

Depression and Cancer Mortality and Morbidity: Prospective Evidence from the Alameda County Study

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The association between the presence of depressive symptoms and cancer incidence and mortality and mortality from noncancer causes was studied in a population-based cohort of 6848 persons free of cancer who were followed from 1965 to 1982 as part of the Alameda County study. Age-adjusted and multivariate analyses involving over 111,000 person-years of follow-up demonstrated an association between high levels of depressive symptoms at baseline and deaths from noncancer causes but no association with either cancer incidence or cancer mortality. Our analyses suggest the possibility that the presence of previously diagnosed cases of cancer and the inclusion of items which tap somatic problems in depression scales may contribute to differences between these results and others in which depression has been linked to cancer mortality.

KEY WORDS: depression; cancer; prospective; morbidity; mortality.

INTRODUCTION

Galen's much-cited observation (Kowal, 1955) that cancer occurred more frequently in "melancholic" than "sanguine" women has been fol-

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lowed by centuries of clinical speculation that the depressed are more prone to cancer than other. There is little research evidence, however, that bears directly on this. What evidence does exist is largely cross-sectional or retrospective with mixed results (Murrell *et al.*, 1983; Bukberg *et al.*, 1984; Niemi and Jaaskelainen, 1978; Surawicz *et al.*, 1976; Kerr *et al.*, 1969; Craig and Abeloff, 1974; Greer and Morris, 1978; Dattore, 1978) and suffers from many of the methodologic problems involved in psychosocial research on cancer which have been addressed by a number of authors (Fox, 1978, 1982; Morrison and Paffenbarger, 1981; Bloom and Ross, 1982).

Perhaps the most compelling bit of evidence for an etiologic association comes from the study by Shekelle *et al.* (1981) of the 17-year prospective cancer mortality experience among a sample of male employees of the Western Electric Company's Hawthorne Works near Chicago, the Western Electric Health Study (WEHS) sample. These investigators reported that men who scored higher on the depression scale of the Minnesota Multiphasic Personality Inventory (MMPI) than on other scales, measured at baseline, were at significantly greater risk of death from cancer over the 17 years of follow-up. This association persisted after adjustment for smoking, alcohol consumption, occupational status, and family history of cancer. It also appeared to be consistent across different sites of cancer.

The present study was designed to examine further this association in a population-based, representative sample of adults followed for both cancer morbidity and cancer mortality for 17 years.

METHODS

The study sample consists of 6928 adults who participated in a 1965 survey of physical, social and psychological indicators of health conducted by the Human Population Laboratory (HPL) of the California Department of Health Services (Berkman and Breslow, 1983). Respondents were selected via a stratified sampling strategy for all households in Alameda County, California, in 1965 and are thought to be a representative sample of the general population in 1965.

Cancer morbidity information was obtained via automated record linkage between the 1965 HPL sample file and the cancer incidence records maintained by the Cancer Prevention Section (CPS) of the California Department of Health Services. The CPS has maintained a population-based cancer registry in Alameda County continuously since 1960—first as the Alameda County Cancer Registry (1960–1968), then expanded to the entire San Francisco–Oakland Standard Metropolitan Statistical Area as part of the National Cancer Institute's (NCI) Third National Cancer Survey (1969–1971), and most recently as part of NCI's ongoing Surveillance, Epidemiology, and End Results

program (1972 to the present). Cancer reporting to the CPS has been estimated to be 98% complete (Resource for Cancer Epidemiology, California Department of Health Services, 1980). Cancer mortality was determined via automated record linkage to the California statewide death files. It should be noted that while cancer incidence ascertainment was restricted to respondents still residing in the San Francisco Bay Area, cancer mortality ascertainment was not so restricted. Thus out-migration from the incidence ascertainment area could lead to potentially spurious findings if those who moved were more depressed than those who did not. There are several reasons which argue against such bias. As shown in the following material, the results of incidence and mortality analyses are very similar. In addition, it is unlikely that depression would be associated with a greater likelihood of residential moves. Finally, 17 cancer decedents had moved outside of the ascertainment area (and hence there was no available information on incidence), leading us to estimate a total underascertainment of approximately 30 incident cases. None of the 17 was classified as depressed at baseline.

