

Re: Chronically Depressed Mood and Cancer Risk in Older Persons

A report by Penninx and colleagues (1) reported the results of a longitudinal study suggesting that chronically depressed elderly individuals have a nearly twofold increase in cancer risk. The role of depression as a risk factor for cancer has been widely debated, and the approach used by Penninx and colleagues to assess it among elderly patients contributes to the issue. We would like to stress some aspects of the study design and the statistical analysis that may have influenced the reported association.

From an original population of nearly 10 000 individuals interviewed in the first study year (i.e., 1982), only 4825 persons constituted the group from which the findings of the study were drawn. Of the approximately 5000 subjects not followed up, 1216 were excluded because they were diagnosed with cancer or were using anticancer drugs within 3 years before 1988—the year in which the cancer assessment started. Thus, the population initially evaluated for the presence of chronically depressed mood and the population evaluated for cancer substantially dif-

fered: Approximately one half of the patients examined for depression were not assessed for cancer risk.

The end point of the study (namely, cancer) was, in fact, a major criterion of exclusion from follow-up, and a differential length-biased sampling might have occurred (2). A similar bias has been described among prevalent cohorts of people with human immunodeficiency virus infection (3). By excluding those individuals enrolled in the study in 1982, and who developed cancer between 1985 and 1988, Penninx and colleagues might have depleted their three cohorts of the case subjects at highest risk for cancer. To what extent this depletion was associated with depression cannot be ascertained from the data presented in the paper. Hypothetically, one can assume that individuals identified as being not chronically depressed in 1982 were at a higher cancer risk than the depressed individuals, and, thus, they developed cancer before 1988. The inclusion of these cases in the follow-up discussion would have reversed the study results.

Two other issues are worth noting. First, the criteria adopted in the proportional hazard model to evaluate the assumption of proportionality of the risks between the two depression score groups might have been misleading, since the lack of interaction between age and sex does not seem to be sufficient to support the hypothesis of proportionality. To better evaluate such an assumption, we think that a time-dependent covariate transformation of the original variable should be added into the model (4). Second, the residual uncontrolled variability could hide an important risk factor associated with both cancer and depression. According to such a possibility [as already seen, for instance, in the association between smoking, human papillomavirus infection, and cervical cancer (5)], the effect of depression could actually be attributable to residual confounding.

In conclusion, we think that the important effort undertaken by Penninx and colleagues to identify older individuals with chronically depressed mood over a long time period may have been negatively counterbalanced by the exclusion of prevalent cancer cases. We are aware that this type of study among elderly patients presents several methodologic difficulties, but we would like

to stress that an alternative analysis, in which time periods for the assessment of depression and of cancer are closer, may offer a further contribution to understanding the relationship between depression and cancer.

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RESPONSE

Serraino and colleagues raise a few questions about our study design and the statistical analysis used that we would like to address.

First, it is not true that the study population initially evaluated for the presence of chronically depressed mood differed from the study population evaluated for cancer. The assessment of both depression and cancer started in 1982 for all persons included in our study. Although we had data about the hospital discharge diagnoses of cancer only for the 3 years before 1988, the assessment of prevalent cancer was further based on the self-report of cancer prior to 1982 and during any of the annual interviews between 1982 and 1988

and the use of anticancer drugs during these 6 years.

In our report, we excluded persons who reported a history of cancer before 1982 and who had cancer between 1982 (and not 1985 as mentioned by Serraino et al.) and 1988, since a possible cause-effect relationship between depression and cancer cannot be determined in these persons. If we had not excluded persons with prevalent cancer from our study population, our study would have been biased by the possibility that the presence of cancer may cause depression. In persons with prevalent cancer, it can never be ascertained whether depression caused a higher risk of cancer or whether depression is the result of a cancer diagnosis. Thus, a further examination of depressed mood status between 1982 and 1988 in persons with cancer, diagnosed between 1982 and 1988 would not give any further information about the role of chronic depression in the onset of cancer.

A statistical issue raised by Serraino et al. is the criterion adopted to evaluate the assumption of proportionality of hazards in the proportional hazard model. As written in the statistical analyses section (1), we did use the time-dependent covariate transformation of the chronic depressed mood variable to check the proportionality of hazards. In addition, we used a Kaplan-Meier analysis to check the association between chronically depressed mood and cancer incidence, since this analysis does not assume proportionality of hazards. This analysis confirmed the association between chronic depression and incidence of cancer.

Finally, we agree with the comment of Serraino and colleagues that residual uncontrolled variability could hide an important risk factor associated with both cancer and depression. Therefore, we adjusted our analyses for important potential confounding variables, such as age, sex, ethnic origin, physical disability, cigarette smoking, and alcohol intake. Since an increased risk for cancer was found for both depressed smokers and depressed nonsmokers and the anatomic sites at which chronically depressed persons showed excess cancers were not predominantly tobacco related, it is not very likely that smoking habits explain the increased cancer risk among chronically depressed persons in our study. As in any observational

study, we can never completely rule out the possibility that an unmeasured confounder explains the observed relationship.

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