American Journal of Epidemiology

Vol. 178, No. 12
DOI: 10.1093/aje/kwt217
Advance Access publication:
September 30, 2013

Original Contribution

Depression and the Risk of Cancer: A 15-year Follow-up Study of the GAZEL Cohort

Cédric Lemogne*, Silla M. Consoli, Maria Melchior, Hermann Nabi, Mireille Coeuret-Pellicer, Frédéric Limosin, Marcel Goldberg, and Marie Zins

* Correspondence to Dr. Cédric Lemogne, Emergency and Liaison Psychiatry and Psychology Unit, European Georges Pompidou Hospital, 20 rue Leblanc, 75908 Paris Cedex 15, France (e-mail: cedric.lemogne@egp.aphp.fr).

Initially submitted July 9, 2013; accepted for publication August 12, 2013.

Depression has long been hypothesized to be associated with cancer incidence. However, there is evidence for a positive publication bias in this field. In the present study, we examined the association between various measures of depression and cancer incidence at several sites. A total of 14,203 members of the French GAZEL (Gaz et Electricité) cohort (10,506 men, 3,697 women) were followed up for diagnoses of primary cancers from January 1, 1994, to December 31, 2009. All medically certified sickness absences for depression recorded between January 1, 1990, and December 31, 1993, were compiled. Depressive symptoms were self-reported in 1993, 1996, and 1999 with the Center for Epidemiologic Studies Depression Scale. During a mean follow-up period of 15.2 years, 1,119 participants received a cancer diagnosis, excluding nonmelanoma skin cancer and in situ neoplasms. Considering 6 cancer sites (prostate, breast, colorectal, smoking-related, lymphoid and hematopoietic tissues, other sites) and 4 measures of depression, we found 1 positive association and 1 negative association. Overall, there was no compelling evidence for an association between depression and cancer incidence. Such null results should be considered when addressing concerns of cancer patients and their relatives about the role of depression in cancer onset.

cohort studies; depression; neoplasms; risk

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; GAZEL, Gaz et Electricité; INSERM, Institut National de la Santé et de la Recherche Médicale; SAD, sickness absence for depression; SD, standard deviation.

Depression has long been hypothesized to be associated with the risk of cancer. Early findings suggested that self-reported depressive symptoms might be associated with increased cancer incidence and mortality (1, 2). However, subsequent well-designed, large-scale prospective studies failed to provide compelling evidence for this relationship, yielding null (3–5) or even negative (6) results. In a 1994 meta-analysis, McGee et al. (7) concluded that there was a weak, nonsignificant trend regarding the association between depression and cancer incidence.

This topic attracted research attention again in 1998, when Penninx et al. (8) found a nearly 2-fold increased cancer risk among persons who experienced chronic or recurrent depressive symptoms. Most epidemiologic studies in this field assess depressive symptoms only once. Instead, Penninx et al. repeatedly administered the Center for Epidemiologic Studies Depression Scale (CES-D) and defined chronic or recurrent depressive symptoms as 3 CES-D scores above the validated cutoff, with a 3-year interval between measures (8).

We are not aware of a formal replication of the study by Penninx et al. However, several epidemiologic studies with positive, null, or negative results were published afterwards, making the case for 2 independent meta-analyses (9, 10). In the former, Oerlemans et al. (9) found a weak, nonsignificant trend regarding the association between major depression and cancer incidence. In the latter, Chida et al. (10) addressed several "stress-related psychosocial factors" and found depressive symptoms to be significantly associated with the incidence of cancer (odds ratio = 1.29, 95% confidence interval (CI): 1.14, 1.46). This result, however, should be tempered by evidence

for a publication bias favoring positive results (10) and by the methodological limitations of the studies included (11).

Given these limitations, the current literature does not allow us to either rule out or confirm a role for depression in cancer onset. The growing prevalence of both cancer and depression in the general population (12, 13), as well as concerns regarding their relationship among health-care professionals, patients, and their relatives, warrants a more authoritative answer from epidemiologists. Therefore, we took advantage of data from a large-scale French prospective study, the GAZEL (Gaz et Electricité) cohort study (14), to examine the association between various measures of depression (repeated self-reports based on the CES-D and clinician-based diagnoses of depression) and incidence of cancer at multiple sites.

MATERIALS AND METHODS

Participants

Details on the GAZEL cohort are available elsewhere (14). The target population consisted of 44,922 employees of the French national gas and electricity company Electricité de France-Gaz de France: 31,411 men aged 40–50 years and 13,511 women aged 35–50 years. The study was approved by the French authority for data confidentiality (Commission Nationale Informatique et Liberté) and by the Ethics Evaluation Committee of the Institut National de la Santé et de la Recherche Médicale (INSERM). In 1989, a total of 20,625 employees (45.9%) (15,011 men and 5,614 women) gave written informed consent to participate. Since 1989, volunteers have been followed through annual mailed questionnaires and administrative databases.

