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Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample

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Abstract

Objective—The objective was to characterize the relationship between depression and incident cancer. Few studies have employed population-based prospective data on subtypes of cancer to address the question.

Method—A population-based sample of 3,177 cancer-free adults from the Baltimore Epidemiologic Catchment Area Study who have been followed for 24 years. Cox proportional hazards models were used to estimate relative hazards for both overall and subtype-specific cancers among those with a history of depression.

Results—The risk set contained 334 incident cancer cases and 40,530 person-years of observation. DIS/DSM-III major depression was associated with a higher hazard for overall cancer (HR: 1.9, 95% CI: 1.2, 3.0) and a statistically significant increased hazard for breast cancer (HR: 4.4, 95% CI: 1.08, 17.6) among women. There was a positive association between history of depression and prostate cancer, but confidence bounds included the null. No reliable associations were found between colon, lung, or skin cancers and depression. The pattern of results was similar for dysphoria, but not for phobia or any other mental disorder studied.

Conclusions—Results reveal a specificity to the association between depression and hormonally mediated cancers, which provides support to hypotheses about a common biological pathway between depression and cancer. Further research can build on observational studies to examine the mechanisms through which our emotions affect our health.

Keywords

Cancer; Depression; Epidemiology; Cohort

Introduction

The extent to which psychosocial factors affect cancer development is important because uncovering risk factors for cancer may open new avenues for prevention and intervention. A link between a history of depression and cancer incidence has been postulated for millennia, since the time of the ancient Greeks [1]. Indeed, statistical evidence for such an association was reported as early as 1893 [1]. Two meta-analyses of large epidemiologic cohort studies have been performed within the past two decades to address this question [2,3]. Both concluded that depression presents a small, barely statistically significant increase in the risk for cancer, but that there is considerable heterogeneity in associations across studies. Modern large-scale epidemiologic studies conducted over the course of the last several decades, in the absence of conclusive biological evidence of common or causal etiologies, have provided the best venues in which to study depression as a risk factor for cancer. Some studies find support [4–6], while others report negative findings [7–15]. Still other studies, analyzing data from the same cohort with different amounts of follow-up, have found associations between depression and specific cancer subtypes, such as breast cancer [13,16].

Several theories and explanations, resting on physiological, psychological, and genetic grounds, have been entertained to explain why depression might be a risk factor for cancer. Physiologically based explanations revolve around hypotheses that depression either compromises immune system function or inhibits DNA repair mechanisms [17]. Stress and depression can inhibit DNA repair enzymes that are critical for apoptosis and, therefore, defense against malignant tumor growth [18,19]. Additionally, decreased natural killer (NK) cell function has consistently been associated with chronic stressors, and these cells are important to immune system function because they fight off viral infections and destroy tumor cells [20]. Theories involving innate psychological reasons for a link between depression and cancer generally propose the existence of such latent risk factors for cancer as poor ego defense mechanisms, coping skills, or a sad disposition following loss [21,22]. These theories are difficult to test empirically with prospective cohort studies. More recently, genetic characteristics have been proposed that might lead to both depression and certain subtypes cancer. For example, dysregulated proto-oncogenes of the ras family, which are proteins that direct cell growth, can inhibit dopamine and serotonin synthesis, thereby leading to depression [23–26]. Certain cancers, specifically of the pancreas, lung, colon, and skin, have been associated with disruption of this oncogene family [23].

