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More Evidence of an Inverse Association Between Cancer and Alzheimer Disease

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The article by Ospina-Romero et al[1] represents an important contribution to the literature on the intriguing inverse association between cancer and neurodegenerative diseases, including Alzheimer disease (AD). Specifically, there is a growing body of evidence showing that the risk of cancer may be lower among patients with AD than those without AD and that cancer survivors may have a lower risk of incident AD than do people who remain cancer free.[2,3] Using a rigorous approach that leveraged the population-based longitudinal design of the Health and Retirement Study, the authors estimated differences in memory function and decline, both before and after diagnosis of cancer, between participants with incident cancers and their cohort peers who remained cancer free during an observation period of up to 16 years. Notable findings included (1) a 10.5% slower rate of memory decline among participants who developed cancer vs those who did not during the period of nearly a decade before diagnosis, (2) observation of short-term memory decline among persons with cancer around the time of diagnosis, and (3) a modest but statistically significantly slower memory decline after diagnosis among cancer survivors, compared with those who remained cancer free.

Although the main findings of Ospina-Romero et al[1] do not represent a new line of inquiry—indeed, the inverse association between cancer and AD or other neurodegenerative diseases has been reported extensively elsewhere[2,4,5]—the methodologic rigor of the approach provided several key advantages. First, the routine biennial assessments ensured that participants with or without cancer had equal opportunity to be characterized with respect to memory function, thus mitigating surveillance or detection bias. Second, continuous assessment of the memory performance outcome, as opposed to the outcome of clinical AD or neurodegenerative disease, across a 16-year span among late midlife and older adults helped to reduce issues of survivor bias or competing risks; although the outcome of AD is not addressed directly, early memory decline is widely regarded as the symptom most relevant to the development of AD.[6] Third, the modeling approach allowed the authors to capture separately the estimated memory trajectories in the longer periods before and after cancer diagnosis, as well as the shorter period close to the time of cancer diagnosis. Fourth, the authors adjusted the models for a range of potential demographic, lifestyle, and health confounders; however, omissions such as diet, depression, and *APOE* status are notable. Fifth, helpful clinical translation is provided, such as the observation that, at 2 years after diagnosis, the mean difference in cognitive decline associated with incident cancer is consistent with a 10% reduction in relative risk of memory impairment for patients with cancer vs those without it.

Although the study by Ospina-Romero et al[1] has many strengths, some important issues cannot be fully addressed. The study design does not permit estimation of whether the associations between cancer and memory decline are equally apparent across clinically important subgroups. Some patients, especially those who undergo certain types of chemotherapy and cranial irradiation, experience late cognitive effects associated with cancer treatment. For example, some researchers have noted that cancer and cancer treatment may ultimately negatively affect the trajectory of normal aging and that exposure to cancer treatments may increase the risk of dementia among patients with key risk factors, such as the *APOE* ε4 allele.[7] However, the study by Ospina-Romero and colleagues[1] does not examine different cancer subtypes (eg, central nervous system vs non–central nervous system cancers), address patient subgroups, or observe later cognitive effects (eg, >5 years after diagnosis). In addition, the pattern of cognitive impairment in individuals with late cognitive effects associated with cancer treatment

generally includes memory, processing speed, and complex attention weaknesses. However, because the authors are limited to the outcome of memory, inferences cannot be made with regard to how performance in nonmemory domains would compare among participants with cancer vs those who remained cancer free. Overall, the study results support prior reports of the negative effects on memory that cancer or cancer treatment may have in the acute phase, and patients who survive indeed appear to have better memory outcomes over the long term. However, there is no evidence offered by the current study that such a protective association exists across attentional, executive, processing speed, and other cognitive domains or for non-AD forms of dementia.

The most puzzling question—one that cannot be answered by the study by Ospina-Romero et al[1] but only considered speculatively—is why individuals who have had cancer or go on to develop it perform better on memory testing than those who remain cancer free. Recent work suggests that a matrix of shared genetic factors may confer risks of cancer and neurodegenerative disease in opposing directions.[2,3] In addition, Driver[2] and Demetrius and Driver,[8] among others, have proposed an explanatory model in which age-associated differences in metabolism and bioenergetic balance may protect against neurodegeneration while increasing the risk of cancer, or may increase the risk of AD while decreasing the risk of cancer, via an inverse Warburg effect.[2,8] Although the study by Ospina-Romero and colleagues[1] cannot answer this question, their compelling results speak to the need for further work to address the origins of the inverse association between cancer and AD, with a view toward identifying new paths to prevention and treatment of both diseases.

ARTICLE INFORMATION

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