Sickness absence for depression

Clinician-based diagnoses of depression were extracted from records on medically certified sickness absences (15–18). All sickness absences exceeding 7 days in a 4-year window from January 1, 1990, to December 31, 1993, were considered. This window was chosen to ensure homogeneity of the period during which exposure was measured across participants. Diagnoses were coded by company physicians using an abridged version of the *International Classification of Diseases, Ninth Revision* (19). Episodes of sickness absence for depression (SAD) corresponded to the codes indicating major depression or dysthymic disorder.

The CES-D

Depressive mood was assessed in 1993, 1996, and 1999 with the CES-D. This 20-item questionnaire has been designed for use in community studies and has a high internal consistency ($\alpha = 0.8$ to $\alpha = 0.9$ across samples) (20, 21). The CES-D asks participants how often they have experienced specific symptoms during the previous week (e.g., "I felt depressed"; "I felt everything I did was an effort"; "My sleep was restless"). Responses range from 0 ("hardly ever") to 3 ("most of the time"). Based on the validation of the French version, a global score of $\geq$17 among men and $\geq$23 among women may signal clinically significant depression (20). Since sole reliance on a binary cutoff may be statistically unsafe (22), we also considered CES-D score in 1993 as a continuous measure of depressive symptoms.

In order to replicate the findings of Penninx et al. (8), we defined chronic or recurrent depressive symptoms as having CES-D scores above the validated cutoff for the years 1993, 1996, and 1999. If a subject was missing a CES-D score in one of the 3 time periods, the 2 remaining CES-D scores were used, and both values had to be above the validated cutoff (8).

Cancer cases

All participants were followed up for diagnoses of primary cancers from January 1, 1994, to December 31, 2009. Diagnoses made during the period of employment came from a registry kept by the medical department at Electricité de France-Gaz de France that has been validated for accuracy and completeness (23). Diagnoses made after retirement came from systematic validation of each self-reported primary cancer through a diagnosis validation survey that began in 2009. Each annual questionnaire asked participants to report whether or not they had been hospitalized or diagnosed with any of several conditions, including cancer, in the preceding 12 months. All participants who self-reported cancer at least once during follow-up were contacted (if alive) and asked to give consent for a detailed diagnostic investigation with their physician.

In a first set of analyses, we considered as cases all participants with a validated diagnosis, as well as participants who reported a diagnosis of primary cancer but died from cancer before the initiation of the diagnosis validation survey. Information on vital status and date of death was obtained annually for all participants from the company, because it pays out retirement benefits. Cause-of-death data were available from baseline (i.e., January 1, 1994) to December 31, 2009, and were coded by the French national cause-of-death registry (Centre d'Épidémiologie sur les Causes Médicales de Décès, INSERM) using the Ninth and Tenth Revisions of the *International Classification of Diseases* (19, 24).

We planned to examine the 4 most frequent types of cancer in France, separately: prostate cancer in men, breast cancer in women, smoking-related cancers (as defined by the French National Institute of Cancer, i.e., cancer of the oral cavity and pharynx, esophagus, larynx, trachea, bronchi and lungs, and bladder), and colorectal cancer (13). We also planned to examine a fifth category encompassing all other cancers. Nonmelanoma skin cancers and in situ neoplasms were not considered as cancer cases.

Covariates

Information on age, sex, and occupational grade (blue-collar worker or clerk; first-line supervisor or sales representative; management) was obtained from company human resources records at the beginning of follow-up. Alcohol consumption, smoking, fruit and vegetable consumption (<1, 1–2, or >2 times per week), height, weight, physical activity (at least 1 time per week, occasionally, or none), and perceived health status were self-reported at the beginning of follow-up. Alcohol consumption, assessed as number of drinks per week, was categorized as follows: nondrinker, occasional drinker

(1–13 drinks/week for men, 1–6 drinks/week for women), and moderate or heavy drinker (≥14 drinks/week for men, ≥7 drinks/week for women). Smoking was categorized into 5 classes: never smoker, ex-smoker of <20 pack-years, current smoker of <20 pack-years, ex-smoker of ≥20 pack-years, and current smoker of ≥20 pack-years. Body mass index was calculated by dividing weight in kilograms by height in meters squared and was categorized as <18.5, 18.5–24.9, 25–29.9, or ≥30. Perceived health status was reported on an 8-point Likert scale ranging from 1 ("very bad") to 8 ("very good").