Existing prospective cohort studies have several limitations that have been cited as potential sources of null or conflicting findings [13,23]. Limitations include relatively short follow-up times, with most studies having between 10 and 15 years of prospective follow-up; incomplete or unreliable ascertainment of depression status at baseline; and a lack of proper statistical control of potential confounders. The Baltimore Epidemiologic Catchment Area (ECA) Study resolves many of these weaknesses. To date, the cohort has been followed for 24 years. Depression status was ascertained in 1981 and again in follow-up waves with fieldwork from 1993 to 1996 (abbreviated below to “1994”) and from 2004 to 2005 (abbreviated below to “2005”) using the Diagnostic Interview Schedule (DIS), a validated lay assessment tool keyed to DSM-III criteria established by the American Psychiatric Association [27]. The depression-cancer link was addressed using ECA data previously in Gallo et al. [13] using 13 years of follow-up and 203 incident cases of cancer. The present study includes 24 years of follow-up data and 334 cancer cases. In this study, we update estimates using more follow-up time and new incident cancer cases. Second, we expand upon previous analyses using different statistical methods, namely survival analysis. Third, we compare cancer risks for other mental health problems to provide information about the specificity of the depression-cancer association.

Methods

The ECA program was the first coordinated large-scale, multi-site, community-based epidemiologic survey of psychiatric disorders among a general population in the United States. Using probability sampling, persons aged 18 and older living in households, prisons, nursing homes, and mental institutions in geographically defined catchment areas were interviewed using the DIS in 1981 at five university-based sites. At this baseline, respondents gave informed consent and permission to be interviewed again at later times. Respondents at all sites were re-interviewed 12 months later, and 3,481 persons residing in households at baseline at the Baltimore site were further interviewed in 1993–1996 (“1994”) and again in 2004–2005 (“2005”). Attempts have been made to trace and re-interview all participants from 1981 at each follow-up wave. The survey completion rate in 1981 was 78% and vital status is currently known for 99% of the original cohort. Further details of the ECA sampling and study design are available elsewhere [28,29]. For these analyses, we excluded persons who at their baseline interview in 1981 reported any lifetime history of cancer, thus creating a “risk set” of persons who did not have a history of cancer.

Measurement strategy

Depression status—Depression status was the primary exposure of interest and was ascertained in a standardized fashion using the DIS in all ECA wave interviews. The DIS is composed of standardized questions that can be used to build DSM-III diagnoses of mental disorders based on symptoms, co-occurrence of symptoms in time, and other relevant factors. Information about history of lifetime major depression and dysphoria was available at the symptom level, and a computerized algorithm was used to construct DSM-III diagnoses. The DIS has been found to be an imperfect though conservative measure of depressive disorder when compared to a psychiatrist’s examination (sensitivity: 0.98; specificity: 0.40) [30]. Lifetime history of dysphoric episode was assessed at baseline and during each follow-up wave using the question, “Have you ever had 2 weeks or more when you felt sad, blue, or depressed, or when you lost interest in things you normally enjoyed?” For the present analysis, we quantified depression status by sorting respondents into three mutually exclusive groups: persons who reported a lifetime history of major depression, a lifetime history of a dysphoric episode, or neither a history of major depression nor dysphoric episode.

Cancer—Cancer status was the primary outcome of interest. It was ascertained through self-reports from respondents interviewed at the 1994 and 2005 follow-up interviews, and also from the National Death Index (NDI) through 2007. Cancer was considered present if it was either a primary or contributing cause of death on a death certificate. Cancer status was further classified by type into breast, colon, lung, prostate, and skin cancers. Year of cancer onset, needed for the survival analyses described below, was determined during the 2004–2005 wave interviews by asking about the year of cancer onset for those who reported having cancer. Participants who reported a history of cancer during the 1994 interview wave, however, were not asked when they were first diagnosed with cancer. Further, time of cancer diagnosis was not available for cancers ascertained through the NDI. Onset dates were imputed for these cancers by using predictive equations that took into account sex, smoking status, and ethnicity among known dates of cancer onset from the 2005 interview wave. A number of sensitivity analyses, described later, tested the robustness of findings by calculating time of onset in different ways.

Other covariates—All variables were selected based on a priori theory. We took into consideration age, self-reported race, sex, marital status at each wave, smoking status at each wave, socioeconomic status (SES), and history of alcohol abuse/dependence as possible confounders in the relationship between depression and cancer. We also controlled for parity

when considering hazards for breast cancer. To control for smoking status, we categorized respondents into never smokers, former smokers, current smokers consuming one pack or less of cigarettes per day, and current smokers consuming more than one pack per day. SES in 1981 was represented by a composite score aggregating occupational status, annual household income level, and highest level of education completed [13]. Race was dichotomized into White and non-White for analytic purposes.

