2000). The incidence of AD, i.e., the diagnosis of new cases during a defined time interval, increases with age in such a manner that some authors believe that if individuals lived to 120 years, almost all would have AD pathology in the brain (Morris, 2005). Parkinson's disease is also a frequently-occurring disorder that is associated with aging; its prevalence is around 10% in persons over the age of 65years (Bennett et al, 1996). Huntington's disease (HD) is a much rarer disorder that has a strong genetic component. The mutated gene in HD, huntingtin, has 100% penetrance, and, although the gene is present from birth, in most cases the disease only manifests itself after the age of 45 years (Myers, 2004).

Although neuronal degeneration seems to be a condition associated with aging of the organism, not all aging individuals develop neurodegeneration. There is evidence of some cognitive deterioration with aging (Levy, 1994; Rubin et al, 1998; Schaie, 2005); however the changes due to dementia are much more profound and pervasive than those associated with normal aging. Cancer, on the other hand, is a disorder that manifests itself at almost any age, but like neurodegenerative diseases, its prevalence and incidence also increase with increasing age.

Both neurodegenerative diseases and cancer then, are two common and important diseases that increase with age, and lead to high morbidity and mortality in the elderly. Neurodegeneration is associated with progressive loss of neuronal cells, whereas cancer is linked with the opposite phenomenon: unregulated and increased cell survival and proliferation. Therefore, it can be hypothesized that a common biological mechanism underlies the two diseases which, when regulated in one direction leads to cell death or senescence (i.e. neurodegeneration), and when regulated in the other direction promotes cell proliferation (cancer). This hypothesis, together with the clinical observation that a history of cancer was uncommon in demented patients in nursing homes, lead us to investigate the possibility of an inverse association between the development of dementia of the Alzheimer's type (DAT) and cancers in a longitudinal study. Findings from this research have been published previously (Roe et al, 2005). Here, we summarize those findings including greater detail regarding the sample and type of cancers examined. In addition, we report additional analyses examining the association between DAT at study entry and the development of skin cancer specifically. Finally, we speculate regarding possible causal mechanisms linking AD and cancer.

Our study used archival data from the Memory and Aging Project at the Washington University Alzheimer's Disease Research Center, a longitudinal study of memory and aging where patients are annually evaluated with the CDR (Clinical Dementia Rating) (Hughes et al, 82; Morris, 93). The CDR is obtained thorough a semi- structured interview of the patient and a knowledgeable informant administered by two experienced clinicians, and is based on intra-individual change in cognition. The disagreements in diagnosis are accorded in consensus meetings. The CDR has high inter-rater reliability (Burke et al, 88) and the clinical diagnosis of DAT has been validated (Morris et al, 88; Morris, 1993), with neuropathological confirmation in 93% of cases (Berg et al, 98). The CDR classifies the cognitive status of individuals with CDRs of 0, 0.5, 1, 2 or 3; ratings which correspond to no dementia, very mild or uncertain, mild, moderate, or severe dementia, respectively.

In addition to the cognitive evaluation, the patient, or his or her knowledgeable informant, also answers several questions about general health, including whether there is a history of cancer or the development of a new cancer after study entry. All cancer types were considered in our study, including relatively benign skin cancers such as basal cell or squamous cell cancers.

As described in (Roe et al, 2005), two sets of analyses were conducted. We examined: (1) the rate of cancer diagnosis over time in participants with and without DAT at study entry, and (2) the rate of first DAT diagnosis with time in patients with and without a history of cancer. For the first set of analyses, the inclusion criteria were no indication of a history of cancer or of having cancer at the first assessment session, and at least one additional assessment following study entry. Inclusion criteria for the second set of analyses were a clinical diagnosis of No Dementia during the first assessment session and at least one additional assessment session following study entry. Length of follow up was measured in months from study entry to the last assessment.

