

EDITORIAL

Understanding the Time Course of Cancer-Associated Cognitive Decline: Does Impairment Precede Diagnosis?

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It is increasingly clear that noncentral nervous system cancers and their treatment are associated with short- and long-term cognitive deficits (1,2). Cancer-associated cognitive decline (CACD) can have a profound effect on patients' lives. Patients often report that CACD is distressing (3) and makes it difficult to resume work, social, and family activities (3,4). Although much empirical work has focused on how cancer treatment may impact cognitive performance, recent evidence suggests that cognition may be negatively impacted at the point of diagnosis (5,6). The source of these pretreatment differences may be shared risk factors for impaired cognitive functioning and cancer (7), as well as biological processes associated with tumor growth (8).

One challenge in understanding why cognition may be negatively impacted at diagnosis is that it is difficult to distinguish the extent to which cancer-associated processes may contribute to worse cognitive functioning from psychosocial reactions to a diagnosis (9). In the current issue of the Journal, van der Willik and colleagues (10) evaluate changes in cognitive performance prior to cancer diagnosis by using data from the Rotterdam Study (11). Specifically, the authors constructed two cohorts from this population-based study: one group that would go on to be diagnosed with cancer and another that would remain cancer-free, matching each incident case of cancer with two controls on the basis of age at cancer diagnosis. One of the key strengths of this study is the ability to investigate trajectories of cognitive decline years prior to the diagnosis of cancer and compare these changes to persons who will remain cancer-free.

The results indicated that only 1 of the 11 cognitive measures that were assessed showed greater declines among the incident cancer group. Specifically, persons who would go on to be diagnosed with cancer exhibited greater changes in memory performance as compared with cancer-free control subjects. However, when the control sample was restricted to persons who remained cancer-free for 5 years after the final follow-up assessment as a way to adjust for yet undiagnosed cancers, the

difference between the groups was no longer statistically significant. The authors concluded that impending cancer diagnosis has little impact on changes in cognitive performance, and there was no evidence for a prodromal phase of cognitive decline, such as those that are seen with dementias or cognitively impairing disorders (12).

There are a number of key strengths of this study. First, study participants were evaluated at a period of time when all persons were naïve as to an upcoming cancer diagnosis. This approach minimizes the selection biases associated with recruiting persons who are newly diagnosed. Second, performance was evaluated using a comprehensive battery of cognitive tests, allowing the investigators to evaluate potential specificity of cognitive deficits associated with the cancer diagnosis. Finally, the sample size of newly diagnosed cases of cancer and noncancer control subjects was many times greater than those typically seen in studies of CACD and also enabled the authors to conduct comparisons with several different cancer diagnoses.

How might we resolve the lack of pretreatment differences in cognitive performance reported by van der Willik (10) with other research that has observed cancer patients performing more poorly prior to the initiation of systemic treatment? The authors identify a number of potential sources for this difference, including the vulnerability of past studies to selection biases when recruiting newly diagnosed cancer patients and the inability to completely account for confounding factors through statistical controls, as well as the more advanced age of their sample; therefore, cancer-related changes in cognitive performance may be competing with those seen in normal aging (13). A critical difference is that the current article focuses on longitudinal changes prior to the cancer diagnosis, whereby all other studies examined cross-sectional differences between healthy controls and newly diagnosed patients. However, even when they were compared at the age of diagnosis and controls were restricted to those who remained cancer-free within

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5 years of the final assessment, no statistically significant differences were observed.

There are other possible reasons for the lack of pretreatment differences observed by van der Willik et al. (10). Increasing evidence suggests that CACD is subtle and may vary considerably across persons and settings (2). In one study, the differences at diagnosis were limited to persons with more advanced breast cancer, as well as those with greater comorbidity burden (6). Therefore, there may be some individuals who are particularly vulnerable to pre- and posttreatment CACD, but these effects are masked when examined at the aggregate. Further, most neuropsychological tests were developed to assess gross cognitive abnormalities such as dementia and may not be sensitive enough to detect the more subtle changes of CACD until they are magnified by cancer treatment. Subjective reports of cognitive impairment may be more sensitive measures of early CACD (14,15) and may precede declines in objective performance (16). Finally, in our own work, we have approached the issue of sensitively measuring CACD by repeatedly assessing persons in daily life and have observed variability between persons but also within and between days of assessment (17).

Lastly, what do the lack of pretreatment differences reported by van der Willik (10) have for future studies of CACD? This does not mean that we can abandon calls for routine assessment of CACD prior to systemic therapies (18). Instead, assessing performance prior to treatment and the identification of individual patient characteristics or methods of assessing CACD that offer the greatest sensitivity to detect impairments will be critical to our understanding of who is most vulnerable and the time course of CACD prior to and following the diagnosis of cancer.

Notes

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