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

Croyle (1), in his excellent editorial regarding the very fine study by Penninx et al. (2), suggested that three areas of follow-up research would be indicated to further delineate the association between depression and cancer. One of those recommendations was to extend the study of a younger population, because it may be that the mechanisms responsible for the relationship between depression and cancer are related to the aging process.

I don't anticipate that a negative study in younger patients would justify the conclusion that aging is the cause of the association between depression and cancer death that was found in the study by Penninx et al. (2). Cancers in general have a long latency. As pointed out by

Croyle, stress and depression have been associated with the causation and acceleration of cardiovascular disease. Cardiovascular disease tends to cause death at a younger age than does cancer. Therefore, one would have a common risk factor (for cardiovascular disease and cancer) and a competing cause of death (from cardiovascular disease and cancer), which would confound any epidemiologic study where death from cancer is in part or in whole an end point.

I think the main value of studies in younger patients would be to determine whether stress and depression can have an effect on the recurrence or progression of cancer. The fact that such an association is being found more frequently (3) would lend further credence to the study by Penninx et al.

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RESPONSE

A replication of our findings—that chronically depressed mood increases risk of cancer—in younger populations will give further credence to this link. However, if we are unable to find an association between chronically depressed mood and cancer in younger populations, this could indicate that age is indeed a modifier of the association between chronically depressed mood and cancer. The effect of many risk factors is attenuated with increasing age. Therefore, finding that the association between chronic depression and cancer is stronger at older age would provide provocative evidence that a synergistic effect exists between chronic depression

and changes in aging that are known to increase vulnerability to cancer.

In our study, we did not have data available about the stage of cancer when diagnosed and the progression speed of the cancer. Consequently, other studies in both young and old populations should provide further information about the association between chronic depression and recurrence or progression of cancer. If these studies are positive, they would add further support to our findings, but studies of stage and progression of cancer may not necessarily reflect the same risk factors as those for incidence. All of these studies are needed to learn about possible pathways in the link between chronic depression and cancer. We would like to emphasize that further studies should focus on people with chronic depression because the most important implication of our study is that *long-term* depression increases risk for cancer.

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EDITOR'S NOTE

Robert T. Croyle declined to respond to David S. David's correspondence.

tumor effects of Linomide. In an editorial accompanying the article by Joseph and Isaacs, Wahl and Kleinman (2) suggested, on the other hand, that tumor therapy protocols that combine Linomide with the antiangiogenic cytokine interleukin 12 (IL-12)—which induces interferon-gamma release and activates rather than inhibits TAMs—would be worth pursuing.

The results of our present studies demonstrate the pertinence of this suggestion. In a murine melanoma model, in which the antitumor activity of Linomide has already been demonstrated (3), we show that administration of IL-12 in combination with Linomide results in potentiated antitumor effects over single-agent therapy (two-sided $P < .05$; Mann-Whitney U test) (Fig. 1).

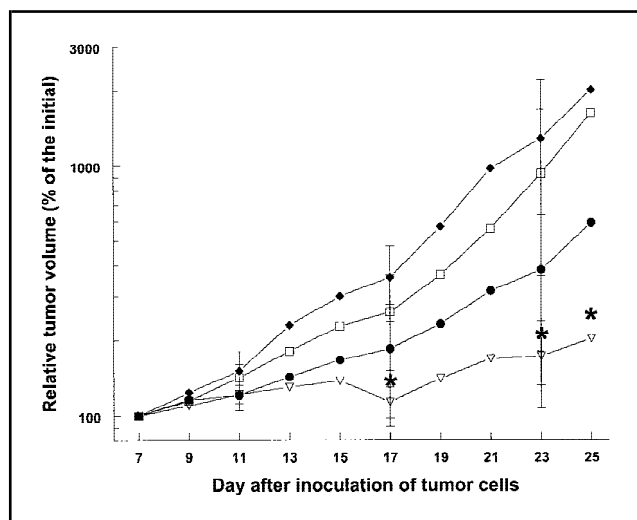
To confirm that IL-12 and Linomide, used alone or in combination, exert the antiangiogenic effects that were expected on the basis of previous reports, we used a tumor-induced angiogenesis model. This model was proven effective in a previous study of IL-12 and tumor necrosis factor (5). Short-term (3 consecutive days) intraperitoneal administration of either 0.1 μg IL-12 or 400 mg Linomide resulted in significant inhibition of blood vessel formation at the site of B16F10 murine melanoma cell injection (16.4 blood vessels per microscope field [95% confidence interval {CI} =

14.7–18.1 vessels] and 16.0 blood vessels per field [95% CI = 15.2–16.8 vessels] in IL-12 and Linomide-treated mice, respectively) as compared with diluent-injected controls (18.7 vessels per field [95% CI = 17.8–19.5 blood vessels]; two-sided $P = .007$ for IL-12 versus control group; two-sided $P = .0003$ for Linomide versus control group; Mann-Whitney U test). Combined treatment with IL-12 and Linomide was statistically significantly more effective in inhibiting the formation of new blood vessels than was the treatment with either agent alone (13.7 blood vessels per field [95% CI = 12.3–15.1 vessels]; two-sided $P = .012$ for IL-12 versus combined treatment group; two-sided $P = .0028$ for Linomide versus combined treatment group).

Our results demonstrate potentiation of antitumor and antiangiogenic effects for combination therapy with IL-12 and Linomide in a murine melanoma model. These observations would appear to be clinically interesting because antitumor efficacy of both these agents is currently being evaluated in clinical trials (6,7).

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Fig. 1. Effects of treatment with interleukin 12 (IL-12) and/or Linomide® on B16F10 melanoma growth (IL-12 was a gift from the Genetics Institute Inc., Boston, MA, and Linomide was a gift from Pharmacia and Upjohn, Lund, Sweden). B6D2F₁ mice were inoculated with 1×10^6 melanoma cells in the footpad of the right hind limb and treated intratumorally with 0.1 μg IL-12 for 7 consecutive days and/or intraperitoneally with 400 mg/kg of Linomide for 21 days starting on day 7 after inoculation of tumor cells. As a control, the following diluents were used: 0.1% bovine serum albumin-phosphate-buffered saline (PBS) administered intratumorally for 7 consecutive days and 0.01% Tween in PBS administered intraperitoneally for 21 consecutive days. Groups consisted of seven to eight mice. Doses of IL-12 and Linomide were established in previous experiments (data not shown). Tumor growth was monitored as described previously (4). Tumor volumes are expressed as means with 95% confidence intervals. * = two-sided $P < .05$ as compared with all other groups (Mann-Whitney U test). ♦ = control; ● = IL-12; □ = Linomide; and ▽ = IL-12 + Linomide.



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