Based on the cancer incidence information from the CPS, it was determined that 80 of the original 6928 HPL respondents had been diagnosed with an invasive primary prior to or during 1965. These "prevalent" cases were excluded from the study sample, resulting in an analytic sample of 6848 adults.

The measure of depressive symptoms used here was developed by Roberts and has been utilized in a number of other studies (Kaplan *et al.*, 1987; Kaplan, 1985; Roberts and O'Keefe, 1981; Roberts, 1981; Roberts *et al.*, 1981; Roberts and Roberts, 1982). A set of 40 items ostensibly related to depression was selected from the 1965 HPL questionnaire from a larger pool of items related to psychological distress. Items selected dealt with mood disturbance, negative self-concept, loss of energy, problems with eating and sleep, and psychomotor retardation or agitation. These items were then rated independently by 10 clinical researchers (psychiatrists and psychologists) in terms of their presumed utility in ascertaining depressive state. Based on these ratings, 20 items were eliminated. The homogeneity of the remaining items was assessed using item-total correlations and other measures of consistency (Nunnally, 1978), and based on these analyses, two additional items were eliminated. A score on these items (Table I) is calculated by assigning one point for each "true" or "false" answer (or for each "often" or "never" response) which is indicative of a depressed response. The 18-item scale has item-total correlations ranging from .18 to .45 and an acceptable internal consistency (coefficient $\alpha = .77$). In the present analyses, depressive "caseness" is defined as a symptom score one standard deviation or more above the mean depression score for the total sample, corresponding to the report of five symptoms or more.

Comparison of these items with those contained in other brief symptom checklists suggests that there is a high correspondence. Comparison of results obtained using this measure (Kaplan *et al.*, 1987; Kaplan,

Table I. Items in the HPL Depression Index^a

1. Felt depressed or very unhappy
2. Appetite poor
3. Trouble getting to sleep or staying asleep
4. Felt lonely or remote from other people
5. Felt on top of the world
6. Felt too tired even to do things I enjoy
7. Little enjoyment from leisure time
8. Less energy than other people
9. Felt pleased about accomplishing something
10. Felt bored
11. Felt so restless, couldn't sit still
12. Felt left out, even in a group
13. Felt excited or interested in something
14. Hard to feel close to others
15. Never satisfied with performance
16. Cannot relax easily
17. Bothered by getting tired in a short time
18. Felt vaguely uneasy without knowing why

^aSource: Kaplan *et al.* (1987).

1985; Roberts and O'Keefe, 1981; Roberts, 1981; Roberts *et al.*, 1981; Roberts and Roberts, 1982) with a number of reviews of similar measures suggests that this measure of depressive symptoms has considerable construct validity. In addition, the HPL 18-item index is correlated ($r = .66$) with the Beck Depression Inventory (Beck *et al.*, 1961) in an outpatient clinical population (J. Coyne, personal communication).

Cancer incidence and mortality rates are calculated using the "density" method described by Kleinbaum *et al.* (1982) for cohort studies. Rates are age-adjusted, using the direct method, to the 1970 adult (age 20+) population of the United States. Multivariate analyses utilize the Cox (1972) proportional hazards regression model to allow for deaths from competing causes. The regression parameter of interest in these analyses is the (log) relative hazard associated with being depressed versus not being depressed at baseline, a measure which can be interpreted as the "instantaneous" relative risk of cancer death or incidence associated with the presence of depression.

