Depression as a Risk Factor for Cancer: Renewing a Debate on the Psychobiology of Disease

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Throughout the 1980s, the relationship between depression and cancer risk was explored by several investigators, with mixed results. Shekelle et al. (1) published the first major study of the decade, reporting a relationship between self-reported symptoms of depression and risk of cancer death over a 17-year follow-up period. A similar 20-year follow-up of the same Western Electric Company employee cohort again found a heightened risk of cancer mortality among study participants who reported depression at baseline (2).

Subsequent research, however, provided evidence concerning the depression–cancer link that was, at best, inconsistent. One large cohort study (3) found no relationship between depression and breast cancer, whereas an analysis of data from the Alameda County study (4) found that depressive symptoms predicted non-cancer deaths but not cancer deaths. Although a slight elevation in cancer risk associated with depression was reported by Friedman (5), the analysis by Zonderman et al. (6) of data from the National Health and Nutrition Examination Survey Follow-up Study found no increase in either cancer morbidity or cancer mortality. Using the Center for Epidemiological Studies-Depression Scale (CES-D), Linkins and Comstock (7) found a strong association between depression and the development of cancer that was limited to smokers. A meta-analytic review (8) of the evidence concerning depression as a risk factor for cancer concluded that depression was a small and marginally statistically significant risk factor.

In this issue of the Journal, Penninx et al. (9) present the most compelling evidence to date that depressed mood heightens the risk of cancer. In a prospective, population-based study of 4825 persons aged 71 years and older, the investigators found an 88% increase in cancer risk over a follow-up period that averaged 3.8 years. In addition, depressed mood was associated with higher cancer mortality. Their analysis controlled for age, sex, race, disability, hospital admissions, alcohol intake, and, most importantly, smoking. These intriguing findings are likely to reopen the debate about the role of depression in the etiology of cancer.

The study by Penninx et al. (9) has a number of strengths, the most important of which is the repeated assessment of depressive symptoms. Individuals were classified as depressed if they met criteria (a score of 20 or higher on the CES-D) at baseline and at 3 and 6 years before baseline. By identifying a group of study participants who reported chronically depressed mood, the investigators provide a more focused and clinically informed test of the depression–cancer hypothesis. As the authors noted, all of the previous studies of depression as a risk factor for cancer relied on a single diagnosis or assessment of depressive symptoms. In further analyses of their own data, they find that depression measured at a single time point is not related to cancer. Therefore, their results both replicate earlier studies and suggest that chronic depression is a more viable risk factor than episodic depression.

Although the findings reported by Penninx et al. (9) are unique in the cancer research literature, they complement a growing body of evidence supporting the role of depression in the etiology and course of another leading cause of death, cardiovascular disease. A recent review of this work by Glassman and Shapiro (10) noted the consistency of research findings linking depression with a heightened risk of ischemic heart disease. It is especially interesting to note that the relative risks of heart disease associated with depression in older cohorts (11) are similar to those reported by Penninx et al. (9). Given the larger and more mature body of research in cardiovascular behavioral medicine, investigators in cancer behavioral medicine must be sure to examine the similarities and differences in these two areas of work. For example, while depression and psychological distress clearly affect the course of cardiovascular disease (10,12,13), similar analyses in the cancer domain have so far yielded only suggestive or negative results (14,15).

Although Penninx et al. (9) rule out a number of important potential confounders (e.g., use of antidepressants), the pathways by which depression might influence cancer etiology are unclear. The plausibility of the immune and central nervous system pathways discussed by the authors awaits the further development of basic research in psychoneuroimmunology and neuroscience. Although diet and physical activity are possible mediators of the observed relationship between depression and cancer, these are unlikely to account for the wide range of cancers associated with depressed mood. In addition, the fact that the study findings were unaffected by adjustments for body mass index and alcohol intake reduces the likelihood that a dietary pathway might explain the relationship.

However intriguing, these findings should be regarded as preliminary until they can be replicated in larger samples drawn from different populations. The examination of a larger sample also would enable separate analyses by type of cancer, an important prerequisite for developing informed hypotheses concerning the depression–cancer relationship. By using other existing cohorts, investigators can extend this work and search more broadly for third variables that might explain the findings reported here. Three lines of follow-up research would be especially important. First, we need a more comprehensive assessment and analysis of health behaviors to determine whether a behavioral pathway exists between depressed mood and cancer risk. Second, a more thorough psychological assessment that includes trait and state measures of anxiety, depression, and...
related personality variables is needed to learn whether general distress, clinical depression, or specific personality traits account for the most variance in health outcomes. Third, it is important to note that the findings reported here are based on data collected from an elderly population and remain to be extended to younger persons. It may be that the mechanisms responsible for the relationship between depression and cancer are part of a more complex aging process, producing age-specific vulnerability to disease. Thus, it would be premature to conclude that adults might reduce their risk of cancer through the treatment of depression. More research is needed. By investing in prospective research that incorporates both biologic and psychosocial measures, we can begin to explore the validity of a comprehensive biopsychosocial model of cancer etiology.

REFERENCES