AD and cancer

Epidemiology makes for strange bedfellows

Catherine M. Roe, PhD
Maria I. Behrens, PhD, MD

Correspondence to Dr. Roe: cathyr@wustl.edu

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The incidence of both Alzheimer disease (AD) and cancer increases with older adult age, and both are characterized by abnormal, but opposing, cellular behavior. In AD, cell death is increased, whereas excessive cell growth occurs in cancer.

In this issue of *Neurology*®, Musicco et al.[1] examined the incidence of AD and cancer as a function of each other within a population-based sample of adults aged 60 years and older in Northern Italy. They found that persons with incident AD (n = 2,832) were less likely to develop cancer in the future, and persons with incident cancer (n = 21,451) were less likely to later develop AD. Specifically, when compared to the general population of persons of the same age and sex, the risk of AD among individuals with cancer was reduced 35%, and the risk of cancer among those with AD was decreased by 43%.

The authors used a clever study design. Broadly speaking, this design relies largely on 2 sets of analyses. First, for persons with an incident diagnosis of the disease of interest (e.g., cancer), they compared the incidence of occurrence of the other disease (e.g., AD) in the periods before and after the diagnosis of the disease of interest. If underdiagnosis of the other disease was due to diagnosis of the disease of interest, then a low incidence of the other disease should tend to occur only after diagnosis of the disease of interest, not before. For example, the authors found that there was a similar, and lower, rate of AD diagnosis for persons with incident cancer both before and after the cancer diagnosis compared to individuals who were cancer-free, suggesting that physicians were not less likely to look for AD among people diagnosed with cancer. Second, the authors compared the incidence of the other disease in the subgroup with the disease of interest to the incidence of the other disease in the larger population. In other words, they looked to see whether the incidence of AD among people with cancer was similar to the incidence found in the larger population, which included people with and without cancer. Likewise, they examined whether the incidence of cancer among people with AD was similar to that measured in the larger population. They also conducted separate analyses for persons who died and those who survived during the period of observation to evaluate possible survival bias.

Other strengths of the study include large sample sizes, which allowed analyses to be conducted separately for cancers occurring at specific sites, and a well-thought-out and generally comprehensive enumeration of the limitations of their approach. As noted by the authors, limitations include the use of administrative data to identify persons with AD, which may have resulted in some milder cases of AD being overlooked; the lack of available information on certain lifestyle-related risk factors for AD and cancer; and the fact that most skin cancers were not captured because the cancer registry data used relied primarily on hospital discharge records.

Considered together with recent work by others[2–4] that approached the issue of epidemiologic links between AD and cancer using different samples, ascertainment methods, and study designs, the results of these analyses add to the growing evidence that suggests an inverse relationship between the development of AD and cancer.

There are several proposed mechanisms that may explain such a relationship (see references 5 and 6 for reviews). Specifically, cancer and AD may be associated with deregulations in overlapping functions at the cellular level. Cancer development and progression are characterized by cell proliferation and resistance to apoptosis, the opposite of what is observed in neurodegenerative diseases. Alterations in the activity of key molecules involved in survival pathways related to the decision to repair encountered damage and survive, or to proceed toward death by apoptosis, may explain a tendency to either develop a tumor or a neurodegenerative disorder such as AD. For example, *p53*, the prototypical tumor suppressor normally in charge of monitoring DNA damage, is inactivated in around 50% of cancers, therefore allowing abnormal cell proliferation. On the other hand, there is evidence of elevated levels of *p53* in the brains of patients diagnosed with AD and several other neurodegenerative disorders such as Huntington disease, amyotrophic lateral sclerosis, and Parkinson disease.[7] Another pivotal molecule with roles in both AD and cancer is

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From the Knight Alzheimer's Disease Research Center and the Department of Neurology (C.M.R.), Washington University School of Medicine, St. Louis, MO; and Departamento de Neurología y Neurocirugía (M.I.B.), Hospital Clínico Universidad de Chile and ClínicaAlemana de Santiago, Santiago, Chile.

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Pin1.[8] *Pin1* is involved in regulating APP processing and Aβ production and also facilitates tau dephosphorylation, restoring its normal binding to microtubules. Conversely, *Pin1* is involved in the activation of multiple oncogenic pathways of tumorigenesis,[8] and overexpression of *Pin1* is present in several human cancers including those occurring at the breast, lung, prostate, colon, and liver. Finally, another mechanism that might explain an inverse relationship between cancer and AD concerns alterations in neurogenesis. New neurons that proliferate and integrate into existing circuits in the dentate gyrus are important for learning and memory, and therefore a deregulation of this process has been proposed to participate in AD.[9] Interestingly, several of the signal transduction pathways involved in cancer development are the same as those involved in the regulation of proliferation and differentiation of neural progenitors.[10]

Future work will determine which, if any, of these mechanisms connect AD and cancer. However, regardless of the particular mechanism underlying the relationship, if future research confirms that the development of cancer and AD are inversely associated, this knowledge may help in gaining a better understanding of and developing new treatments for both diseases.

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