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EDITORIAL

Depression and Risk of Cancer Progression: An Elusive Link

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The connection between depression and cancer has been debated for more than two decades. After publication of two major epidemiologic studies of the Western Electric Company employee cohort that showed a relationship between self-reported depression symptoms and risk of mortality over 17- and 20-year follow-up periods,[1,2] some imagined that depression would be identified as a risk factor for cancer, much as it had been for cardiovascular disease.[3] However, this initial link proved elusive, and a number of subsequent studies failed to find an association between depression and cancer deaths.[4,5] Although Linkins and Comstock[6] suggested that depression predicted cancer mortality in smokers but not in nonsmokers, a meta-analytic review concluded that depression was only a small, marginally significant risk factor for cancer.[5] However, interest in the link between depression and cancer mortality was renewed by the report of Penninx et al.[7] In this prospective study of 4,825 persons aged 71 years and older, an 88% increase in cancer risk was found over a follow-up period of nearly 4 years. Notably, this increase in cancer risk was detected using a standardized and validated measure of depression, the Center for Epidemiological Studies Depression Scale; and the presence of chronic depression, rather than depression at a single period in time, was found to be associated with cancer mortality.

Among persons with a cancer diagnosis, depression occurs at a high rate, with a median point prevalence (15% to 29%) that is approximately three to five times greater than the general population.[8] Unfortunately, depression remains largely underdiagnosed and undertreated in cancer patients, and such chronic depression might impact disease progression. Indeed, investigations examining depression and cancer progression have led to a more consistent set of associations compared with investigations of depression and cancer incidence.[8] However, variable results have also been reported, possibly as a result of the heterogeneity of cancer diagnoses and cancer types. Depression, for example, may impact cancer progression through physiologically relevant mechanisms (eg, increases in proinflammatory cytokine activity) but only in cancers where such pathways are implicated (eg, lymphoproliferative disorders).[9] Moreover, conclusions are often constrained by the use of nonstandardized assessment of depressive symptoms without diagnostic specificity or by the use of varying follow-up times. Interestingly, in studies with longer follow-up time, the results seem to be less definitive, suggesting that intervening health factors are more likely to come into play as survival time is extended.[8] Finally, studies have rarely tested the possibility that underlying physiologic processes driven by tumor biology and tumor burden (eg, increases in inflammation) may produce changes in behaviors, notably fatigue, decreased vigor, and poor sleep. This constellation of symptoms can be promoted by inflammatory processes and might be interpreted as depression.[10]

The study by Steel et al[11] presents new findings that advance the hypothesis that depression impacts survival times in cancer patients. In a prospective study of 101 patients diagnosed with hepatobiliary cancer, the investigators found that depression (a score of 16 or higher on the Center for Epidemiological Studies Depression Scale) occurred in more than one third of the patients, and these patients showed a significantly shorter survival time. These differences were particularly striking among patients who had evidence of tumor vascular invasion; in this group, depressed patients survived for only 5 months, whereas the nondepressed patients had a survival time more than twice as long at 11 months. Importantly, the analyses adjusted for clinical demographic factors including age, sex, race, alcohol and tobacco use, and life stress. Moreover, cancer type, presence or absence of hepatitis B and/or C, presence or absence of cirrhosis, vascularity of the lesions, and vascular invasion did not significantly account for differences in survival time between depressed and nondepressed patients; however, vascular invasion did have independent effects on survival. It seems that these results might be specific to depression because the link between depression and survival held even after measures of somatic symptoms, including loss of appetite and restless sleep, were removed.

The study by Steel et al[11] has an additional strength in its exploration of a potential mechanism that might mediate the association between depression and cancer survival. Depression is well recognized to be associated with alterations in cellular immune response and with declines in natural killer (NK) cell activity.[12] The findings reported here extend these observations to depressed patients with hepatobiliary cancer and provide novel evidence in a small subsample of patients ($n = 23$) that such declines in NK activity correlate with survival time. Statistical analyses yield further provocative evidence that a decline in NK activity is an intermediary step between depression and mortality risk in this patient population. Others have shown that severity of psychological stress is associated with lower NK cell activity in ovarian cancer patients, and this decline is found in peripheral blood as well as in tumor-infiltrating lymphocytes.[13] Animal models further implicate NK cells as a key mechanism in stress-induced tumor progression of

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experimental mammary adenocarcinoma; this effect is driven by catecholamine-induced suppression of NK activity and prevented by an NK-enhancing intervention, low-dose poly I-C (polyriboinosinic acid-polyribocytidylic acid) injection.[14] However, alternative mechanisms independent of the immune system also require consideration. Depression is well known to be associated with increases of sympathetic catecholamines,[15] and recent data suggest that such stress mediators modulate tumor growth by inducing the release of angiogenic cytokines and promoting angiogenesis and tumor growth.[16] Of further relevance to hepatobiliary carcinoma, in which hepatitis B and hepatitis C viral pathology may play a role, catecholamines and other aspects of neuroendocrine function (eg, glucocorticoids) can modulate viral replication, activate viral oncogenes, and increase tumor metabolism.[17]

The high prevalence of depression in this population and its apparent influence on survival challenge clinicians to identify effective interventions that can ameliorate depressive symptoms with potential impacts on mortality risk. Psychosocial interventions in patients with malignant melanoma are reported to increase measures of NK cell activity along with decreases in depressive symptoms,[18-20] although a survival advantage of such treatments has not been confirmed.[21] Nevertheless, there is extensive evidence that behavioral interventions are effective in reducing depressive symptoms in cancer patients, at least in the short term.[22] Likewise, interventions with antidepressant medications (eg, paroxetine) reduce major depression incidence among patients undergoing active immunotherapy or chemotherapy.[22] In addition to improving health functioning in these patients, other nonpsychological benefits have also emerged, including possible improved adherence to cancer treatment.[23] Rigorous investigations that examine the efficacy of both pharmacologic and behavioral interventions for the treatment of depression and depressive symptoms in cancer patients are needed. Design of such treatment approaches also needs to be examined and understood within an evidence-based framework of scientific method, with rigorous consideration of the mechanisms by which treatment effects are achieved.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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