Statistical analyses

All statistical analyses were conducted with PASW 18.0.0 software (SPSS Inc., Chicago, Illinois). All *P* values were 2-sided. Associations between depression measures as well as covariates and cancer incidence were estimated with hazard ratios and 95% confidence intervals computed in Cox regression analyses. For SAD and depressive symptoms measured in 1993, the follow-up period ran from January 1, 1994, to the date of cancer diagnosis, death, refusal to receive any further questionnaires, or December 31, 2009, whichever came first. For depressive symptoms measured between 1993 and 1999, the follow-up period began on January 1, 2000. For participants who reported a diagnosis of cancer after retirement but died from cancer before the diagnosis validation survey, the estimated date of diagnosis was the date of the first self-report minus 180 days (i.e., the mean interval between 2 annual questionnaires). Discrete covariates were considered as nominal variables. The presence of at least 1 SAD exceeding 7 days from 1989 to 1993 and the presence of chronic or recurrent depressive symptoms from 1993 to 1999 were considered as binary variables. Depressive symptoms measured in 1993 were considered either as a continuous variable (i.e., CES-D score) or as a binary variable (i.e., whether the CES-D score met the validated sex-specific cutoff). Since all covariates were associated with cancer incidence at 1 or more sites, they were all simultaneously entered into multivariate models.

RESULTS

Study population

Among the 20,488 GAZEL volunteers who were still alive in 1993, data on all of the covariates were available for 15,030 (73.4%). Volunteers with complete data were more likely to be male, to be older, to have a higher occupational grade, to be occasional drinkers, to eat fruits and vegetables more than twice a week, and to engage in physical activity at least once a week, and they were less likely to be current smokers and to have an extreme body mass index (all *P*'s < 0.05).

Among these volunteers, 827 (5.5%) were excluded from this study. One person asked not to receive further questionnaires; 32 died before the beginning of follow-up (i.e., January 1, 1994); 224 had previously had a cancer diagnosis at baseline; 136 participants died from cancer without having reported a cancer diagnosis or hospitalization during the follow-up period; and 434 reported either a diagnosis of cancer or a hospitalization for cancer, but their cases were neither validated nor invalidated owing to 1) a lack of written consent to participate in the diagnosis validation survey ($n = 322$ volunteers, including 20 who died before initiation of the survey), 2) death ($n = 8$), 3) refusal to respond to the survey when contacted ($n = 1$), or 4) failure to contact the volunteer and his or her physician ($n = 103$). We excluded these persons to increase the specificity of cancer diagnoses. Table 1 displays the characteristics of the 14,203 participants included in the study.

As expected, participants with at least 1 SAD had a higher mean CES-D score in 1993 than those without any SADs (mean score: 20.8 (standard deviation (SD), 12.1) vs. 12.4 (SD, 8.7); $t = 17.63$, $P < 0.001$) and were more likely to have chronic or recurrent depressive symptoms (33.1% vs. 10.2%; $\chi^2 = 160.87$, $P < 0.001$). They also reported more diseases at baseline (mean number of diseases: 4.5 (SD, 3.1) vs. 2.8 (SD, 2.3); $t = 14.93$, $P < 0.001$), as did participants with chronic or recurrent depressive symptoms (4.5 (SD, 3.0) vs. 2.8 (2.3); $t = 19.19$, $P < 0.001$).

Cancer incidence

During a mean follow-up period of 15.2 years, 1,119 (7.9%) participants (872 men) received at least 1 diagnosis of a primary cancer, including 118 participants (102 men) who self-reported a cancer diagnosis or cancer hospitalization during follow-up but died from cancer before the initiation of the diagnosis validation survey. Among participants who received at least 1 diagnosis of a primary cancer, the mean duration of follow-up prior to cancer diagnosis was 9.2 years. There were 412 prostate cancer cases among men, 138 breast cancer cases among women, 125 colorectal cancer cases, and 128 smoking-related cancer cases. Owing to a sufficient number of cases, we were able to further split the residual category into cancers of lymphoid and hematopoietic tissue ($n = 94$) and cancers at other sites ($n = 252$). In this residual category, the most frequent cancers were melanomas ($n = 50$), cancers of urinary organs ($n = 48$), noncolorectal digestive cancers ($n = 47$), cancers of the female genital organs ($n = 23$), and cancers of the endocrine glands ($n = 23$). Associations between covariates in 1993 and cancer incidence in multivariate analyses are displayed in Table 2.