Analysis plan—We estimated the relative hazard, which approximates a relative risk, of incident cancer among those with a history of depression using semi-parametric Cox proportional hazards models. This model type allows for a nonparametric baseline hazard rate and requires that the ratio of a hazard rate to that baseline hazard be constant over time; this is called the proportional hazards assumption. Models estimate the hazard ratio, or risk, of cancer onset as an exponential function of covariates, and allow for incomplete covariate information due to censoring, which is common in epidemiological cohort studies with a long duration like the ECA [31]. Our models were also able to take into account time-varying independent variables. Proportional hazards models were chosen over logistic regression because logistic regression is unable to account for differential amounts of follow-up time.

Person-years of follow-up were calculated in the following fashion. The risk set began in 1981 with the first baseline interview, and respondents stopped contributing person-time when they died or were diagnosed with cancer. For cancer cases in which year of onset was unavailable, we used predictive equations to predict years of onset that took into account sex, smoking status, and ethnicity among known dates of cancer onset from the 2005 wave.

We estimated hazard ratios for cancer over time separately for major depression and dysphoria. First, crude, unadjusted models were fit, with cancer as the outcome and depression type as the only predictor. Second, models were further adjusted for age, self-reported race, sex, marital and smoking status, baseline SES, and alcohol abuse/dependence. Age and SES were centered at their means. Marital status, smoking status, alcoholism, and lifetime history of depression (to allow for inclusion of incident cases over 24 years of follow-up) were allowed to vary over time. The reference group for all analyses was those without a history of major depression or dysphoria.

Proportional hazards models were fit in a similar fashion for each subtype of cancer. Covariates that were statistically nonsignificant for overall cancer were dropped in these models for cancer subtypes because the number of outcomes for specific cancers was smaller than that for all cancers combined. For these cancer subtypes, depression was also characterized in several new ways. For each cancer subtype, depression was quantified at the level of symptom counts, disregarding cut points used for a clinical diagnosis. History of major depression was separated into cases of single and recurrent episodes, under the supposition that if stress-related dysregulation of immune system function or hormonal allostasis does lead to some subtypes of cancer, then risks for cancer should be higher among those with recurrent episodes of major depression. A single-episode history of major depression is more indicative of exogenous life circumstances than of an enduring trait.

To provide a contrast with estimates associated with depression, we calculated hazards of cancer onset given DIS/DSM-III phobia at baseline using Cox proportional hazards models. Phobia was selected because it is also a mood-related disorder, and there were plenty of DIS/DSM-III cases in the ECA data. We next executed similar models for any mental health problem except major depression, which included DIS/DSM-III alcohol abuse or dependence, mania, drug abuse or dependence, obsessive compulsive disorder, phobia, and somatization disorder.

A series of three sensitivity analyses were performed to evaluate the robustness of our findings. First, because some studies have suggested cancer risk among those with depression is only higher among smokers [10], models were fit with interaction terms between smoking status and depression type. Second, participants who at baseline rated their health status as “poor” on a scale of “Excellent,” “Very Good,” “Good,” “Fair,” or “Poor” were excluded so as to rule out potentially spurious associations driven by prevalent cancer cases. Third, follow-up time for those with cancer was calculated in three additional ways to test robustness of results. Specifically, we calculated follow-up time under the following assumptions: cancer onset coincided with year of death or report of cancer for those 1994 wave respondents who reported cancer, cancer onset was 10 years prior to death or 10 years prior to the 1994 report, and that cancer onset was 15 years prior to death or 10 years prior to the 1994 report. In all cases, model fits and the validity of the proportional hazards assumption were assessed using graphical displays of Schoenfeld residuals as well as both covariate-specific and global chi-squared tests of the proportional hazards assumption [32].

