Chronically depressed mood and cancer risk in older persons [reply]

Penninx, B.W.J.H.; Guralnik, J.M.

published in
Journal of the National Cancer Institute
1999

DOI (link to publisher)
10.1093/jnci/91.9.804a

document version
Publisher's PDF, also known as Version of record

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.

DAVID S. DAVID

REFERENCES

(1) Croyle RT. Depression as a risk factor for cancer: renewing a debate on the psychobiology of disease. J Natl Cancer Inst 1998;90: 1856–57.

(2) Penninx BW, Guralnik JM, Pahor N, Ferrucci L, Cerhan JR, Wallace RB, et al. Chronically depressed mood and cancer risk in older persons. J Natl Cancer Inst 1998;90:1888–93.

(3) Spiegel D, Sephton SE, Terr AI, Stites DP. Effects of psychosocial treatment in prolonging cancer survival may be mediated by neuroimmune pathways. Ann N Y Acad Sci 1998; 840:674–83.

NOTE

Correspondence to: David S. David, M.D., F.A.C.P., Clinical Professor of Medicine, U.C.L.A. School of Medicine, 2222 Santa Monica Blvd., Suite 302, Santa Monica, CA 90404.

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 neccesarily 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.

BRENDA W. J. H. PENNINX
JACK M. GURALNIK

NOTES

Affiliations of authors: B. W. J. H. Penninx, Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam, The Netherlands; J. M. Guralnik, Epidemiology, Demography and Biometry Program, National Institute on Aging, Bethesda, MD.

Correspondence to: Brenda W. J. H. Penninx, Ph.D., Institute for Research in Extramural Medicine, Vrije Universiteit, v.d. Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.

EDITOR'S NOTE

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

titumor 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)*.

ANNA DABROWSKA
JAKUB GOLAB
ADAM GIERMASZ
MARIA MARCZAK
MAREK JAKÓBISIAK

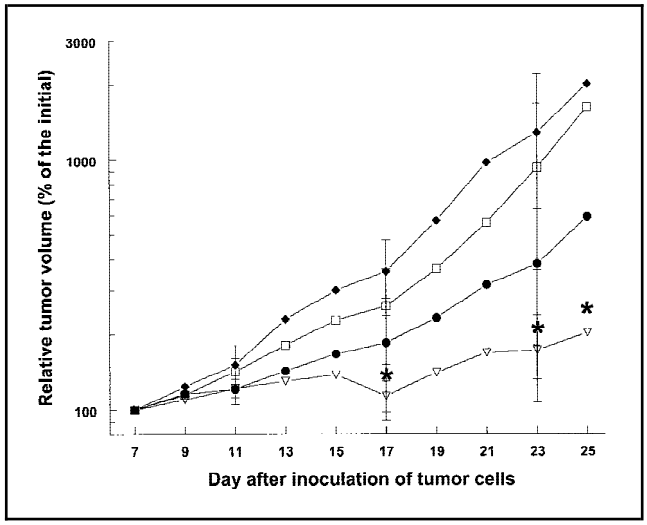

Fig. 1. Effects of treatment with interleukin 12 (IL-12) and/or Linomide® on B16F10 melanoma growth (IL-12 was a gift from the Genetics Institute Inc., Boston, MA, and Linomide was a gift from Pharmacia and Upjohn, Lund, Sweden). $B6D2F_1$ mice were inoculated with 1×10^6 melanoma cells in the footpad 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.

REFERENCES

(1) Joseph IB, Isaacs JT. Macrophage role in the anti-prostate cancer response to one class of antiangiogenic agents. J Natl Cancer Inst 1998;90:1648–53.
(2) Wahl LM, Kleinman HK. Tumor-associated macrophages as targets for cancer therapy [editorial]. J Natl Cancer Inst 1998;90:1583–4.
(3) Kalland T. Effects of the immunomodulator LS 2616 on growth and metastasis of the murine B16F10 melanoma. Cancer Res 1986;46: 3018–22.
(4) Golab J, Stoklosa T, Zagozdzon R, Kaca A, Giermasz A, Pojda Z, et al. G-CSF prevents the suppression of bone marrow hematopoiesis induced by IL-12 and augments its antitumor activity in a melanoma model in mice. Ann Oncol 1998;9:63–9.
(5) Lasek W, Feleszko W, Golab J, Stoklosa T, Marczak M, Dabrowska A, et al. Antitumor effects of the combination immunotherapy with interleukin-12 and tumor necrosis factor alpha in mice. Cancer Immunol Immunother 1997;45:100–8.
(6) Atkins MB, Robertson MJ, Gordon M, Lotze MT, DeCoste M, DuBois JS, et al. Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies. Clin Cancer Res 1997;3:409–17.
(7) de Wit R, Pawinsky A, Stoter G, van Oosterom AT, Fossa SD, Paridaens R, et al. EORTC phase II study of daily oral Linomide in metastatic renal cell carcinoma patients with good prognostic factors. Eur J Cancer 1997;33: 493–5.

NOTES

Supported in part by grant II D/79 from the Medical University of Warsaw and by grant 4 P05A 071 13 from the State Committee for Scientific Research.

Affiliations of authors: A. Dabrowska, Department of Immunology, Institute of Biostructure, Medical University of Warsaw, and Department of Lymphoproliferative Diseases, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland; J. Golab, A. Giermasz, M. Jakóbisiak (Department of Immunology, Institute of Biostructure), M. Marczak (Department of Dermatology), Medical University of Warsaw.

Correspondence to: Marek Jakóbisiak, M.D., Ph.D., Department of Immunology, Institute of Biostructure, Medical University of Warsaw, ul. Chalubinskiego 5, 02–004 Warsaw, Poland (e-mail: mjakobis@ib.amwaw.edu.pl).