American Journal of Epidemiology
Vol. 162, No. 9
DOI: 10.1093/aje/kwi302
Advance Access publication October 5, 2005

Original Contribution

Depressive Symptoms and Prospective Incidence of Colorectal Cancer in Women

Candyce H. Kroenke[1], Gary G. Bennett[2,3], Charles Fuchs[1,3], Ed Giovannucci[1,4], Ichiro Kawachi[1,2], Eva Schernhammer[1], Michelle D. Holmes[1], and Laura D. Kubzansky[2]

[1] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA.
[2] Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, MA.
[3] Center for Community-based Research, Division of Population Sciences, Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA.
[4] Department of Epidemiology, Harvard School of Public Health, Boston, MA.

Received for publication January 21, 2005; accepted for publication June 9, 2005.

The authors examined depressive symptoms and prospective incidence of colorectal cancer and distal colorectal adenomas in 81,612 women without prior cancer from the Nurses' Health Study; 400 cases of colorectal cancer and 680 distal colorectal adenomas accrued between 1992 and the year 2000. Depressive symptoms were assessed in 1992 and 1996 with the five-question Mental Health Index (MHI-5), a subscale of the Short-Form 36 health status survey. Scores ranged from 0 to 100, and women with scores between 0 and 52 were defined as having significant depressive symptomatology. The authors also created four categories across the range of Mental Health Index scores: 0–52, 53–75, 76–85, and 86–100 (referent). Cox proportional hazards models were used to analyze the extent of depressive symptoms and colorectal events. Analyses were stratified by body mass index. In multivariate analyses with updated exposure, women with the highest levels of depressive symptoms had an elevated risk of incident colorectal cancer (hazard ratio = 1.43, 95% confidence interval: 0.97, 2.11) compared with women with the lowest levels of symptoms ($p_{trend} = 0.04$). Associations appeared stronger in overweight women. However, depressive symptoms were unrelated to risk of colorectal adenomas. Associations are consistent with a possible role in late promotion of the disease.

colorectal neoplasms; depression; women

Abbreviations: CI, confidence interval; MHI-5, five-question Mental Health Index, a subscale of the Short-Form 36 health status survey; RR, relative risk.

There is a longstanding notion that psychological depression may play a role in the etiology of cancer (1, 2). However, empirical data are scarce, and the evidence of an association between depression and cancer is inconclusive. Investigators have typically combined numerous cancers with disparate etiologies in their studies, though there is little reason to believe that psychological factors should influence the development of all cancers. In hypothesis testing, it is necessary to consider previous literature and mechanistic evidence to determine the best a priori hypothesis of a relation between a particular exposure and cancer outcome.

In past research, depression has been associated with several risk factors for colorectal cancer. Depression may cause lower estrogen levels in premenopausal women (3), subsequently reducing time to perimenopause (4).

Correspondence to Dr. Candyce Kroenke, Channing Laboratory, 181 Longwood Avenue, Third Floor, Boston, MA 02115 (e-mail: candyce.kroenke@channing.harvard.edu).

Postmenopausal estrogen use has been related to a lower risk of colorectal cancer (5), suggesting that low estrogen levels may predispose women to a higher risk of this cancer. Depression has also been related to dysregulated immune function, including increased levels of the inflammatory markers interleukin-6 (6, 7) and C-reactive protein (8), and immune suppressors such as prostaglandin E_2 (9), each of which has been linked to an elevated risk of colorectal cancer (10–12). Depression has also been linked to higher levels of smoking (13, 14) and to other behavioral risk factors related to the metabolic syndrome, including overweight, weight gain, increased central obesity, physical inactivity, and excessive energy intake (13, 15). Importantly, depressive symptoms may influence the risk of colon cancer through adverse effects on metabolic control, through hyperinsulinemia (16), central adiposity (17–20), and other markers of metabolic dysfunction (21–24), as a result of cortisol overproduction. In previous work (25, 26) and in recent work in the Nurses' Health Study, depressive symptoms have been related to an increased risk of diabetes (relative risk (RR) = 1.29, 95 percent confidence interval (CI): 0.96, 1.72) (27), another risk factor for colon cancer.

No studies to date have explicitly examined the association between depression and colorectal cancer. Our hypothesis that women with depressive symptoms would have a higher risk of incident colorectal cancer is consistent with the above mechanisms. Because colorectal adenomas are thought to precede colorectal cancers (28), we also hypothesized a higher risk of colorectal adenoma among women who were endoscopically screened.

MATERIALS AND METHODS

Nurses' Health Study subjects

The Nurses' Health Study is a prospective study of 121,700 US female nurses, 30–55 years of age at baseline in 1976. At baseline and during biennial follow-up periods, participants provided detailed health behavior and medical history information through a mailed questionnaire.

The study population consisted of women aged 46–71 years in 1992 from the Nurses' Health Study who responded to a health-related quality-of-life assessment in 1992 or 1996. Women from the full cohort and those who responded to the psychosocial assessment were similar with regard to age, body mass index, family history of colorectal cancer, physical activity, smoking, alcohol, aspirin use, vitamin use, and postmenopausal hormone use. However, compared with the full cohort, those who completed the psychosocial assessment consumed slightly more alcohol (4.8 vs. 3.8 g/day) and were slightly more likely to be postmenopausal (86 percent vs. 83 percent).

Women with any prior cancer except skin cancer other than melanoma were excluded. To reduce the likelihood of reverse causality (that existing cancer symptomatology caused depressive symptoms), we also excluded women diagnosed with colorectal cancer within the year following the mental health assessment, leaving 81,612 women in analyses.