RESULTS

A total of 446 individuals among the HPL study respondents was diagnosed with 476 incident cancers (including multiple primaries) between 1966 and 1982, and 257 individuals died during this time period with cancer coded as the underlying cause of death. The site-group distribution for these

Table II. Cancer Incidence and Mortality in HPL Respondents, 1965-1982: Distribution of Sites^a

Site group (ICD-O codes ^b)	Incident cases		Deaths	
	Males	Females	Males	Females
Total	215	261	123	134
Lip, oral cavity, pharynx (140-149)	14	8	3	1
Digestive system (150-159)	59	49	36	32
Respiratory system (160-165)	40	26	32	19
Hematopoietic & reticuloendothelial systems (169) ^c	13	9	16	10
Connective tissues & skin (170-173)	5	4	3	1
Breast (174-175)	1	76	1	30
Genitourinary organs (179-189)	63	68	16	25
Nervous system, eye, & endocrine glands (190-194)	9	9	4	3
Lymph nodes (196)	8	6	10	4
Primary unknown (199)	3	6	2	9

^aSpecific cause-of-death site specifications are as reported on the death certificate and not necessarily consistent with the site specified at diagnosis.

^bFrom *International Classification of Diseases for Oncology* (World Health Organization, 1976).

^cDeaths include two myelofibrosis cases, which are not reportable in the SEER (incidence) system.

cancers by sex is presented in Table II and is comparable to that for all Alameda County residents during the same time period.

The prevalence of depression at baseline was 11.8% for men and 17.0% for women. For a subsample of employed men aged 40-55, similar to those in the WEHS sample, the prevalence of depression was 10.2%.

There is no evidence from this sample for an overall association between depression and subsequent cancer incidence or mortality. Table III

Table III. Age-Adjusted Cancer Rates (per 100,000)^a for Depressed and Nondepressed Respondents: Alameda County Cohort (N = 6801), 1965-1982

	Person-years at risk	Incidence		Deaths	
		Cases	Rate	Cases	Rate
Males					
Depressed	5,446	24	379.8	13	198.3
Nondepressed	44,831	189	404.0	109	238.8
Females					
Depressed	9,938	53	435.0	27	223.3
Nondepressed	51,582	207	342.2	107	173.6

^aAdjusted by the direct method to the 1970 U.S. adult population, excluding all respondents with missing values for depression score (N = 47).

compares the age-adjusted rates of cancer among men and women who scored as depressed versus not depressed on the baseline 1965 survey. Although these rates do not differ significantly from one another, females depressed at baseline appear to have experienced slightly more cancer during the followup interval. Males depressed at baseline show no differences or possibly even a lower cancer mortality. Figure 1 further examines this association by presenting the age-adjusted incidence and mortality rates for cancer from all sites, for men and women, for the depression score divided into quartiles. As in the analyses with the dichotomized score, there is no indication of an association between the number of depressive symptoms and cancer rates.

Table IV presents the results of proportional hazard analyses, adjusting for age only, for the association between depression at baseline and cancer mortality and incidence (all sites and selected sites) as well as for all-cause mortality and noncancer mortality in this study sample. Although there is a significant association between depression and noncancer mortality [relative hazard (RH) = 1.58, $p < .001$], there is no evidence for such an association for cancer among either men or women. The association between depression and cancer outcomes was also examined using a continuous measure of the number of depressive symptoms reported. There was no significant ($p < .2$) or otherwise important association between the number of depressive symptoms and the incidence or mortality from any site or all sites combined. In addition, the mean number of depressive symp-

Table IV. Association Between Depression and Cancer Incidence and Mortality:^a Alameda County Cohort ($N = 6801$), 1965-1982

	Males		Females	
	<i>N</i>	RH	<i>N</i>	RH
Mortality				
All causes	634	1.43*	596	1.43*
Noncancer	512	1.58*	462	1.49*
Cancer—all sites	122	0.83	134	1.19
Lung	31	1.34	19	0.87
Breast	—	—	30	1.24
Prostate	11	—	—	—
Colon	14	0.54	17	0.97
Cancer incidence—all sites	203	0.97	240	1.27
Lung	38	1.33	27	1.09
Breast	—	—	63	1.13
Prostate	42	1.13	—	—
Colon	22	0.34	26	1.08

^aProportional hazard analyses for all 1965 respondents not known to have a previous diagnosis of cancer (47 respondents with missing values for depression are also excluded).

* $p < .001$; all others, $p > .05$.