SAD and cancer incidence

Complete data on SAD were available from January 1, 1989, to December 31, 1993, for a subset of 13,287 participants (93.6%), whereas 916 participants retired before January 1, 1994. A total of 299 men (3.0%) and 434 women (12.5%) had at least 1 SAD exceeding 7 days between January 1, 1989, and December 31, 1993. Among these participants, the median cumulative length of SAD was 3.4 weeks.

Adjusting for age only, SAD was not associated with the incidence of cancer, regardless of cancer site (all *P*'s ≥ 0.125), except for the "other sites" category (hazard ratio = 1.87, 95% CI: 1.22, 2.88; $P = 0.004$). This association remained significant after adjustment for the whole set of covariates in 1993 (Table 3). There was no significant interaction with sex regarding the other categories (all *P*'s ≥ 0.33). Similar results were obtained regardless of whether participants who died

Table 1. Characteristics of Participants in the GAZEL Cohort Study, France, 1993

Characteristic	Men ($n = 10,506$)			Women ($n = 3,697$)		
	Mean (SD)	No.	%	Mean (SD)	No.	%
Continuous variables						
Age, years	48.5 (2.9)			45.7 (4.2)		
Perceived health status[a]	5.7 (1.3)			5.6 (1.3)		
Categorical variables						
Occupational grade						
Blue-collar worker, clerk		1,156	11.0		811	21.9
First-line supervisor, sales representative		5,497	52.3		2,481	67.1
Management		3,853	36.7		405	11.0
Alcohol consumption[b]						
Nondrinker		884	8.4		849	23.0
Occasional drinker		5,450	51.9		1,970	53.3
Moderate or heavy drinker		4,172	39.7		878	23.7
Smoking						
Never smoker		3,935	37.5		2,532	68.5
Ex-smoker, <20 PY		2,924	27.8		529	14.3
Ex-smoker, ≥20 PY		986	9.4		372	10.1
Current smoker, <20 PY		1,465	13.9		96	2.6
Current smoker, ≥20 PY		1,196	11.4		168	4.5
Fruit consumption, times/week						
<1		802	7.6		218	5.9
1–2		1,466	14.0		354	9.6
>2		8,238	78.4		3,125	84.5
Vegetable consumption, times/week						
<1		272	2.6		61	1.6
1–2		3,796	36.1		1,023	27.7
>2		6,438	61.3		2,613	70.7
Body mass index[c]						
<18.5		34	0.3		136	3.7
18.5–24.99		4,700	44.7		2,760	74.7
25–29.99		5,046	48.0		625	16.9
≥30		726	6.9		176	4.8
Physical activity						
≥1 time/week		3,843	36.6		1,234	33.4
Occasionally		3,492	33.2		984	26.6
None		3,171	30.2		1,479	40.0

Abbreviations: GAZEL, Gaz et Electricité; PY, pack-years; SD, standard deviation.

[a] Perceived health status was reported on an 8-point Likert scale ranging from 1 ("very bad") to 8 ("very good").

[b] Occasional drinking was defined as 1–13 drinks/week for men and 1–6 drinks/week for women; moderate or heavy drinking was defined as ≥14 drinks/week for men and ≥7 drinks/week for women.

[c] Weight (kg)/height (m)^2.

from cancer before the diagnosis validation survey were included or excluded.

Depressive symptoms in 1993 and cancer incidence

A subset of 12,245 participants (86.2%) completed the CES-D in 1993. The mean CES-D score in 1993 was 11.8 (SD, 8.2) among men and 15.9 (SD, 10.7) among women. A total of 2,065 men (22.8% of 9,060) and 800 women (25.1% of 3,185) had a score above the validated sex-specific cutoff.

Adjusting for age only, neither CES-D score as a continuous variable nor a CES-D score above the cutoff was associated with the incidence of cancer, regardless of site (all P's ≥ 0.15). Similar results were obtained after adjustment for the

Table 2. Associations Between Covariates Measured in 1993 and Cancer Incidence From January 1, 1994, to December 31, 2009, in Multivariate Cox Regression Analyses, GAZEL Cohort Study, France