Data collection

Measurement of depressive symptoms. We assessed depressive symptoms in both 1992 and 1996 with the five-question Mental Health Index (MHI-5), a subscale of the Short-Form 36 health status survey (29, 30). The MHI-5 includes five items designed to capture psychological distress versus well-being (27, 31, 32). It asks respondents how much of the time over the past month (all, most, good bit, some, little, or none) they felt nervous, felt so down that nothing could cheer them up, felt calm and peaceful, felt down and blue, or felt happy. The scale is scored from 0 to 100, with lower scores indicating higher levels of depressive symptomatology. Cronbach's alpha for the MHI-5 in the present sample was 0.80. By use of receiver-operating characteristic curve analysis in a sample of patients diagnosed by clinical criteria, it was determined that a score of 52 or less on the MHI-5 scale was highly predictive of clinical depression (33, 34); this criterion was used to define the group with "significant depressive symptoms." Therefore, the MHI-5 scale is not a clinical diagnostic tool but identifies those who exhibit elevated depressive symptomatology.

Though we focused on examining the association between depressive symptoms and incident colorectal cancer, we were also interested in determining whether the association between MHI-5 scores and this outcome might better be characterized as threshold or linear. On the basis of both prior work (33, 34) and the distribution of the data in our sample, we created four categories across the range of MHI-5 scores: 0–52, 53–75, 76–85, and 86–100 points. Women with scores between 0 and 52 were defined and will be noted in the text as having depressive symptoms. Women with scores between 86 and 100 comprised the referent group. Because women with lower MHI-5 scores may also be considered to have greater depressive symptomatology, we will describe women according to "extent of depressive symptomatology" when we describe analyses of the full MHI-5 scale.

We also created a measure to examine the stability of depression over time. Respondents were categorized as having no depressive symptoms in 1992 or 1996 (referent), depressive symptoms in 1992 only, depressive symptoms in 1996 only, and depressive symptoms in both 1992 and 1996. A total of 1,530 women met criteria for depressive symptoms at both assessments. Pearson's correlation coefficient for depressive symptoms in both 1992 and 1996 was $r = 0.30$ ($p < 0.01$) and for the continuous MHI-5 was 0.59 ($p < 0.01$).

Assessment of colorectal cancer. Incident colorectal cancer was ascertained by biennial mailing of the questionnaire to participants. For any report of colorectal cancer, written permission was obtained from study participants to review their medical records. Physicians, blinded to exposure information from questionnaires, subsequently reviewed medical records and pathology reports. The histologic type, anatomic location, and stage of cancer were reported. We excluded in situ carcinoma. Ascertainment of deaths in the Nurses' Health Study cohort included reporting by the family or postal authorities or occurred through searches in the National Death Index.

Identification of colorectal adenomas. Women who reported colorectal polyps in a biennial survey were asked for permission to review their medical records for reports of identified colorectal adenomas. More than 90 percent of the adenomas were diagnosed in women who underwent an endoscopic procedure for routine screening or for unrelated gastrointestinal conditions. Because most procedures were sigmoidoscopies, we primarily studied adenomas of the distal colon and rectum rather than of the proximal colon. We excluded hyperplastic polyps, which are not precursors of colorectal cancer. Information on adenoma size was extracted from the endoscopy report or the pathology report; when both sources provided information, we used the size given on the endoscopy report. Large adenomas were defined as colorectal adenomas larger than 10 cm.

Measurement of covariates. Data on numerous biomedical, lifestyle, psychosocial, and hormonal factors have been collected through previous Nurses' Health Study surveys. Age and smoking history before age 30 years were assessed at study baseline, in 1976. Psychosocial data were assessed in 1992 and in 1996. Dietary variables including alcohol, energy intake, and red and processed meat intake were assessed by food frequency questionnaire in 1994 and 1998. Physical activity was assessed in 1992 and 1996 in terms of metabolic equivalent task-hours per week (35). Other covariates (tables 1 and 2) were assessed biennially. We included in the analyses covariates related to depression that are considered to be important predictors of colorectal cancer. Covariates were updated in all analyses.

Statistical analyses

Using analysis of covariance, we examined the association between depressive symptoms and each potential confounding variable, adjusted for continuous age.

We used Cox proportional hazards models (SAS PROC PHREG) (36) for failure-time data to evaluate associations between depressive symptoms or extent of depressive symptomatology and time to colorectal cancer or colorectal adenoma (37, 38). Person-years of follow-up were counted from the date the 1992 or 1996 psychosocial questionnaire was returned until the date of death, colorectal event, or age at end of follow-up, whichever came first. We conducted tests for linear trend by modeling MHI-5 scores continuously and computing the Wald statistic. Age-adjusted results were compared with those adjusting for several covariates (table 2).

Because the potential latency period between depressive symptoms and colorectal cancer is unknown, we first conducted analyses assigning the most recent exposure status to subsequent outcomes (1992 depressive symptomatology with outcomes between 1993 and 1996, 1996 depressive symptomatology with outcomes between 1997 and 2000). To provide a more conservative test of our hypothesis, we subsequently conducted a lagged analysis, examining the relation between depressive symptomatology as assessed in 1992 and the risk of colorectal cancer from 1996 through 2000. This was also designed to address the issue that depressive symptoms may be aggravated by early symptoms of colorectal cancer. To evaluate whether stability of depressive symptoms predicted cancer incidence, outcomes between 1997 and 2000 were regressed on the measure of stable depression.

