Is there a link between cancer and Alzheimer disease?

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Cancer and Alzheimer disease (AD) are common age-related conditions. Cancer arises from dysfunction of genetic and epigenetic processes that control cellular differentiation and proliferation. Recent data suggest that molecular machinery that is involved in maintaining neural function in neurodegenerative disease may be shared with oncogenetic pathways. For example, some studies suggest that cancer incidence is lower among persons with Parkinson disease.[1] Few data are available regarding a link between cancer and AD.[2] However, the presence of an association could further stimulate investigations related to molecular changes underlying neurodegenerative diseases. In this issue of *Neurology*®, Roe et al.[3] use data from the Cardiovascular Health Cognition Study to investigate the relationship between cancer and AD.

The Cardiovascular Health Study is a population-based cohort study of nearly 5,900 persons. The Cognition Study is an ancillary study of about 3,600 persons who had an MRI brain scan and completed annual brief cognitive testing for up to 5 years. Several years later, subjects were divided into high- and low-risk groups for dementia based on cognitive tests available in the Cardiovascular Health Study. A sample of surviving high-risk white subjects, and all minorities, were invited to participate in a clinical evaluation. Medical records were obtained for deceased participants and those who refused the evaluation. Records were adjudicated for diagnoses of prevalent and incident dementia and its subtypes, and mild cognitive impairment (MCI). Prevalent cancer was based on self-report. Incident cancer was based on hospitalization records with surveillance over more than 8 years.

For these analyses, persons with MCI were excluded, leaving about 3,000 persons. The authors first examined the relation of prevalent dementia to incident cancer. Among 165 persons with prevalent dementia and 2,107 persons without prevalent dementia, there were 376 cases of incident cancer. After adjustment for relevant covariates, prevalent AD was associated with a 60% reduced risk of incident cancer. Prevalent vascular dementia was not associated with cancer incidence. The second set of analyses examined the relation of prevalent cancer to incident dementia separately for white and minority subjects. Among 423 persons with prevalent cancer (394 white and 29 minority subjects) and 1,973 persons without prevalent cancer (1,768 white and 205 minority subjects), there were 478 cases of incident dementia. After adjustment for relevant covariates, prevalent cancer was associated with a 30% reduced risk of incident AD among white subjects, whereas the association in minority subjects was in the opposite direction, but not significant. No association was found between prevalent cancer and incident vascular dementia.

The study has a number of limitations, many of which were acknowledged by the authors. For example, the authors used hospital records to identify incident cancer cases. Patients with dementia tend to be diagnosed with cancer at a later stage, have significantly higher cancer mortality rates, and may not be hospitalized as frequently for cancer relative to those without dementia.[4] This could result in the appearance of a reduced incidence of cancer among those with dementia. The findings on incident dementia are less prone to bias because the diagnoses are based in part on a clinical evaluation. However, since all minority subjects were evaluated clinically whereas only a sample of white subjects were evaluated, there may have been better dementia case finding among minority subjects. Further, data suggest that racial and ethnic minorities are diagnosed with cancer at a later stage of illness and have higher cancer mortality rates.[5] These factors could account in part for the reported racial differences.

Both cancer and dementia are associated with an increased risk of death. Treating cancer-free mortality among those with dementia, and dementia-free mortality among those with cancer, as censoring events in a conventional Cox proportional hazards

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model has the potential to markedly underestimate the association between these conditions, giving the appearance of protective effects. This occurs because death as a result of an unrelated yet competing condition reduces the likelihood of all late-onset diseases. In other words, the most important reason older persons with grade IV glioblastoma do not get AD is short survival. A related issue is that some persons without prevalent dementia will develop dementia prior to incident cancer; likewise, some persons without prevalent cancer will develop cancer prior to incident dementia. By not accounting for these transitions, the analyses may underestimate the associations between these conditions. Competing risk and multistate survival methods that address both of these issues are currently available and will need to be employed in future studies.[6]

Despite these limitations, the study has many strengths and the associations are worthy of exploration in other cohorts. Further, recent data already have identified molecular processes that may be involved in both cancer and neurodegeneration. For example, the enzyme Pin1 targets a number of proteins, some of which are putative oncogenes and oncosuppressors, whereas others are pathologic hallmarks of AD.[7] DNA methylation, histone acetylation, and other epigenetic modifications play a role in the activation and suppression of cancer genes[8] and have been implicated as a means of memory storage in the CNS and a potential mechanism in the development of AD.[9,10] Histone deacetylase inhibitors such as valproic acid are available, are relatively safe, and exhibit therapeutic effects in a variety of mental health conditions.[11] Thus, the identification of molecular mechanisms linking cancer and AD may lead to novel therapeutic targets and interventions.

DISCLOSURE

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REFERENCES

1. Inzelberg R, Jankovic J. Are Parkinson disease patients protected from some but not all cancers? Neurology 2007; 69:1542–1550.
2. Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC. Alzheimer disease and cancer. Neurology 2005;64:895–898.
3. Roe CM, Fitzpatrick AL, Xiong C, et al. Cancer linked to Alzheimer disease but not vascular dementia. Neurology 2010;74:106–112.
4. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Arch Intern Med 2008;168:2033–2040.
5. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med 2003;163:49–56.
6. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statist Med 2007; 26:2389–2430.
7. Takahashi K, Uchida C, Shin RW, Shimazaki K, Uchida T. Prolyl isomerase, Pin1: new findings of post-translational modifications and physiological substrates in cancer, asthma and Alzheimer's disease. Cell Mol Life Sci 2008;65:359–375.
8. Esteller M. Epigenetics in cancer. N Engl J Med 2008;358: 1148–1159.
9. Mehler MF. Epigenetics and the nervous system. Ann Neurol 2008;64:602–617.
10. Mastroeni D, McKee A, Grover A, Rogers J, Coleman PD. Epigenetic differences in cortical neurons from a pair of monozygotic twins discordant for Alzheimer's disease. PLoS One 2009;4:e6617.
11. Szyf M. Epigenetics, DNA methylation, and chromatin modifying drugs. Annu Rev Pharmacol Toxicol 2009;49: 243–263.

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