	Cancer Type or Site											
	Prostate (Men) ($n = 412$)		Breast (Women) ($n = 138$)		Colorectal ($n = 125$)		Smoking-related ($n = 128$)		Lymphoid and Hematopoietic Tissues ($n = 94$)		Other Sites ($n = 252$)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age (per year)	1.12***	1.09, 1.16	1.04†	1.00, 1.08	1.09**	1.03, 1.15	0.98	0.92, 1.04	1.05	0.99, 1.12	1.03	0.99, 1.07
Sex												
Male					1.00		1.00		1.00		1.00	
Female					0.58†	0.33, 1.03	0.14***	0.05, 0.35	0.96	0.55, 1.66	1.34†	0.96, 1.86
Occupational grade												
Blue-collar worker, clerk	1.00		1.00		1.00		1.00		1.00		1.00	
First-line supervisor, sales representative	1.38	0.93, 2.06	1.02	0.67, 1.56	1.26	0.68, 2.33	0.56**	0.36, 0.86	1.22	0.59, 2.49	1.01	0.69, 1.48
Management	1.89**	1.27, 2.82	1.31	0.72, 2.37	1.25	0.65, 2.40	0.36***	0.21, 0.61	1.86	0.88, 3.94	1.31	0.86, 1.99
Alcohol consumption[a]												
Nondrinker	1.00		1.00		1.00		1.00		1.00		1.00	
Occasional drinker	1.14	0.76, 1.70	1.17	0.74, 1.85	1.83	0.88, 3.83	1.14	0.60, 2.15	1.57	0.70, 3.51	0.93	0.63, 1.36
Moderate or heavy drinker	1.34	0.89, 2.02	1.64	0.99, 2.70	1.41	0.65, 3.03	0.96	0.51, 1.82	1.97	0.86, 4.48	0.79	0.52, 1.20
Smoking												
Never smoker	1.00		1.00		1.00		1.00		1.00		1.00	
Ex-smoker, <20 PY	1.14	0.91, 1.44	0.95	0.57, 1.58	0.91	0.57, 1.43	2.01†	0.99, 4.05	0.87	0.51, 1.48	0.80	0.57, 1.13
Ex-smoker, ≥20 PY	0.97	0.68, 1.38	1.03	0.59, 1.82	0.96	0.50, 1.84	2.94*	1.30, 6.64	1.29	0.67, 2.46	1.02	0.66, 1.58
Current smoker, <20 PY	0.76	0.55, 1.05	0.84	0.27, 2.67	1.27	0.75, 2.16	5.06***	2.54, 10.06	0.85	0.40, 1.79	1.07	0.70, 1.62
Current smoker, ≥20 PY	0.64*	0.44, 0.95	1.01	0.46, 2.21	0.71	0.34, 1.46	15.08***	8.27, 27.47	0.87	0.40, 1.89	1.03	0.66, 1.62
Fruit consumption, times/week												
<1	1.00		1.00		1.00		1.00		1.00		1.00	
1–2	1.33	0.86, 2.08	0.82	0.33, 2.05	1.24	0.56, 2.77	0.50*	0.27, 0.94	0.41	0.09, 1.82	1.14	0.67, 1.95
>2	1.02	0.68, 1.52	1.07	0.52, 2.21	0.99	0.49, 2.01	0.64†	0.40, 1.03	1.90	0.69, 5.27	0.80	0.50, 1.29
Vegetable consumption, times/week												
<1	1.00		1.00		1.00		1.00		1.00		1.00	
1–2	0.63†	0.37, 1.08	2.76	0.38, 20.12	0.32**	0.15, 0.70	1.07	0.43, 2.70	1.85	0.25, 13.64	1.05	0.46, 2.41
>2	0.61†	0.36, 1.04	2.28	0.32, 16.48	0.36**	0.17, 0.77	0.89	0.35, 2.24	1.90	0.26, 13.79	0.98	0.43, 2.24
Body mass index[b]												
<18.5	0.74	0.10, 5.31	0.83	0.31, 2.27	2.35	0.56, 9.87	1.96	0.46, 8.32	0.95	0.13, 6.98	0.97	0.31, 3.07
18.5–24.99	1.00		1.00		1.00		1.00		1.00		1.00	
25–29.99	0.90	0.74, 1.10	0.92	0.58, 1.44	1.14	0.78, 1.66	0.76	0.53, 1.10	0.66†	0.42, 1.03	1.12	0.85, 1.48
≥30	1.01	0.68, 1.51	0.42	0.13, 1.35	0.61	0.24, 1.54	0.36*	0.15, 0.92	0.72	0.28, 1.82	1.08	0.63, 1.84

Table continues

Table 2. Continued

	Cancer Type or Site											
	Prostate (Men) (n = 412)		Breast (Women) (n = 138)		Colorectal (n = 125)		Smoking-related (n = 128)		Lymphoid and Hematopoietic Tissues (n = 94)		Other Sites (n = 252)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Physical activity												
≥1 time/week	0.79†	0.61, 1.01	0.84	0.56, 1.25	0.86	0.55, 1.34	0.60*	0.36, 1.00	0.83	0.49, 1.41	1.23	0.90, 1.70
Occasionally	1.03	0.81, 1.30	0.77	0.50, 1.19	0.92	0.59, 1.43	1.08	0.73, 1.60	1.11	0.68, 1.83	1.30	0.95, 1.78
None	1.00		1.00		1.00		1.00		1.00		1.00	
Perceived health status (per unit)[c]	1.02	0.94, 1.10	0.99	0.87, 1.12	1.07	0.93, 1.24	0.96	0.84, 1.09	0.85*	0.73, 0.99	0.92†	0.83, 1.01