Results

At baseline, 3,481 participants were interviewed at the Baltimore ECA site. Of these, 157 respondents were excluded after reporting a history of cancer. Lifetime depression status at baseline was not known for another 147 respondents. This resulted in a risk set of 3,177 persons, representing 40,530 person-years, who had complete information on depression status and no prevalent cancer at baseline. Of these, 1,028 were alive and re-interviewed in 2005, death certificates were available from the NDI for 1,112 persons, and mortality information was gathered from the field during either the 1994 or 2005 follow-ups for another 137 participants. The remaining 900 were assumed to be alive in 2005, but either were lost to follow-up or refused to be re-interviewed at the 2005 wave, although most of them were interviewed at the 1994 wave. Baseline participant characteristics are shown in Table 1. Most respondents at each wave were female and white (Table 1). The mean age in 1981 was 46 years.

Associations between depression and overall cancer

Among 334 cases of cancer reported, 17 cases had a history of DIS/DSM-III major depression and 85 had a history of dysphoria prior to 1981. In an unadjusted Cox proportional hazards model, major depression was not significantly associated with an increased hazard for overall cancer, but it was after adjusting for covariates (Table 2). Dysphoric episode was also significantly associated with an increased hazard of cancer (Table 2). Older age was significantly associated with an increased risk for overall cancer, and never having married was protective. Current and heavy smoking was progressively more strongly associated with an increased risk for cancer, although the associated hazard ratios only barely included the null (Table 2).

Associations between depression and subtypes of cancer

Table 3 shows relative hazards from unadjusted and adjusted models for the risk of incident cancer type and history of depression. Because of concerns about over-fitting models due to low counts among cancer subtypes, covariates that failed to reach statistical significance in models with overall cancer (alcohol abuse/dependence, ethnicity, and SES) were dropped. Depression was quantified in separate models as DIS/DSM-III major depression, dysphoria, DIS/DSM-III major depression with recurrent episodes, DIS/DSM-III single-episode major depression, and number of depressive symptom groups out of nine. When we estimated hazards for any cancer given these subtypes of depression, hazards were not increased for any of the latter three subtypes (results not shown).

Four of the 119 women with history of major depression had an onset of breast cancer, significantly more than that among the women without a history of depression (Table 3). There was also evidence of a linear dose–response relationship between breast cancer risk and number of symptom groups ever present for depression (Table 3). Statistical significance at the standard level of $p = 0.05$ was not reached in either case, however ($p = 0.08$ and $p = 0.06$, respectively). Dysphoria did significantly increase the hazard for breast cancer among women. There were no statistically significant associations between breast cancer and any subtypes of major depression, although the point estimates indicated associations in a positive direction.

An increased hazard of prostate cancer was not significantly associated with a history of major depression or dysphoria among men, but there was a significant relationship for single-episode major depression (Table 3). Dysphoria increased the hazard for colon cancer (Table 3). For prostate and colon cancers, however, there was only one case of cancer each among those with major depression, and analyses of Schoenfeld residuals suggested poor model fits due to violations of proportional hazards assumptions. Lung and skin cancers were not statistically associated with any quantification of exposure status, although wide confidence intervals reflect limited power (Table 3). It is worth observing here that while current smoking status was only marginally associated with overall cancer (Table 2), it was very strongly associated with hazard for lung cancer (HR for current smoking: 34.3; 95% CI: 4.30, 273.74). Several hazard ratios could not be calculated due to insufficient numbers of cancer cases.

Comparisons with other disorders

We constructed a forest plot to graphically display our results for the hazard of cancers and depression alongside hazard ratios between cancer types and any mental health problem and also DIS/DSM-III Phobia (Fig. 1). Neither DSM-III phobia nor any mental health problem in the aggregate was significantly associated with overall cancer or any subtype, though associations were generally in a positive direction.