In the statistical analyses, the Kaplan-Meier method was used to estimate survival curves reflecting time to first DAT or cancer diagnosis, and Cox proportional hazards models were used to test the effect of a history of cancer on time to first DAT diagnosis, and to test the effect of DAT at study entry on time to first cancer diagnosis, while adjusting for sex, race, age at first assessment, and years of education. For each of the two sets of analyses, multiple Cox proportional hazards analyses were conducted to ensure that the results were consistent regardless of the particular covariates in the model. Specifically, the effect of a history of cancer, or DAT at entry was tested with each demographic variable individually, and with all demographic variables simultaneously.

Rate of Cancer Diagnosis in the Dat and Nondemented Groups

Five-hundred ninety-four participants had no history of cancer at the initial assessment, and had at least one follow-up assessment. Of these, 395 had diagnoses of DAT and 199 were diagnosed with no dementia at baseline. These participants were followed to determine the development of cancer over subsequent assessments. The groups were similar with regard to sex (about 65% female, p=.71) and age at first assessment (around 75 years, p = .589). The DAT group had significantly lower education (12.9 vs. 14.5 years, p <.001) and shorter length of follow-up (3.2 vs. 4.3 years, p < .001) compared with the nondemented group. More than 80% of cases in the DAT group had CDR 0.5 or 1 at first assessment (195 participants (49.4%) with CDR= 0.5; 175 participants (44.3%) with CDR=1; and 25 participants (6.3%) with CDR=2).

Kaplan-Meier survival analysis of the rate of development of cancer across time in participants having a diagnosis of DAT at baseline, versus those without dementia, showed that the DAT group had a slower rate of developing cancer compared to nondemented participants, (log-rank test p < .001) (Lawless, 1982). Cox proportional hazard models confirmed this finding; DAT group membership was associated with a reduced rate of cancer diagnosis over time, even when demographic factors (sex, age at study entry, education), were controlled. The hazard ratios associated with the DAT variable ranged from 0.338 to

0.391 across the Cox proportional hazards models, with all p<0.005. In addition, when sensitivity analyses were conducted by repeating the survival analyses: (1) without including data from 35 participants (of the 199 initially nondemented) who developed dementia during the follow-up period, and (2) after censoring data at the time of first follow-up assessment with a DAT diagnosis, the results were similar to those shown for the entire sample (Roe et al, 2005).

Table 1. Cancers developed by participants in the DAT and Nondemented Groups during the follow-up period.

	Nondemented (N = 29)		DAT (N = 16)	
Site of cancer	**N**	**%**	**N**	**%**
skin	16	55.2	6	37.5
breast	3	10.3	0	0.0
colon	2	6.9	1	6.3
lung	1	3.4	1	6.3
prostate	1	3.4	2	12.5
bladder	1	3.4	1	6.3
ovarian + ovarian*	1	3.4	0	0.0
skin + breast	1	3.4	0	0.0
prostate + skin	1	3.4	0	0.0
skin + skin + skin	1	3.4	0	0.0
skin + prostate	0	0.0	1	6.3
nasopharinx + nasopharinx + nasopharinx	0	0.0	1	6.3
lymphoma	1	3.4	0	0.0
multiple myeloma	0	0.0	1	6.3
chronic lymphocytic leukemia	0	0.0	1	6.3
myelodisplastic syndrome	0	0.0	1	6.3

*The recurrence of cancer, and/or receipt of multiple cancer diagnoses, and the order of occurrence is shown separated by addition signs.

Table 1 shows the types of cancers diagnosed in the participants during the follow-up period in the DAT and no-dementia groups. Skin cancer was diagnosed in 26 of the 45 participants who developed cancer (57%), and the majority of these cancers were basal cell or squamous cell, with only two participants reporting melanomas, a distribution of skin cancer which is similar to that in the general population (Jemal et al, 2004). When the survival analyses were repeated using skin cancer alone as the dependent variable, it was found that, as with the analysis of all cancers, the rate of skin cancer diagnosis was slower for participants with DAT compared to nondemented individuals in both the log-rank test ($p < .001$) and the Cox proportional hazard models ($p < .005$; hazard ratios associated with the DAT variable ranged from 0.22 to 0.26). Other cancers types were too infrequent in our sample to analyze them separately. When combining the non-skin cancers into a single group, the rate of cancer diagnosis was slower with time for the DAT group participants, although the difference between the groups was not statistically significant (all p>0.05, and the hazard ratios associated with the DAT variable ranged from 0.65 to 0.83).