Abbreviations: CI, confidence interval; GAZEL, Gaz et Electricité; HR, hazard ratio.
† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (2-sided P values).
[a] Occasional drinking was defined as 1–13 drinks/week for men and 1–6 drinks/week for women; moderate or heavy drinking was defined as ≥14 drinks/week for men and ≥7 drinks/week for women.
[b] Weight (kg)/height (m)^2.
[c] Perceived health status was reported on an 8-point Likert scale ranging from 1 ("very bad") to 8 ("very good").

Table 3. Association Between Sickness Absence for Depression (≥1 Absences vs. 0) and Cancer Incidence From January 1, 1994, to December 31, 2009, After Adjustment for All Covariates Measured in 1993, GAZEL Cohort Study, France

Cancer Site or Type	No. of Cases	Total No. of Participants	HR	95% CI	P Value[a]
Prostate (men)	370	9,818	1.39	0.79, 2.43	0.26
Breast (women)	130	3,466	0.97	0.57, 1.66	0.92
Colorectal	112	13,286	0.43	0.11, 1.79	0.25
Smoking-related	118	13,281	0.44	0.14, 1.42	0.17
Lymphoid and hematopoietic tissues	90	13,286	1.28	0.54, 3.04	0.57
Other sites	241	13,286	1.76	1.12, 2.78	0.01

Abbreviations: CI, confidence interval; GAZEL, Gaz et Electricité; HR, hazard ratio.
[a] P values are 2-sided (Cox regression).

whole set of covariates in 1993 (Table 4). There was no significant interaction with sex regarding the other categories (all P's ≥ 0.33). Similar results were obtained regardless of whether participants who died from cancer before the diagnosis validation survey were included or excluded.

Chronic or recurrent depressive symptoms and cancer incidence

Among the 13,789 participants who were alive and cancer-free on January 1, 2000, a subset of 11,877 (86.1%) completed the CES-D at least 2 times in 1993, 1996, and 1999. During a mean follow-up period of 9.6 years, 779 (6.6%) participants (633 men) received at least 1 diagnosis of a primary cancer, including 82 (71 men) who self-reported a cancer diagnosis or cancer hospitalization during follow-up but died from cancer before initiation of the diagnosis validation survey. The mean duration of follow-up prior to cancer diagnosis was 5.3 years. There were 359 prostate cancer cases among men, 72 breast cancer cases among women, 82 colorectal cancer cases, 70 smoking-related cancer cases, 64 cases of cancer of lymphoid and hematopoietic tissue, and 154 cases of other cancers.

A total of 848 men (9.6% of 8,873) and 335 women (11.2% of 3,004) had a CES-D score above the validated sex-specific cutoff at each available point from 1993 to 1999.

Adjusting for age, chronic or recurrent depressive symptoms were not associated with the incidence of cancer, whatever the site ($P \geq 0.27$), except negatively for prostate cancer among men (hazard ratio = 0.58, 95% CI: 0.37, 0.91; P = 0.02). This association remained significant after adjustment for the whole set of covariates in 1999 (Table 5). There was no significant interaction with sex regarding the other categories (all P's ≥ 0.39). Excluding or including the participants who died from cancer before the diagnosis validation survey yielded similar results. Using a CES-D cutoff of ≥20 for both men and women, as in the study by Penninx et al. (8), also yielded similar results. Finally, using a CES-D cutoff of ≥26 for both men and women, in order to obtain similar

Table 4. Association Between Depressive Symptoms and Cancer Incidence From January 1, 1994, to December 31, 2009, After Adjustment for All Covariates Measured in 1993, GAZEL Cohort Study, France

Cancer Site or Type	No. of Cases	Total No. of Participants	CES-D Score in 1993[a]			CES-D Score in 1993 > Threshold[b]		
			HR	95% CI	*P* Value[c]	HR	95% CI	*P* Value[c]
Prostate (men)	377	9,058	0.99	0.86, 1.13	0.85	1.07	0.84, 1.38	0.58
Breast (women)	128	3,184	0.87	0.66, 1.15	0.33	1.01	0.66, 1.55	0.95
Colorectal	113	12,244	0.86	0.65, 1.12	0.26	0.71	0.43, 1.17	0.18
Smoking-related	117	12,239	0.91	0.71, 1.17	0.47	0.91	0.59, 1.42	0.69
Lymphoid and hematopoietic tissues	82	12,244	0.98	0.74, 1.31	0.90	0.89	0.52, 1.52	0.67
Other sites	221	12,244	0.92	0.78, 1.10	0.38	0.80	0.57, 1.12	0.19

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; GAZEL, Gaz et Electricité; HR, hazard ratio.