Sensitivity analyses

An analysis of interactions between smoking status and depression type revealed that smoking did not significantly modify the association between major depression and overall cancer; there were insufficient cases to estimate reliable interaction coefficients for any of the cancer subtypes. In a second set of analyses, we excluded 145 respondents who at baseline rated their health status as poor, 24 of whom had a lifetime history of major depression. For overall cancer, although the magnitude of the association remained relatively high, major depression was no longer statistically significantly associated with an increased cancer hazard (HR: 1.56, 95% CI: 0.90, 2.70). All other associations otherwise remained constant, and no other inferences changed. Third, recalculating follow-up time using parameters described earlier did not change any inferences.

Discussion

We investigated depression as a risk factor for incident cancer using a community-based population of adults followed between 1981 and 2005. We found a significant relationship between both a lifetime history of DSM-III major depression as well as of dysphoria and risk of overall cancer. Major depression appeared to increase the hazard for cancer, particularly in the case of breast cancer among women. Further, the hazard for breast cancer increased linearly with the number of depressive symptom groups. While the absolute risk of cancer is not high given depression, the population attributable risk is likely sizeable given the considerable prevalence of depression in the general population, lifetime prevalence estimates of which range from 4.4% to 14.1% across US-based studies [33,34].

Compared with other epidemiologic studies that have studied associations between depression and either overall cancer or certain subtypes using standardized interview-administered diagnostic criteria, the ECA has among the largest number of cancer cases and one of the longest follow-up times [3]. Studies with longer follow-up times tend to report stronger associations especially for cancer subtypes with hormonally mediated pathologies such as breast cancer [3,16], perhaps because most cancers have long latent periods [3]. Other advantages include the ECA's prospective design and statistical control for time-varying confounder information. Most studies have adjusted at least for age and sex, and here we have adjusted for those characteristics as well as SES, ethnicity, marital status, smoking status, and history of alcohol abuse/dependence.

A common limitation in many epidemiologic studies involving depression generally revolves around the method of depression ascertainment; here, major depression was determined using the DIS, which is a standardized, interviewer-administered assessment tool. While any measure of depression inevitably must rely on self-reports, the DIS is a validated tool that shows good reliability and moderate concordance with structured clinical examinations [30]. Further, because dysphoria was measured using just one item, it is inherently less reliable than a scale with several items. Unless dysphoria was systematically endorsed differentially by cancer status, however, this should attenuate hazard estimates toward null values, which gives somewhat stronger meaning to our significant findings.

Several limitations should be addressed. First, loss to follow-up might be differential by either cancer status or depression status, which could give rise to biased estimates of associations and standard errors. Participants' cancer status was ascertained during follow-up interviews and from the NDI for all deceased persons as of 2005. However, 560 respondents in 1981 were neither dead nor followed up in 1994 or 2005. While these missing participants did not differ statistically by baseline depression status, sex, marital status, or ethnicity, the potential remains for bias due to differential follow-up. Another limitation relates to misspecification of the risk model. There might still be other important confounders not accounted for, such as genetic predispositions or innate, unmeasured psychological traits [21,23]. A third limitation relates to measurement of our exposure variable of depression. While the specificity of the DIS is relatively high for detecting major depression (between 95% and 98% of true negatives are found to be negative), sensitivity estimates vary from approximately 30% to 40% [30,35]. We believe misclassification of the exposure variable will bias our estimates toward the null so that estimates are conservative. The finding of a marginally significant linear association between number of depressive symptom groups and probability of breast cancer alleviates this concern to some degree because it shows a relationship between cancer and depression that is not dependent on selection of a particular threshold, as implied by diagnostic criteria. A fourth potential limitation is that cancer status was self-reported for participants interviewed in the 1994 or 2005 waves but who were not yet dead when the NDI was consulted. This measurement error should also attenuate our estimates.

A final limitation is that since the entire cohort has not yet been followed to death or until a cancer onset, it is conceivable that some members of the ECA cohort are too young to have reached an age typically associated with the onset of most cancers. The youngest participant in 2005 was 41 years old, and the median age of onset for lung cancer, to use an example, is 70 years [36]. Median ages of onset vary across subtypes of cancer, and depend to a certain extent on new technologies and screening programs [37].