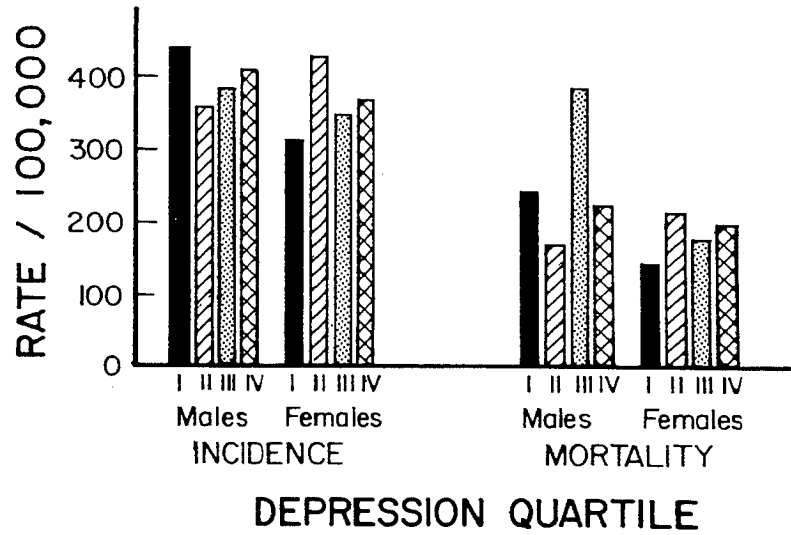


Fig. 1. Age-adjusted cancer incidence and mortality rates (per 100,000) for depression quartiles.

toms did not differ significantly ($p > .1$) between those who were alive and those who died from cancer.

In order to examine the discrepancies between these results and those found in the WEHS study for men, a subset of the HPL study cohort, consisting of all employed men between 40 and 55 years of age, was selected. There were 1010 men in the HPL sample filling these criteria.

As in the full cohort, there is no association between depression and cancer in this subset of employed males. The relative hazards (RH) associated with depression for dying of cancer or of being diagnosed with cancer are not significantly different from 1.0 (Table V). In addition, men in

Table V. Association Between Depression and Cancer Incidence and Mortality:^a HPL Employed Men Aged 40-55 (N = 1010)

	Cases	RH	p
Mortality			
Cancer	30	1.2	.748
Noncancer	110	1.3	.377
Cancer incidence	69	1.1	.754

^aProportional hazard analyses with adjustment for age, excluding all respondents known to have a previous diagnosis of cancer.

this group who are depressed are not at a significantly increased risk of death from noncancer causes. Similar findings were obtained when the continuous measure of depressive symptoms was utilized.

DISCUSSION

The present study does not demonstrate an association between depressive symptoms and cancer morbidity and mortality. Because the WEHS analyses, using a similar prospective design and length of follow-up, demonstrated a strong and consistent association between depressive symptoms measured by the MMPI and cancer mortality, it is important to examine differences between the two studies.

There are substantial differences between the WEHS and the HPL study populations. The HPL cohort is a population-based sample, and the WEHS cohort is a selected sample of volunteers from a particular workplace. The WEHS cohort consists only of men in a limited age group, actively employed at Western Electric's Hawthorne plant, who were selected to be free of heart disease at entry into the study. However, the absence of a significant association between depression and cancer morbidity and mortality in employed men aged 40-55 in the HPL sample suggests that such differences do not account for the variance in findings.

There are other demographic differences between the two cohorts (aside from differences in geographic location). These include differences in the occupational distribution (the HPL cohort includes a higher proportion of men in technical/professional occupations, 48 vs 32%) and the ethnic distribution (75% of the WEHS cohort is of eastern European descent). Further selecting on these criteria would result in an HPL comparison cohort too small for meaningful analyses. These differences may reflect general differences in socioeconomic status; however, adjustment for education and family income (adjusted for family size) leads to no change in the results.