[a] The 25th and 75th percentile values were used for scaling.

[b] CES-D score ≥17 among men or ≥23 among women.

[c] *P* values are 2-sided (Cox regression).

rates of chronic and recurrent depressive symptoms (i.e., 3%), yielded null results for all cancer sites.

DISCUSSION

Main findings

To our knowledge, this was the first large-scale prospective study to examine the association between both clinician-based and repeated self-reported measures of depression and cancer incidence at several sites. Overall, we did not find compelling evidence for an association between depression and an increased risk of cancer, regardless of the measure considered. Out of the 24 statistical tests performed, we found only 2 statistically significant associations. The first was a positive association between SAD and the incidence of cancer at "other sites." The second was a negative association between chronic or recurrent depressive symptoms and the incidence of prostate cancer. Both would have fallen short of any corrected statistical threshold for multiple comparisons (e.g., $P < 0.0083$ according to a Bonferroni correction considering 6 tests).

Table 5. Association Between Chronic Depressive Symptoms[a] and Cancer Incidence From January 1, 2000, to December 31, 2009, After Adjustment for All Covariates Measured in 1999, GAZEL Cohort Study, France

Cancer Site or Type	No. of Cases	Total No. of Participants	HR	95% CI	*P* Value[b]
Prostate (men)	359	8,873	0.60	0.38, 0.96	0.03
Breast (women)	72	3,002	1.32	0.67, 2.60	0.43
Colorectal	81	11,877	1.32	0.64, 2.71	0.45
Smoking-related	70	11,866	0.84	0.37, 1.89	0.67
Lymphoid and hematopoietic tissues	64	11,877	0.66	0.26, 1.69	0.39
Other sites	154	11,875	0.93	0.54, 1.59	0.79

Abbreviations: CI, confidence interval; GAZEL, Gaz et Electricité; HR, hazard ratio.

[a] Defined as Center for Epidemiologic Studies Depression Scale scores greater than the threshold (≥17 among men or ≥23 among women) in 1993, 1996, and 1999.

[b] *P* values are 2-sided (Cox regression).

Findings in the context of the literature

Strengths of this study include its large sample size, the long duration of follow-up (15.2 years, on average), the wide set of covariates, the study of different cancer sites, and the study of cancer incidence rather than mortality. Cancer diagnoses were carefully ascertained and validated. In sensitivity analyses, including or excluding the participants who died from cancer before the diagnosis validation survey yielded similar results. Our data are consistent with known associations for established risk factors such as age, alcohol consumption, and smoking, as well as for social and demographic variables and protective factors (13). The inclusion of both self-reported and clinician-based measures of depression allowed us to examine the internal consistency of our results. For instance, it is noteworthy that there was not even a trend for the 2 above-mentioned associations when another measure of depression was used.

The results obtained by Penninx et al. (8) suggested a form of dose-response relationship between exposure to depressive symptoms and cancer. We did not replicate these results in the GAZEL cohort. Statistical power is unlikely to account for this discrepancy, owing to a 2-fold number of cases and duration of follow-up. Likewise, differences in CES-D cutoff values may not explain this lack of replication, since we obtained similar, mostly null results using either the same CES-D cutoff as in Penninx et al.'s study or a CES-D cutoff yielding a similar rates of chronic and recurrent depressive

symptoms. However, although the two studies had similar designs, differences in study population and follow-up may account for this discrepancy. Our population was predominantly male and middle-aged at inception, whereas Penninx et al. included older, predominantly female adults in their study (8). Depression may be associated with cancer incidence to a greater extent in women than in men (25, 26). A longer follow-up period may have decreased the likelihood of reverse causality (i.e., depressive symptoms' being caused by occult cancer) (27). In the two studies, CES-D data were collected 6 and 3 years before baseline, making reverse causality unlikely. However, because Penninx et al. mainly identified cancers through hospital discharge records (8), they may have failed to ascertain the date of diagnosis as precisely as we did. Therefore, they may have overestimated the duration of follow-up from the psychological assessment to the actual onset of the disease.