The forest plot (Fig. 1) provides evidence for the specificity of the association between depression or depressive mood and hormonally mediated cancers because such an association does not exist for phobia or for other mental health disorders. While it appears that the association of depression with colon cancer was strongly associated with a history of major

depression, the estimate was influenced by the one person who had both colon cancer and major depression. Some inferences about possible etiologic theories for the relation between depression and cancer can be drawn from our findings. With respect to genetic theories, we found no empirical evidence to support the hypothesis that ras proto-oncogenes are responsible for the association between depression and cancer. This theory predicts that subtypes of cancer most associated with these oncogenes, specifically skin and lung cancers, should be significantly associated with depression more than other types of cancer, and prostate and breast cancers should be least associated [23]. This was not found. Presence of a common underlying genetic factor is still plausible, but further genetic association and linkage studies are needed to identify more candidate genes. We were unable to quantify such characteristics as coping style or ego defense mechanisms using ECA data because specific measures of these constructs were not available, and so we cannot comment on psychologically based theories. Behaviors that may influence risk of cancer related to medical screening or lifestyle may operate through psychological factors.

Hypotheses about a common biological pathway leading to depression and cancer, or a physiological process by which depression causes cancer, appear to be supported by our study as well as from recent reviews of other studies with large epidemiological cohorts [3]. We found that a history of major depression was associated with a higher risk of breast cancer. Further, single-episode cases of major depression were significantly associated with a higher risk of prostate cancer, though the estimate had wide confidence bounds. Breast and prostate cancers are both hormonally mediated types of cancer. One conceivable biological mechanism for the association between depression and cancer involves the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol, a stress hormone, is released from the adrenal glands after detection of increased levels of ACTH in the bloodstream secreted from the pituitary gland and activated by CRF released from the hypothalamus. Chronic stress and aberrant activation of the HPA axis disregulates cortisol levels, such that chronic stressors over time destroy regular cortisol response patterns and disrupt one's ability to respond to stresses [38]. As irregular patterns of excitement become the norm, as is the case for depression, risk for mental psychopathology in turn increases via a feedback loop. At the same time, cortisol is also involved in the activation of signaling that controls cell growth and regulation of the cell cycle [39–41]. In particular, flattening of cortisol levels throughout the course of a day has been shown to increase the risk for breast cancer in particular [42,43]. The role of the HPA axis may not tell the whole story because breast cancer risk was not elevated among major depression cases with a recurrent episode in the present study, as would be predicted by a chronically acting biological mechanism.

Depression's role in altering biological processes directly may be small compared with other risk factors for cancer, such as smoking and advancing age. However, the prevalence of depression suggests a considerably large attributable risk. Depression may either have a long delayed effect on cancer risk, or depression may primarily act in combination with known risk factors like advanced age to increase cancer risk. Further studies should build on observational studies to further examine the mechanisms through which our emotions and psychological well-being affect our health.

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Fig. 1. Hazard ratios with 95% CIs for associations between depression type and cancer type for depression in the Baltimore ECA, for any other mental health problem, and for phobia in the Baltimore ECA. Any mental health (MH) problem encompasses DSM-III alcohol abuse or dependence, mania, drug abuse or dependence, obsessive compulsive disorder, phobia, and somatization disorder

Table 1

Demographic characteristics among respondents in 1981 and at subsequent waves through 2005: data from the Baltimore Epidemiologic Catchment Area Study