Using the most recent exposure status, analyses were subsequently stratified by variables that might moderate the influence of depressive symptoms on colorectal cancer including ever smoking, overweight status (body mass index of $\geq$25 vs. $<$25 kg/m^2), physical activity (median split at 19 metabolic equivalent task-hours per week), and hormonal status (premenopausal or taking postmenopausal hormones vs. postmenopausal and not taking exogenous hormones). We additionally stratified by screening status (i.e., whether women had ever undergone colorectal endoscopy). When results differed by strata, interaction terms were computed for categorical depressive symptoms and dichotomous versions of each of these variables and were evaluated by Wald tests.

We also conducted several sensitivity analyses. To help establish temporal order of exposure and outcome and to determine whether reverse causality might explain findings, we conducted the following analyses: 1) including colorectal cancers within the first year after each psychosocial assessment, 2) excluding women with ulcerative colitis or Crohn's disease, and 3) stratifying by Dukes' stage (stages 1 and 2 vs. stages 3 and 4). Despite the limited number of cases, we examined associations separately with colon and rectal cancer, because a positive association for one cancer but not the other might provide insight into possible mechanisms. Furthermore, to avoid bias that might occur with differential methods of screening by depressive status, we explored whether associations differed by colorectal site (proximal vs. distal cancers). Finally, to reduce the chance that associations would be driven by the differential likelihood of being screened, we conducted analyses of depression and colorectal cancer including only those women who reported undergoing endoscopy.

We conducted similar updated, lagged, and stratified analyses with colorectal adenomas. All tests of statistical significance were two sided. This research was approved by the Institutional Review Board at Brigham and Women's Hospital in Boston, Massachusetts.

RESULTS

Of the 81,612 women who contributed 571,691 person-years, 400 cases of colorectal cancer were diagnosed. Of the 28,230 women who underwent endoscopy, 966 had colorectal adenomas. Of these, 680 were distal adenomas, 286 were proximal, and 253 were large adenomas.

Age-adjusted distributions of multiple baseline covariates are presented according to level of depressive symptomatology (table 1). Only about 8 percent of women in this cohort were characterized as having high levels of depressive symptoms (MHI-5 score: $<$53). Women with depressive symptoms had less healthy lifestyle behaviors than those without; they were slightly more likely to be overweight, were more likely to smoke, engaged in lower levels of physical activity, had a higher energy intake, and ate more red and processed meat. They were more likely to be postmenopausal and to have an earlier age at menopause.

TABLE 1. Selected characteristics by level of depressive symptomatology among 67,244 women from the Nurses' Health Study in 1992*

	Level of depressive symptomatology/category of MHI-5†			
	Referent (86–100)	76–85	53–75	Depressive (0–52)
Person-years	191,190	198,696	141,490	40,316
No.	19,585	24,059	18,198	5,402
Colorectal cancer cases ($n = 400$)	128	140	99	33
Age-adjusted incidence rate (per 100,000)	66.9	70.5	70.0	81.9
Median MHI-5 score	92	80	68	47
Mean age at diagnosis (years)	60	59	58	57
Family history of colorectal cancer (%)	11.5	11.0	11.1	11.0
Underwent screening due to family history (%)	8.9	9.0	9.2	9.7
Previous report of colorectal polyps (%)	3.8	4.3	5.0	5.5
Height of >66 inches‡ (%)	21.5	20.4	20.0	20.3
Diabetes (%)	4.5	4.9	6.2	7.4
Ulcerative colitis (%)	1.1	1.5	2.1	2.6
Ever colonoscopy/sigmoidoscopy (%)	32.2	34.2	36.7	39.6
Among those with a family history	47.3	48.1	49.9	52.3
Among those with no family history	30.3	32.4	35.1	38.0
Colorectal screening in 1994 or 1996 (%)§	23.8	25.0	25.7	27.8
Dietary and lifestyle variables				
BMI† (kg/m^2)	25.9	26.0	26.2	26.6
Overweight (% with BMI of $\geq$25 kg/m^2)	47.9	47.7	49.2	50.4
Energy intake (mean kcal)	1,726	1,760	1,759	1,768
Processed and red meat intake (servings/day)	8.2	8.6	8.7	8.8
Alcohol (g/day)	4.7	4.9	4.8	4.7
Current smoking (%)	11.9	13.0	16.2	18.6
Physical activity (MET†-hours/week)	21.8	19.8	17.2	14.8
Any aspirin use (%)	52.0	55.8	56.4	56.8
Current vitamin use (%)	41.1	43.1	44.2	44.9
Reproductive variables				
Ever oral contraceptive use (%)	47.5	48.4	48.3	48.6
Postmenopausal (%)	83.9	84.4	84.6	85.9
Age at menopause (years)¶	46.3	46.5	46.1	45.8
Hormone replacement (%)¶	41.7	41.9	42.2	41.8

* All variables are age standardized.
† MHI-5, five-question Mental Health Index, a subscale of the Medical Outcomes Study Short-Form 36 health status survey; BMI, body mass index; MET, metabolic equivalent task.
‡ One inch = 2.54 cm.
§ For 72,458 women who responded to the MHI-5 in 1996.
¶ Among postmenopausal women.

However, women with depressive symptoms were more likely to use aspirin, take vitamins, and be screened with colonoscopy or sigmoidoscopy, whether or not they had a family history of colorectal cancer.