These differences in findings do not appear to be a function of differential mortality in the two study groups. The 17-year mortality experience for the cohort of employed HPL men is quite similar to the 17-year mortality experience of the WEHS cohort (Table VI), except that the HPL men have a somewhat lower proportion of ischemic heart deaths. Likewise, the distribution by specific sites of cancer (Table VII) is also reasonably comparable between the two cohorts.

Another difference between the WEHS and the HPL cohorts is the method of exclusion of those previously diagnosed with cancer. Exclusion of prevalent cancer cases in the WEHS study was based on the baseline

Table VI. Percentage Distribution of Deaths for the HPL and WEHS^a Samples

	WEHS (%)	HPL (%)
Alive	82.0	85.9
Cancer	4.0	3.2
Cardiovascular death	10.0	4.9
Accidents and suicide	1.0	1.4
Other causes of death	3.0	4.8

^aSource: Shekelle *et al.* (1981).

medical examination and report of medical history (R. Shekelle, personal communication). In addition, the WEHS investigators attempted to follow back the medical records for cancer decedents. They succeeded for 57 of the 82 men who died of cancer (69.5%), finding that only 5 of the 57 cancer decedents could be characterized as "prevalent" cases at baseline. Four of these five cases had been diagnosed around the time of the baseline examination, and one had been diagnosed 2 or 3 years earlier.

In the HPL sample, prevalent cancer (including diagnoses up to 5 years prior to entry and including diagnoses during the baseline year) were independently ascertained via record linkage to the population-based tumor registry serving this geographic area. This resulted in the exclusion of 80 respondents in the total sample. Of these 80, 78 (98%) were diagnosed within 5 years of baseline, and only 7 of these 78 (9%) were diagnosed within the year prior to baseline. All in all, 12.2% of the cancer deaths occurred in the 1.2% who were prevalent cases up to 5 years before baseline.

Table VII. Site Distribution of Cancer Deaths, Employed Men Aged 40-55: Comparisons of HPL and WEHS^a Results

Site	WEHS		HPL	
	N	%	N	%
Head and neck	6	7.3	0	—
GI tract				
Stomach/esophagus	4	4.9	3	10.0
Rectum	7	8.5	0	—
Lung	13	15.9	8	26.7
Prostate	5	6.1	2	6.7
Urinary/bladder	5	6.1	0	—
Kidney	5	6.1	1	3.3
Hematopoietic & lymphatic	9	11.0	5	16.7
Other	18	22.0	7	23.3
Total, all sites	82	100.0	30	100.0
Number in cohort		2020		1010

^aSource: Shekelle *et al.* (1981).

We do not know to what extent these differences in the ascertainment of baseline cancer or in the definition of prevalent cases might contribute to the different results. However, if there were underascertainment of prevalent cases, including those diagnosed several years before the baseline examination, it could have a significant effect on the observed association if the prevalence of depression is higher in those with prevalent cancer. In the HPL sample, the prevalence of depression at baseline for those with previously diagnosed cancer was twice as high as for those without previous diagnoses.

Different statistical models were used in the present study and the WEHS study. The WEHS study utilized a competing risk multiple logistic model (Cox, 1970), whereas the present analyses utilize a Cox (1972) proportional hazards approach. However, one would not expect substantially different results from these two techniques. Furthermore, analyses utilizing multiple logistic techniques did not demonstrate an association between depression and cancer mortality in the HPL sample. Inspection of age-adjusted or age-specific rates in the current analyses also fails to indicate any association between depression and either cancer mortality or cancer morbidity. Finally, although we found no significant association, a proportional hazards analysis was carried out for all study women, for all study men, and for the sample most equivalent to that in the WEHS analyses (employed men 40-55 years of age) in which there was adjustment for smoking, education, income, self-reported physical health status, alcohol consumption, and race. The results of these analyses also failed to confirm the existence of an association between depression and cancer. Indeed, for the total analytic sample of men, there was a suggestion of an inverse association (RH = 0.53, $p = 0.08$).

It would appear that neither differences in sample characteristics nor statistical methodology is adequate to explain the different results obtained by the WEHS and HPL studies. We are left with two prospective studies, similar in many ways, which use different measures of depression and which arrive at opposite conclusions. It would seem appropriate, then, to examine the differences between these two measures for a clue to reasons for these different results.

