Cancer as a Risk Factor for Dementia: A House Built on Shifting Sand

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As advances in therapy have improved the survival rates of patients diagnosed with cancer, various survivorship issues have received attention, including the incidence of cognitive dysfunction and its relative impact on patient quality of life. For example, patients with breast and prostate cancer have 5-year relative survival rates of approximately 86% and 98%, respectively *(1)*. However, recent studies have demonstrated that cognitive dysfunction may be present before treatment, may worsen acutely secondary to treatment-related neurotoxicity, and may continue after cessation of therapy *(2–5)*. Concerns that exposure to cancer and cancer treatments may augment a patient's chance of developing future neurologic diseases, including dementia, have also received recent attention. These concerns are amplified in an aging population that has an increased risk for both cancer and dementia. Studies identifying links between cancers, cancer therapies, and cognitive dysfunction are necessary. It must also be determined if the neurotoxicities associated with these diseases and agents are persistent and if the mere history of cancer and exposure to these therapies create a diathesis for late emerging neurologic diseases such as dementia.

Diminished "cognitive reserve" has been hypothesized as a mechanism that increases the likelihood that patients with cancer may be later diagnosed with other neurologic diseases *(6)*. Cognitive reserve is a theory that has been posited to help explain why individuals with a similar degree of brain pathology manifest different clinical sequelae *(7)*. This theory has been conceptualized along two primary dimensions that consider either threshold differences (e.g., synapse counts) or cognitive processing differences (e.g., intelligence) between individuals. Reserve is purported to moderate the appearance of the clinical symptoms of a disease. Thus, patients with a history of cancer and exposure to antineoplastic therapies may experience a reduction in their cognitive reserve that leaves them vulnerable to later developing cognitive dysfunction from other neurologic illnesses that might have otherwise remained dormant.

In this issue of the Journal, Heflin et al. *(6)* report the results of a retrospective study of Swedish twin pairs discordant for a history of cancer. They report no statistically significant differences in the rate of clinician-determined dementia in twins with a history of non–central nervous system cancer, relative to their cancer-free co-twin controls. Using a telephone mental status screening interview or informant report as the basis for determining cognitive dysfunction, they reported that twins with a history of cancer had an increased risk of being classified as cognitively impaired compared with the unaffected twin. Subgroup analyses further demonstrated that this was true only for long-term survivors, those who had survived an average of 14 years since their cancer diagnosis. The authors hypothesized that this differential rate of cognitive dysfunction was due to reductions in cognitive reserve. However, a number of cautionary notes are warranted before accepting these conclusions.

Unfortunately, the use of mental status screening measures, including telephone screening instruments and informant reports, is of dubious value and should be abandoned in studies in which the expected cognitive sequelae are less severe than that of frank dementia *(8,9)*. The HARMONY study, from which data for the Heflin et al. study were in part derived, demonstrated the poor diagnostic accuracy associated with the telephone mental status screen. Of the 1557 subjects in the HARMONY study who screened positive for cognitive dysfunction, only 46.4% received a clinician consensus diagnosis of dementia *(10)*. This represents a very high false-positive error rate, which is acceptable for the purpose of screening case patients to undergo more rigorous diagnostic workup. However, the diagnostic error associated with this screening tool should preclude its use in analyses that attempt to determine if cancer history is associated with changes in cognitive function and dementia.

In the Heflin et al. study, all case patients suspected of having cognitive dysfunction underwent comprehensive neurologic and neuropsychological evaluations that resulted in a consensus clinical opinion regarding the presence or absence of dementia. Analysis of the clinician consensus diagnosis of dementia status did not show a statistically significant association between cancer history and dementia. A recent investigation by Roe et al. *(11)* using a prospective longitudinal design that included comprehensive neuropsychological assessment of cognitive function and histopathologic determination of dementia subtype also failed to find increased risk of developing dementia in patients with a history of cancer compared with cancer-free participants. In fact,

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they reported a statistically nonsignificant trend suggesting that the risk of developing dementia of the Alzheimer's type was actually marginally less in patients with a prior history of cancer than in cancer-free participants *(11)*.

Although growing evidence supports the view that a subgroup of patients with non–central nervous system cancer experience cognitive dysfunction, not all patients are at equal risk, and data on the persistence of these deficits are scant. The challenge to date has been to convincingly demonstrate the existence of this subgroup of cancer patients through methodologically sound longitudinal trials. Altered cognitive function is best established by longitudinal neuropsychological assessments that allow the clinician to ascertain if there have been changes from a baseline state in association with the onset of a new condition or subsequent to a therapeutic intervention. Although Heflin et al. did not have the benefit of a longitudinal trial with complete medical and treatment histories, using the extensive neuropsychological and medical data collected in conjunction with the HARMONY study may have helped to clarify their conclusions. Issues that could have been clarified include: 1) whether differences in cognitive function between twins are evident on neuropsychological testing, 2) whether these group differences are due to a history of cancer or whether twins with a history of cancer have differential rates of other comorbid medical or psychiatric illness, 3) what controls were in place to diminish subjects' recall error when establishing that cancer predated the onset of dementia, and *(4)* what controls were in place to diminish expectancy effects on the part of the screening interviewer and the clinician evaluators (i.e., were they blind to the medical history and screening result of each subject they assessed)?

The suggestion by Heflin et al. that diminished cognitive reserve is the causal mechanism underlying the development of subsequent neurologic diseases is premature. Alternatively, cancer patients may demonstrate poor cognitive function due to: persistent neurotoxicity of their treatment; treatment toxicities affecting other organs systems, such as cardiotoxicity or endothelial damage, that contribute indirectly to cognitive dysfunction; secondary cancers, such as acute leukemias *(12,13)* that produce cognitive dysfunction; or new unrelated neurologic illnesses.

Thus, after a thorough diagnostic workup, Heflin et al. did not demonstrate a preponderance of dementia in co-twins with a history of cancer. Methodologic limitations, including their use of a poor measure of cognitive function, cross-sectional design, and failure to adequately rule out competing causes of suspected cognitive dysfunction, diminish confidence in their interpretation that cancer survivors demonstrated an increased risk of cognitive dysfunction than cancer-free co-twins. Support for their theory that diminished cognitive reserve was the mechanism through which long-term cognitive dysfunction comes to manifest itself was also lacking. There is evidence that cancer patients may experience acute and possibly persistent cognitive dysfunction *(2,3,9)*. The conclusion by Heflin et al. that cancer patients are at risk for developing new late-onset cognitive dysfunction and dementia, however, was not supported and could potentially alarm patients and providers.

Longitudinal, multidisciplinary investigations are needed that can determine which agents and treatment regimens are most neurotoxic, the course of the cognitive and behavioral dysfunction, the cognitive and behavioral domains most affected, the mechanisms for these effects, the host risk factors that mediate the expression of this neurotoxicity, and the risk of developing late-emerging nononcologic neurologic diseases. Thereafter, intervention strategies can rationally be employed. Solid experimental design is the foundation from which meaningful conclusions can be drawn so that investigators can ensure that they do not find themselves with a house built on shifting sand.

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