In both age-adjusted and multivariate-adjusted analyses using the updated, most recent exposure, women with greater depressive symptomatology had an elevated relative risk of colorectal cancer (table 2). A dose-response relation was apparent; women with more depressive symptomatology had a higher risk of colorectal cancer than did those with fewer symptoms ($p_{trend} = 0.04$). Adjustment for smoking was the most important variable in attenuation of associations. In lagged analyses with the 4-year latency, depressive symptoms were no longer associated with an increase in the risk of colorectal cancer (multivariate RR = 0.97, 95 percent CI: 0.50, 1.87; $p_{trend} = 0.24$). There was also no support for an elevated risk of colorectal cancer among women with depressive symptoms in both 1992

TABLE 2. Relative risk of colorectal cancer by level of most recent* depressive symptomatology among 81,612 women from the Nurses' Health Study

	Level of depressive symptomatology/category of MHI-5†				*p* value‡
	Referent (86–100)	76–85	53–75	Depressive (0–52)	
Person-years	191,190	198,696	141,490	40,316	
Colorectal cancer cases	128	140	99	33	
Age-adjusted relative risk	1.00	1.14	1.18	1.47	0.03
95% confidence interval		0.89, 1.44	0.90, 1.53	1.00, 2.15	
Multivariate-adjusted relative risk§	1.00	1.13	1.16	1.43	0.04
95% confidence interval		0.89, 1.43	0.89, 1.51	0.97, 2.11	

* Most recent exposure status was assigned to subsequent outcomes (i.e., 1992 depressive symptomatology with outcomes between 1993 and 1996 and 1996 depressive symptomatology with outcomes between 1997 and 2000).

† MHI-5, five-question Mental Health Index, a subscale of the Medical Outcomes Study Short-Form 36 health status survey.

‡ *p* value, continuous MHI-5 score.

§ Multivariate-adjusted analyses adjusted for age (continuous), family history of colorectal cancer (yes, no (referent)), diabetes (yes, no (referent)), smoking prior to 1976 (never (referent), 1–14 pack-years, 15–29 pack-years, ≥30 pack-years), body mass index (<21 (referent), 21–22, 23–24, 25–29, ≥30 kg/m^2), energy intake (kcal, quintiles, quintile 3 (referent)), red and processed meat consumption (g/day, quintiles, quintile1 (referent)), physical activity (0–2 (referent), 3–17, ≥18 metabolic equivalent-hours/week), alcohol intake (0 (referent), 1–14, 15–25,>25 g/day), multivitamin use (yes/no (referent)), aspirin use (none (referent), usual use up to half the week, approximate daily use), menopausal status (postmenopausal, premenopausal (referent)), postmenopausal hormone use (never (referent), past, current), oral contraceptive use (yes, no (referent)), and screening with sigmoidoscopy or colonoscopy (yes, no (referent)).

and 1996 when compared with those who were free from depressive symptoms at both time points.

In stratified analyses, using the most recent exposure status, the elevated risk of colorectal cancer was most apparent among women with depressive symptoms who were postmenopausal and not taking hormone replacement therapy and among those who were overweight (body mass index of ≥25 kg/m^2). Interactions were marginally significant (table 3). No other covariate interactions were apparent (data not shown).

In sensitivity analyses, using the most recent exposure, associations did not differ appreciably when including or excluding women diagnosed with colorectal cancer within a year of psychosocial measurement. We did not initially adjust for a previous report of colorectal polyps or ulcerative colitis, because of their low prevalence. However, associations changed little with their adjustment or exclusion (data not shown). When we examined the relation between depressive symptomatology and stage 1 and 2 cancers versus stage 3 and 4 cancers, we found similar associations for each outcome. In site-specific subanalyses, the elevation in risk among women with greater depressive symptoms was similarly apparent with colon cancer (excluding rectal cancers) in both age- and multivariate-adjusted analyses (data not shown). Likewise, women with depressive symptoms also had a higher risk of rectal cancer than those without depressive symptoms (hazard ratio = 3.26, 95 percent CI: 1.06, 10.02). Finally, the association between depression and colorectal cancer was equally evident among women who were endoscopically screened and those in the total study population (data not shown).

Recent depressive symptoms were unrelated to sigmoid and rectal adenomas in both age- and multivariate-adjusted analyses (table 4). In additional analyses of adenomas in the proximal colon or of large adenomas, we also found no associations. There was a significant interaction (p = 0.02) between overweight status and depressive symptoms, the association between depressive symptomatology and colorectal adenomas appearing slightly stronger in overweight women (data not shown).

DISCUSSION

To our knowledge, this is the first study to explicitly examine the association between depressive symptoms and prospective incidence of colorectal cancer and colorectal adenomas. Consistent with expectations, depressive symptoms were associated with an approximately 40 percent excess risk of incident colorectal cancer in women over 8 years of follow up. Additionally, we found evidence of a dose-response relation across the range of the MHI-5 scores, with greater depressive symptomatology associated with increasing risk. The association between depressive symptoms and colorectal cancer attenuated little with adjustment for a comprehensive array of potential risk factors for colorectal cancer. In contrast, depressive symptoms were unrelated to colorectal adenomas. Our investigation, guided by a priori attention to potential biologic mechanisms, represents an advance to the literature.