The HPL measure of depressive symptoms has been utilized in a number of studies and compares favorably to other measures of depression used in community studies. It is one of a class of depression measures which tap an underlying dimension of "demoralization" (Link and Dohrenwend, 1980). Half of those who score high on such a measure of depression are clinically impaired (Link and Dohrenwend, 1980). It should be noted that this measure of depression does bear some relationship to mortality outcomes from noncancer causes in these analyses (Table IV) and in others (Kaplan, 1985).

It is possible that the two measures of depression detect different levels of severity of depression. The MMPI measure used in the WEHS study would be expected to index more severe depression than the HPL 18-item index. However, the prevalence of depression was actually higher in the WEHS sample (18.8%) than in the equivalent HPL sample of employed men (10.2%). This difference in prevalence is not consistent with the notion that depressed men in the WEHS sample were more severely depressed than depressed men in the HPL sample.

Examination of the content of the two depression scales reveals differences in item content. As Shekelle *et al.* (1981, p. 118) point out, the 60 items on the MMPI D scale tap "general apathy, denial of happiness and personal worth, impaired mental and physical abilities, concern about failing health, disturbance of sleep and gastrointestinal functions, sensitivity to criticism, and lack of sociability." Comparison with the content of the 18-item HPL depression index (Table I) indicates that the only domain where there is not conceptual overlap is in the area of physical health and functioning. That is, the reports of impaired mental and physical abilities and concern over failing health in the MMPI are not duplicated in the HPL index. Given that these are the only areas in which there is no overlap, and the possible influence of depressed prevalent cases indicated earlier, it is possible that the association between depression and cancer mortality seen in the WEHS analyses is due to some extent to the presence of sick and depressed individuals at baseline. It is interesting to note, in this regard, that in Plumb and Holland's (1977) study of depression among cancer patients, the only depressive items on the Beck Depression Index (Beck *et al.*, 1961) which differentiated the patients from healthy controls were those related to somatic symptoms. Further analyses of the WEHS data utilizing a modified D scale could partially test this possibility.

It is worth noting that the HPL results are consistent with three other studies which address this general association for men. One of these is a prospectively designed study in which depression scores (as measured by the MMPI) were not associated with cancer mortality in a population of hospitalized U.S. military veterans (Watson and Schuld, 1974). The second, also a study of U.S. veterans, found no differences in cancer mortality when men discharged with psychoneurotic diagnoses were compared with a sample of birth year-matched men with regular discharges (Keehn *et al.*, 1974). In a third prospective study, Dattore *et al.* (1980) found that men who were subsequently diagnosed with cancer actually had lower D scores on the MMPI than men without cancer diagnoses at follow-up.

In summary, we found no evidence for an association between the presence of depression and subsequent cancer mortality or cancer morbidity. A comparison with the WEHS study which did find such an association leads to the possibility that an association between physical health status and

depression may be partially responsible for the reported prospective link between depression and cancer. Certainly, a number of studies document that people with chronic conditions such as cancer are more "depressed" than healthy respondents (Kaplan *et al.*, 1987; Frerichs *et al.*, 1982). There is no way of knowing if the exclusion of prevalent cancer cases based on medical examination and history led to an inadvertent underascertainment of prevalent cancer in the WEHS study. Based, however, on the possibility of such an underascertainment, it would seem desirable to use independent registries when possible to eliminate at baseline respondents with cancer and to exclude those with cancer several years earlier. Finally, valuable information may be lost with the use of summary scales which combine items from disparate domains. Although complaints of physical health problems may be important in the diagnosis of depression, their presence in depression scales may contribute to spurious associations with health outcomes. Careful attention to the constituent items in psychosocial scales may help to explain the specific pathways by which psychosocial variables are associated with health outcomes. In the case of the reported etiologic association between depression and cancer, further studies, with attention to these issues, will be necessary to clarify the reasons for the conflicting pattern of results.

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