	1981 Wave (n = 3,177)	1994 Wave (n = 1,817)	2005 Wave (n = 1,028)
Age			
18–29	860 (27.1%)	–	–
30–44	783 (24.7%)	701 (38.9%)	80 (7.8%)
45–64	766 (24.1%)	555 (30.5%)	679 (66.1%)
65 and older	768 (24.2%)	561 (30.9%)	269 (26.2%)
Sex (# female, %)	1945 (61.2%)	1136 (62.5%)	639 (62.2%)
Ethnicity			
White	1952 (61.4%)	1131 (62.3%)	628 (61.1%)
African-American	1125 (35.4%)	623 (34.3%)	365 (35.5%)
Other	100 (3.2%)	63 (3.5%)	35 (3.4%)
Marital status			
Married	1335 (42.0%)	826 (48.9%)	560 (56.2%)
Widowed	468 (14.7%)	285 (16.9%)	143 (14.3%)
Divorced/separated	609 (19.2%)	331 (19.6%)	182 (18.3%)
Never married	764 (24.1%)	247 (14.6%)	112 (11.2%)
DSM-III Alcohol abuse/dependence	400 (12.7%)	249 (13.7%)	56 (5.5%)
Smoking Status			
Never	902 (32.3%)	51 (4.5%)	342 (34.4%)
Former	354 (12.7%)	521 (45.9%)	378 (38.1%)
Current, ≤1 pack/day	1,209 (43.3%)	453 (39.9%)	259 (26.1%)
Current, >1 pack/day	324 (11.6%)	111 (9.8%)	14 (1.4%)
Lifetime depression history			
Major depressive episode	163	186	145
Dysphoric episode	752	589	391
None	2262	1993	535

Respondents with a history of cancer at the baseline interview or who did not have information on depression status at baseline are excluded here

Table 2

Hazard ratios for the associations of DIS/DSM-III MDE or dysphoric episode with cancer at 24 year follow-up

	Proportion with cancer	Unadjusted model	Adjusted model
Depression type (reference: No depression in 1981)			
DIS/DSM-III MDE	17/163	1.15 (0.75, 1.78)	1.87 (1.16, 3.01)
Dysphoric episode	85/752	1.30 (1.02, 1.66)	1.69 (1.30, 2.19)
Age (reference: 45 years of age)			1.03 (1.02, 1.04)
Marital Status in 1981 (reference: married)			
Widowed			0.66 (0.41, 1.07)
Divorced/separated			1.05 (0.69, 1.59)
Never married			0.37 (0.18, 0.75)
Socio-economic status (SES)			0.99 (0.98, 1.01)
DIS/DSM-III alcohol abuse/dependence			1.14 (0.73, 1.80)
Gender (reference: males)			0.80 (0.56, 1.15)
Ethnicity (reference: non-White)			0.89 (0.62, 1.28)
Smoking status (reference: never smokers)			
Former			1.59 (0.99, 2.56)
Current, <1pack/day			1.39 (0.88, 2.18)
Current, >1pack/day			1.73 (0.96, 3.11)

95% Confidence intervals are given in parentheses

Table 3
Hazard ratios and 95% CIs for associations between cancer subtypes and depression

	Number with cancer at follow-up	Number with major depression	Number with dysphoric episode	Dysphoric episode	DIS/DSM-III MDE	DIS/DSM-III MDE, recurrent episode	DIS/DSM-III MDE, single episode	Depressive symptom count
Breast	50	4	16	2.42 (1.17, 4.98)	3.38 (0.83, 13.76)	2.03 (0.25, 16.13)	2.14 (0.31, 14.76)	1.15 (0.99, 1.34)
Colon	34	1	9	3.54 (1.55, 8.10)	4.31 (0.71, 26.18)	No cases	No cases	0.97 (0.75, 1.25)
Lung	64	4	13	0.76 (0.39, 1.46)	0.82 (0.25, 2.64)	No cases	No cases	0.97 (0.84, 1.12)
Prostate	28	1	6	1.39 (0.51, 3.80)	1.09 (0.14, 8.73)	No cases	6.88 (1.98, 23.90)	1.03 (0.83, 1.29)
Skin	29	1	6	1.28 (0.48, 3.44)	1.71 (0.38, 7.68)	5.43 (0.72, 41.12)	No cases	1.02 (0.78, 1.33)

Models adjusted for age, sex, and smoking status. Breast cancer models also adjust for parity. Breast and prostate cancer coefficients are among females and males only, respectively