Prior findings

Numerous studies have examined the link between depression and total cancer incidence or mortality (39, 40), and several have examined breast cancer specifically

TABLE 3. Relative risk of colorectal cancer by level of most recent* depressive symptomatology among 81,612 women from the Nurses' Health Study, with multivariate-adjusted models stratified by biologic modifiers

	Level of depressive symptomatology/category of MHI-5†				*p* value‡	*p* value§
	Referent (86–100)	76–85	53–75	Depressive (0–52)		
Hormonal status¶						
Premenopausal or hormone replacement therapy						
Person-years	93,497	102,837	74,948	21,722		
Colorectal events	43	44	28	7		
Multivariate-adjusted relative risk	1.00	1.00	0.94	0.91	0.90	0.19
95% confidence interval		0.66, 1.53	0.58, 1.52	0.40, 2.03		
Postmenopausal, no hormone replacement therapy						
Person-years	97,593	95,859	66,541	18,594		
Colorectal events	85	96	71	26		
Multivariate-adjusted relative risk	1.00	1.17	1.25	1.68	0.02	
95% confidence interval		0.88, 1.57	0.91, 1.72	1.07, 2.62		
Overweight status						
BMI† of $\geq$25 kg/m^2						
Person-years	99,063	100,799	74,342	21,718		
Colorectal events	62	73	55	21		
Multivariate-adjusted relative risk	1.00	1.27	1.35	1.90	<0.01	0.27
95% confidence interval		0.90, 1.78	0.93, 1.95	1.25, 3.15		
BMI of <25 kg/m^2						
Person-years	92,127	97,897	67,148	18,599		
Colorectal events	66	67	44	12		
Multivariate-adjusted relative risk	1.00	1.01	0.97	0.99	0.99	
95% confidence interval		0.71, 1.42	0.66, 1.42	0.53, 1.85		

* Most recent exposure status was assigned to subsequent outcomes (i.e., 1992 depressive symptomatology with outcomes between 1993 and 1996 and 1996 depressive symptomatology with outcomes between 1997 and 2000).

† MHI-5, five-question Mental Health Index, a subscale of the Medical Outcomes Study Short-Form 36 health status survey; BMI, body mass index.

‡ *p* value, continuous MHI-5.

§ *p* value, test for interaction.

¶ Multivariate-adjusted analyses adjusted for the covariates indicated in table 2, except that the analysis stratified by hormonal status was not adjusted for menopausal status or postmenopausal hormone use, and the analysis stratified by overweight status was not adjusted further for body mass index.

(41, 42), producing mixed results (39, 43–45). However, most investigators have examined depression with multiple cancer sites with varying etiologic mechanisms, some of which are unlikely to be influenced by depression.

We found no prior studies of depression and colorectal adenomas. The few previous investigations of depression and colorectal cancer have been embedded in studies examining associations with cancers at multiple sites (39, 40, 46–49). A major issue for all of these studies is an insufficient number of endpoints to critically examine associations. Gallo et al. (50), using data from the Baltimore Epidemiologic Catchment Area, found a twofold increased risk of colon cancer over 13 years among persons with any lifetime history of dysphoric episode after adjusting for age, smoking, and alcohol abuse. However, they had only 19 colon cancer cases in total, and the association was not significant. Penninx et al. (46), using data from the Established Populations for the Epidemiologic Study of the Elderly, also found no association between chronically depressed mood and colon cancer (60 total events: RR = 1.37, 95 percent CI: 0.33, 5.74) or rectal cancer (22 events: RR = 2.82, 95 percent CI: 0.35, 22.83) over 6 years but similarly had

TABLE 4. Relative risk of colorectal adenomas by level of most recent* depressive symptomatology among 28,230 women from the Nurses' Health Study who underwent endoscopy

	Level of depressive symptomatology/category of MHI-5†				p_{trend}‡
	Referent (86–100)	76–85	53–75	Depressive (0–52)	
No.	8,342	9,953	7,631	2,304	
All colorectal adenomas	312	344	242	68	
Age-adjusted relative risk	1.00	1.02	0.98	0.96	0.78
95% confidence interval		0.87, 1.19	0.83, 1.16	0.74, 1.25	
Multivariate-adjusted relative risk§	1.00	1.02	0.97	0.96	0.68
95% confidence interval		0.87, 1.18	0.82, 1.15	0.73, 1.25	
Distal colorectal adenomas	215	248	172	45	
Age-adjusted relative risk	1.00	1.06	1.01	0.92	0.67
95% confidence interval		0.89, 1.28	0.83, 1.24	0.67, 1.28	
Multivariate-adjusted relative risk§	1.00	1.06	1.00	0.93	0.65
95% confidence interval		0.88, 1.28	0.82, 1.23	0.67, 1.29	
Proximal colorectal adenomas	97	96	70	23	
Age-adjusted relative risk	1.00	0.91	0.92	1.05	0.87
95% confidence interval		0.69, 1.21	0.68, 1.26	0.66, 1.65	
Multivariate-adjusted relative risk§	1.00	0.91	0.90	1.02	0.99
95% confidence interval		0.68, 1.21	0.66, 1.22	0.64, 1.62	
Large adenomas	78	92	65	18	
Age-adjusted relative risk	1.00	1.12	1.10	1.07	0.71
95% confidence interval		0.83, 1.52	0.79, 1.53	0.64, 1.80	
Multivariate-adjusted relative risk§	1.00	1.13	1.14	1.16	0.47
95% confidence interval		0.84, 1.54	0.82, 1.59	0.69, 1.96	

* Most recent exposure status was assigned to subsequent outcomes (i.e., 1992 depressive symptomatology with outcomes between 1993 and 1996 and 1996 depressive symptomatology with outcomes between 1997 and 2000).