Rate of Dat Diagnosis in the Cancer and no Cancer Groups

There were 249 individuals who met the inclusion criteria of at least two assessments and no dementia at study entry. Fifty of these participants had a history of cancer at the first assessment. These participants, together with the 199 participants without cancer at study entry, were followed to investigate the rate of development of DAT. There was no significant difference between the Cancer and No Cancer groups with regard to sex ($p = .08$), race ($p = .06$), age at first assessment ($p = .16$), number of years of education ($p = .74$) and years of follow-up ($p = .33$). Table 2 shows the types of cancers reported by participants at study entry. The majority were skin cancers ($N = 26$), followed by cancers of the breast ($N = 7$), uterus ($N = 6$), prostate ($N = 5$), and colon ($N = 3$). The Kaplan-Meier survival analysis and the hazard ratios associated with a cancer diagnosis (range of hazard ratio point estimates in the Cox proportional hazards models = .34 to .40) suggested a slower rate of developing DAT among participants with a history of cancer, however, the difference did not reach significance at an alpha level of .05 in the log-rank test ($p = .06$) or in the proportional hazard models (p range = .07 to .13), probably due to low power (Roe et al, 2005). Similar results were found after excluding the 29 participants without a cancer diagnosis at study entry who developed a cancer during the follow-up period (Roe et al, 2005). Although the majority of participants with cancer at baseline had skin cancer, we were unable to examine the association of skin cancer, specifically, with time to DAT diagnosis because no participants with skin cancer became demented over the follow-up period.

Table 2. Previous cancer diagnoses in the cancer group.

Site of cancer	N	%
skin	16	32.0
breast	6	12.0
prostate	5	10.0
uterus	5	10.0
skin + skin*	5	10.0
skin + skin + skin	2	4.0
breast + breast + skin	1	2.0
colon	1	2.0
colon + skin	1	2.0
colon + throat + breast	1	2.0
lung + prostate + skin	1	2.0
rectal	1	2.0
bladder	1	2.0
skin + kidney + lung	1	2.0
skin + throat	1	2.0
thyroid	1	2.0
uterus + skin + skin	1	2.0

* The date of diagnosis of the first cancer listed occurred prior to study entry.

Conclusion

As discussed previously (Roe et al, 2005) the results of this longitudinal study are congruent with previous cross-sectional and case-control studies which show a lower prevalence of cancer among participants with DAT. A history of cancer, identified by chart review, was significantly less common ($p < .01$) among hospitalized patients with a diagnosis of DAT (N=63), than in 61 age-matched non-demented patients (11% versus 35%) (DeSouky, 1992). In another study, which screened for the presence of DAT among residents of Hiroshima and Nagasaki (N = 2222), a logistic regression model controlling for sex, age, education, radiation dose, and history of head trauma showed that the likelihood of a DAT diagnosis decreased with a history of cancer (odds ratio = 0.3, $p < .05$) (Yamada et al, 1999). Other studies using autopsy data also show significantly less cancer in participants with AD than in control groups (Corsellis, 1962; Tirulamasetti et al, 1991, Beard et al, 1996). The presence of DAT among individuals with cancer has been seldom studied.

The inverse association between the development of cancers of all types and the presence of DAT previously demonstrated (Roe et al, 2005) was also found when only skin cancers (benign; basal and squamous cell carcinomas and melanomas) were analyzed. That is, participants with dementia were slower to develop skin cancers than individuals without dementia. The analysis in the opposite direction; whether individuals who had survived a skin cancer (26 participants in our study) are less prone to develop DAT could not be studied, because no participants with a history of skin cancer developed dementia. A greater N should be analyzed to clarify this point. Fifty-seven percent of individuals who developed cancer during our study period developed skin cancer. These cancers were mostly of the relatively benign baso cellular or squamous carcinomas; a prevalence of skin cancer types that is similar to that reported nationally (Jemal et al 2004). The relationship between having a relatively benign cancer and the development of dementia deserves further study.