† MHI-5, five-question Mental Health Index, a subscale of the Medical Outcomes Study Short-Form 36 health status survey.

‡ *p* value, continuous MHI-5.

§ Multivariate-adjusted analyses adjusted for the covariates indicated in table 2.

insufficient statistical power. In the Alameda County Study, Kaplan and Reynolds (49) also failed to find an association between depression and colon cancer, but they accrued only 22 colon cancer events over 17 years. Though Shekelle et al. (51) found an increased risk of cancer overall among those who scored high on the Minnesota Multiphasic Personality Inventory depression scale, they did not report the association with colorectal cancer because the 17 cases available did not permit a meaningful site-specific analysis. In one large study of 89,491 adults from Denmark with 304 cases of colon cancer, Dalton et al. (40) found an increased risk of colon cancer over 24 years' follow-up among those who had ever been hospitalized with reactive depression or dysthymia (RR = 1.16, 95 percent CI: 1.03, 1.30), excluding cancers occurring in the first year after diagnosis of affective disorder. However, because of data limitations, they were able to adjust for only age, sex, and calendar year. In previous studies, investigators have typically not adjusted for important confounding variables such as body weight and smoking.

Our results are consistent with those from the largest previous study conducted in Denmark, in that we found an elevated risk of colorectal cancer among those with depressive symptoms. Nevertheless, it is unclear whether prior null findings have resulted from a true lack of association or insufficient power to detect an effect. Our study, with 400 colorectal cancer outcomes, is among the few investigations with the power to examine this question.

Study validity

We considered whether our findings might result from differential screening by women with and without depressive symptoms. Prior findings have repeatedly shown that women with depressive symptomatology are more likely to seek medical care than are nondepressed women (52–58). We were therefore concerned that, if women with depressive symptoms were more likely to be screened, they would subsequently be more likely to be diagnosed with colorectal cancer. This could explain, in part, the positive association

with colorectal cancer and the positive linear association we noted in a subanalysis examining the extent of depressive symptomatology and (self-reported) colorectal polyps ($p_{trend} < 0.001$). However, the association between depressive symptoms and colorectal cancer was apparent in the analysis restricted to women who were screened, providing support that the association could not fully be explained by differential likelihood of screening by depressive status. Our failure to find a stronger association with earlier versus later stage cancer and the different findings for colorectal adenoma and colorectal cancer also contradict this notion. In fact, results could be biased toward the null if depressive symptoms cause women to be screened substantially earlier in the development of a potential tumor than they would otherwise be. Unless all women in this observational cohort are screened, it may be impossible to evaluate associations without bias.

Though we excluded cancers occurring within the first year, the fact that depressive symptoms were associated with colorectal cancer but not adenoma may raise concerns about the directionality of the effect. There is an approximate 10-year interval between the appearance of a small adenoma and diagnosis of colorectal cancer. Thus, depressive symptoms could be a subclinical marker for the disease or for other etiologic factors. A study by North et al. (59) showed that depression in patients with inflammatory bowel disease, a risk factor for colorectal cancer, was positively correlated with illness severity, suggesting that the experience of symptoms may lead to depression. The notion that depression is simply a prodromal marker of disease, however, is challenged by the extended asymptomatic nature of early stage colorectal cancer (60).

Biologic mechanisms

Some investigators have hypothesized that depression may exert a late effect in the promotion of cancer (61, 62). In the present study, the lack of association with colorectal adenomas and the positive association with colorectal cancer are consistent with this notion. Indeed, it is unlikely that depression should influence the early development of adenomas given that the initiation of a cancer is thought to occur with a more powerful exposure. Consistent with this, others have found that low physical activity, high energy intake, and obesity are more predictive of the onset of large (>1 cm) adenomas and colorectal cancer than of smaller adenomas (63–66), similarly suggesting a late-stage promoting effect. Unfortunately, our ability to assess associations with large adenomas was hampered by limited numbers of women with this outcome.

It was not possible to fully evaluate biologic mechanisms with our data, though we found the strongest evidence for a metabolic effect in women already exhibiting signs of metabolic dysregulation. The stronger association observed in overweight women for both colorectal cancer and adenomas suggests that the presence of depressive symptoms may exacerbate the adverse effects of obesity on the development of cancer, perhaps through its influence on central adiposity. Higher body mass has been more strongly related to colon cancer in men, possibly because of the differential pattern of fat accumulation, with men tending to accumulate more intraabdominal fat than do women. Depressive disorders have been associated with disruption of the sympathoadrenal system and dysregulation of the hypothalamopituitary adrenal axis, which may impair carbohydrate uptake, thereby leading to increased glucose intolerance (67) and central fat accumulation (17). Depressive symptoms may augment risk of colorectal cancer in women who are already overweight, but these symptoms may have comparatively little influence in normal-weight women. This result is consistent with other findings in the Nurses' Health Study in which depression was more strongly related to diabetes in overweight (body mass index of 25–29.9 kg/m^2: RR = 1.43, 95 percent CI: 0.97, 2.11) than in normal-weight (body mass index of <25 kg/m^2: RR = 0.89, 95 percent CI: 0.40, 1.89) women (27). Nonetheless, adjustment for body mass and several risk factors for obesity did not substantially attenuate associations, suggesting the possible importance of other biologic effects.

Strengths and limitations

This investigation has numerous strengths including prospective data, a large study population with adequate power to examine associations, extensive data on potential confounding factors, validation of cancer diagnosis and of adenomas, and use of a standardized measure of depressive symptoms.

However, we had limited power to evaluate most interactions and must therefore interpret the stratified analyses with caution. Another limitation is that the MHI-5 evaluates depressive symptoms during the past month and does not assess either depressive disorders or lifetime history of depression; it may capture the chronicity of depression only weakly. However, depression is episodic by nature, and people who are prone to depression may be more likely to be identified with this measure at any given point in time. Nevertheless, our measure may lead to misclassification of the exposure, potentially underestimating the true association of depression with colorectal cancer. A more detailed measure of lifetime experience of depression may facilitate a more precise evaluation of the nature of the association between depression and colorectal cancer.

An additional limitation is the issue of generalizability, given our population of predominately White, female nurses. The Nurses' Health Study is also characterized by a narrower range of socioeconomic status than is the general population. Though these factors may reduce the potential for confounding and improve the validity of the findings, it is possible that findings may differ in the general population. The positive association in the subgroup of women who underwent screening provides some evidence that the association is not solely an artifact. As with any observational study, there is the concern that confounding by some unmeasured third variable, such as some genetic factor or possibly childhood socioeconomic status (68, 69), could explain findings. However, with the exception of previous smoking (prior to 1976), adjustment for covariates had little effect on the studied associations.

In summary, depressive symptoms in women were related to an elevated risk of colorectal cancer, consistent with a possible late promotional effect on colorectal cancer. Future research should explore possible explanatory mechanisms.

ACKNOWLEDGMENTS

This research was supported by grant CA87969, supplied by the National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Conflict of interest: none declared.

REFERENCES

1. Kowal SJ. Emotions as a cause of cancer; 18th and 19th century contributions. Psychoanal Rev 1955;42:217–27.
2. Blumberg EM, West PM, Ellis FW. A possible relationship between psychological factors and human cancer. Psychosom Med 1954;16:277–86.
3. Young EA, Midgley AR, Carlson NE, et al. Alteration in the hypothalamic-pituitary-ovarian axis in depressed women. Arch Gen Psychiatry 2000;57:1157–62.
4. Harlow BL, Wise LA, Otto MW, et al. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2003;60:29–36.
5. Grodstein F, Martinez ME, Platz EA, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med 1998;128:705–12.
6. Glaser R, Robles TF, Sheridan J, et al. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. Arch Gen Psychiatry 2003;60:1009–14.
7. Miller GE, Freedland KE, Carney RM, et al. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. Brain Behav Immun 2003;17:276–85.
8. Ford DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2004;164:1010–14.
9. Lieb J, Karmali R, Horrobin D. Elevated levels of prostaglandin E_2 and thromboxane B_2 in depression. Prostaglandins Leukot Med 1983;10:361–7.
10. Kinoshita T, Ito H, Miki C. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. Cancer 1999;85:2526–31.
11. Erlinger TP, Platz EA, Rifai N, et al. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004;291:585–90.
12. Bennett A, Tacca MD, Stamford IF, et al. Prostaglandins from tumours of human large bowel. Br J Cancer 1977;35:881–4.
13. Rutledge T, Reis SE, Olson M, et al. Psychosocial variables are associated with atherosclerosis risk factors among women with chest pain: the WISE study. Psychosom Med 2001;63:282–8.
14. Breslau N, Peterson EL, Schultz LR, et al. Major depression and stages of smoking. A longitudinal investigation. Arch Gen Psychiatry 1998;55:161–6.
15. Barefoot JC, Heitmann BL, Helms MJ, et al. Symptoms of depression and changes in body weight from adolescence to mid-life. Int J Obes Relat Metab Disord 1998;22:688–94.
16. Okamura F, Tashiro A, Utumi A, et al. Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism 2000;49:1255–60.
17. Weber-Hamann B, Hentschel F, Kniest A, et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med 2002;64:274–7.
18. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? Metabolism 2002;51:1573–7.
19. Rosmond R, Lapidus L, Marin P, et al. Mental distress, obesity and body fat distribution in middle-aged men. Obes Res 1996;4:245–52.
20. Raikkonen K, Hautanen A, Keltikangas-Jarvinen L. Association of stress and depression with regional fat distribution in healthy middle-aged men. J Behav Med 1994;17:605–16.
21. Raikkonen K, Matthews KA, Kuller LH. Trajectory of psychological risk and incident hypertension in middle-aged women. Hypertension 2001;38:798–802.
22. Davidson K, Jonas BS, Dixon KE, et al. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA Study? Coronary Artery Risk Development in Young Adults. Arch Intern Med 2000;160:1495–500.
23. Jonas BS, Lando JF. Negative affect as a prospective risk factor for hypertension. Psychosom Med 2000;62:188–96.
24. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Fam Med 1997;6:43–9.
25. Kawakami N, Takatsuka N, Shimizu H, et al. Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care 1999;22:1071–6.
26. Eaton WW, Armenian H, Gallo J, et al. Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care 1996;19:1097–102.
27. Arroyo C, Hu FB, Ryan LM, et al. Depressive symptoms and risk of type 2 diabetes in women. Diabetes Care 2004;27:129–33.
28. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–81.
29. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
30. Ware JE, Snow KK, Kosinski M. SF-36 health survey: manual & interpretation guide. Lincoln, RI: QualityMetric Incorporated, 2000.
31. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–63.
32. Ware J, Snow K, Kosinski M, et al. SF-36 Health Survey: manual and interpretation guide. Boston, MA: The Health Institute, New England Medical Center, 1993.
33. Berwick DM, Murphy JM, Goldman PA, et al. Performance of a five-item mental health screening test. Med Care 1991;29:169–76.