Another possible explanation of the differences in the rate of a diagnosis of cancer between the groups with and without dementia, and in the rate of a diagnosis of DAT in the groups with and without a history of cancer could be differences in lifestyles or modifiable risk factors, such as diet or smoking. These factors should have opposing effects on cancer and Alzheimer's disease in order to explain the association. For example, it is feasible that people with lifestyles favoring outdoors are exposed to a higher risk of skin cancer, and at the same time, because of their outdoors style of life, they are more prone to exercise, which has been shown to be associated with a lower risk of dementia (Larson et al 2006). Another example is tobacco use, which is a risk factor for many types of cancers (Belpomme et al, 2007) and has been suggested as protective against AD (Lee, 1994; Court et al 2005). Current tobacco use has a protective effect against Parkinson's disease according to a recent pooled analysis (Ritz et al 2007). Additional studies based on population samples are needed to address whether environmental factors with opposing effects on cancer and AD are responsible for the association between the two conditions. The inverse association between cancer and AD shown in our study (Roe et al 2005) is an important observation that needs to be replicated in a population sample, since the group we studied is mainly composed of voluntary white participants of the St Louis area in Missouri. The history of a previous cancer was taken from a knowledgeable informant and by self report of patients; nonetheless there is evidence that this information is accurate (Bergmann et al, 1998, Ziogas & Anton-Culver

2003). In addition, the presence of occult cancers was not ascertained in our study. Since it was a longitudinal study and participants were followed annually, most probably occult cancers would become clinically apparent in following evaluations. However, some of the patients in our study could have had slowly growing cancers that remained occult at their last assessment.

Speculatively, a common biological mechanism with opposing effects in cancer and dementia could explain an inverse association between the development~~s~~ of these disorders. Genetic polymorphisms, DNA methylation or other mechanisms that determine changes in the activity of molecules with key roles in survival pathways could be involved in the pathogenesis of the two disorders. In this~~,~~ respect, it has been recently found that progranulin, the mutated gene in several families with frontotemporal dementia with ubiquitin-positive intraneuronal inclusions (FTLD-U) (Baker et al 2006; Cruts et al 2006; Mukherjee et al 2006; Behrens et al, 2006), is a molecule involved in uncontrolled cell growth in several cell types when overexpressed, whereas null alleles cause neurodegeneration (Daniel et al, 2000, Malaspina et al 2001). Furthermore, a recent study shows that HIV dementia could be mechanistically associated with a reduced risk of cancer (Okamoto et al 2007). In a strain of mice genetically engineered to make the HIV virus's gp120 protein they found that many of their neural stem cells were in a neutral (non-dividing) state, therefore, dementia could be produced by a lack of replenishment of neural cells. In addition, they found that these stem cells contained more protein p38, which is normally involved in preventing cancer by halting cell division when DNA strands get broken.

Emerging research suggests inverse associations between cancer and other neurodegenerative diseases characterized by increased progressive cell death, such as Parkinson's disease (PD), frontotemporal dementia and other tauopathies, and Huntington's disease; or, that both types of diseases may be linked by common genes. Overall cancer mortality risk and tumor frequency are reported reduced in individuals with PD, for smoking-related and non-smoking related cancers (Vanacore et al, 1999; D'Amelio et al, 2004; Olsen et al, 2005; Inzelberg & Jankovic, 2007). A significantly lower incidence of cancer has been described among patients with Huntington's disease (Sorensen et al, 1999) and recent research suggests that a tumor suppressor gene may be implicated in the development of Huntington's disease. Mutant huntingtin, the protein synthesized by the gene known to cause Huntington's disease causes upregulation of the p53 gene (Bae et al, 2005; Walker, 2007). These observations, along with our findings of an inverse relationship between cancer and DAT, should stimulate studies of possible genetic and mechanistic links between neurodegenerative disorders and cancer.

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