34. Weinstein MC, Berwick DM, Goldman PA, et al. A comparison of three psychiatric screening tests using receiver operating characteristic (ROC) analysis. Med Care 1989;27:593–607.
35. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80.
36. SAS Institute, Inc. SAS/STAT software. Cary, NC: SAS Institute, Inc, 2000.
37. Cox DR. Regression models and life tables (with discussion). J R Stat Soc (B) 1972;34:187–220.
38. Cupples LA, D'Agostino RB, Anderson K, et al. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med 1988;7:205–22.
39. Zonderman AB, Costa PT Jr, McCrae RR. Depression as a risk for cancer morbidity and mortality in a nationally representative sample. JAMA 1989;262:1191–5.
40. Dalton SO, Mellemkjaer L, Olsen JH, et al. Depression and cancer risk: a register-based study of patients hospitalized with affective disorders, Denmark, 1969–1993. Am J Epidemiol 2002;155:1088–95.
41. Bleiker EM, van der Ploeg HM, Hendriks JH, et al. Personality factors and breast cancer development: a prospective longitudinal study. J Natl Cancer Inst 1996;88:1478–82.
42. Hahn RC, Petitti DB. Minnesota Multiphasic Personality Inventory-rated depression and the incidence of breast cancer. Cancer 1988;61:845–8.
43. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry 2003;54:269–82.
44. Dalton SO, Boesen EH, Ross L, et al. Mind and cancer. Do psychological factors cause cancer? Eur J Cancer 2002;38:1313–23.
45. Bleiker EM, van der Ploeg HM. Psychosocial factors in the etiology of breast cancer: review of a popular link. Patient Educ Couns 1999;37:201–14.
46. Penninx BW, Guralnik JM, Pahor M, et al. Chronically depressed mood and cancer risk in older persons. J Natl Cancer Inst 1998;90:1888–93.
47. Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom Med 1996;58:113–21.
48. Linkins RW, Comstock GW. Depressed mood and development of cancer. Am J Epidemiol 1990;132:962–72.
49. Kaplan GA, Reynolds P. Depression and cancer mortality and morbidity: prospective evidence from the Alameda County Study. J Behav Med 1988;11:1–13.
50. Gallo JJ, Armenian HK, Ford DE, et al. Major depression and cancer: the 13-year follow-up of the Baltimore Epidemiologic Catchment Area sample (United States). Cancer Causes Control 2000;11:751–8.
51. Shekelle RB, Raynor WJ Jr, Ostfeld AM, et al. Psychological depression and 17-year risk of death from cancer. Psychosom Med 1981;43:117–25.
52. Katon WJ, Lin E, Russo J, et al. Increased medical costs of a population-based sample of depressed elderly patients. Arch Gen Psychiatry 2003;60:897–903.
53. Kimerling R, Ouimette PC, Cronkite RC, et al. Depression and outpatient medical utilization: a naturalistic 10-year follow-up. Ann Behav Med 1999;21:317–21.
54. Unutzer J, Patrick DL, Simon G, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. JAMA 1997;277:1618–23.
55. Callahan CM, Kesterson JG, Tierney WM. Association of symptoms of depression with diagnostic test charges among older adults. Ann Intern Med 1997;126:426–32.
56. Saravay SM, Pollack S, Steinberg MD, et al. Four-year follow-up of the influence of psychological comorbidity on medical rehospitalization. Am J Psychiatry 1996;153:397–403.
57. Kavan MG, Engdahl BE, Kay S. Colon cancer: personality factors predictive of onset and stage of presentation. J Psychosom Res 1995;39:1031–9.
58. Simon G, Ormel J, VonKorff M, et al. Health care costs associated with depressive and anxiety disorders in primary care. Am J Psychiatry 1995;152:352–7.
59. North CS, Alpers DH, Helzer JE, et al. Do life events or depression exacerbate inflammatory bowel disease? A prospective study. Ann Intern Med 1991;114:381–6.
60. Rudy DR, Zdon MJ. Update on colorectal cancer. Am Fam Physician 2000;61:1759–70, 1773–4.
61. Persky VW, Kempthorne-Rawson J, Shekelle RB. Personality and risk of cancer: 20-year follow-up of the Western Electric Study. Psychosom Med 1987;49:435–49.
62. Rogers MP, Dubey D, Reich P. The influence of the psyche and the brain on immunity and disease susceptibility: a critical review. Psychosom Med 1979;41:147–64.
63. Terry MB, Neugut AI, Bostick RM, et al. Risk factors for advanced colorectal adenomas: a pooled analysis. Cancer Epidemiol Biomarkers Prev 2002;11:622–9.
64. Boutron-Ruault MC, Senesse P, Meance S, et al. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. Nutr Cancer 2001;39:50–7.
65. Giovannucci E, Colditz GA, Stampfer MJ, et al. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253–63.
66. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
67. Winokur A, Maislin G, Phillips JL, et al. Insulin resistance after oral glucose tolerance testing in patients with major depression. Am J Psychiatry 1988;145:325–30.
68. Gilman SE, Kawachi I, Fitzmaurice GM, et al. Socioeconomic status in childhood and the lifetime risk of major depression. Int J Epidemiol 2002;31:359–67.
69. Sandhu MS, Luben R, Day NE, et al. Self-reported birth weight and subsequent risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2002;11:935–8.