Although most previous studies in the field used self-reported measures of depression, those that used clinician-based diagnoses provided mixed results at best (27, 28). In the present study, we found a weak yet significant association between SAD and cancer incidence at "other sites." In addition to the above-mentioned multiple-comparisons issue and the lack of internal consistency, the heterogeneity of this residual category prevents us from further interpreting this result. Indeed, it is difficult to imagine a plausible biological pathway that would be general enough to apply to most of these cancers but not to the more frequent types. Likewise, the finding of a weak negative association between chronic or recurrent depressive symptoms and the incidence of prostate cancer could be a chance finding in the opposite direction, as one might expect owing to the number of tests performed.

Limitations

Several limitations of this study should be acknowledged. First, cancer cases were thoroughly ascertained and validated, thus making false-positive diagnoses unlikely, but there may have been false negatives. Indeed, 136 persons died from cancer without having reported a diagnosis of cancer or a hospitalization for cancer during follow-up. Several of them died from a cancer with a poor prognosis (e.g., lung cancer), and the lack of self-reported cancer incidence data may have been due to the short time period between diagnosis and death. Given the possibility of false-negative data, reporting bias may have resulted in type 2 error. For instance, depressive symptoms may have been associated with a lower tendency to report cancer or to engage in screening procedures. Indeed, it may partially account for the negative association with prostate cancer incidence, which may capture both real incidence and excessive screening based on the prostate-specific antigen test (13). However, participants with at least 1 SAD or with subsequent chronic or recurrent depressive symptoms reported more diseases at baseline, making this hypothesis less likely. Second, although medically certified sickness absence episodes have been shown to be a valid global measure of physical and mental health (16–18, 29), clinical depression might have been underreported. Third, exposure to potentially carcinogenic hazards, such as low-frequency electric or magnetic fields or carcinogenic chemicals found at the workplace, were not taken into account. In the context of mostly null results, however, including these data as covariates might have been unlikely to uncover significant associations between measures of depression and cancer incidence. Finally, although the GAZEL cohort covers all regions of France, various areas ranging from small villages to large cities, and a wide range of socioeconomic statuses and occupations, it is not representative of the general population because it includes only middle-aged employed persons (14).

Conclusion

Naive beliefs about the causes of cancer may add to its psychological burden. Unfortunately, there is evidence for positive publication bias regarding the association between depression and cancer incidence (10). The present study did not find evidence of such an association, regardless of cancer site or the duration of depressive symptoms. These negative results should be considered when addressing concerns of cancer patients and their relatives about the role of depression in cancer onset.

ACKNOWLEDGMENTS

Author affiliations: Faculté de médecine, Sorbonne Paris Cité, Université Paris Descartes, Paris, France (Cédric Lemogne, Silla M. Consoli, Frédéric Limosin); Service universitaire de Psychiatrie de l'adulte et du sujet âgé, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France (Cédric Lemogne, Silla M. Consoli, Frédéric Limosin); Center for Psychiatry and Neurosciences, Unit 894, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France (Cédric Lemogne, Frédéric Limosin); Population-based Cohorts Research Platform Team, Center for Research in Epidemiology and Population Health, Unit 1018, INSERM, Villejuif, France (Cédric Lemogne, Mireille Coeuret-Pellicer, Marcel Goldberg, Marie Zins); University of Versailles Saint-Quentin, Versailles, France (Maria Melchior, Hermann Nabi, Mireille Coeuret-Pellicer, Marcel Goldberg, Marie Zins); and Epidemiology of Occupational and Social Determinants of Health Team, Center for Research in Epidemiology and Population Health, Unit 1018, INSERM, Villejuif, France (Maria Melchior, Hermann Nabi).

The present study was funded by the French Institute for Public Health Research (Institut de Recherche en Santé Publique), the Pasteur Mutuality Foundation (Fondation d'Entreprise du Groupe Pasteur Mutualité), and the Paris Mutual Insurance Medical Society (Société Mutualiste des Médecins du Département de Paris). The GAZEL Cohort Study was funded by Electricité de France-Gaz de France and INSERM and received grants from the Very Large Research Infrastructures Health Cohorts Program (Programme Très Grandes Infrastructures de Recherche–Cohortes Santé), the French National Research Agency (Agence Nationale de la Recherché), and the French Agency for Environmental and Occupational Health and Safety (Agence Française de Sécurité Sanitaire de l'Environnement et du Travail).

We thank Electricité de France-Gaz de France, especially the Department of Occupational Medicine (Service Général

de Médecine de Contrôle) and the French Electricity and Gas Industries Central Fund for Social Action (Caisse Centrale d'Action Sociale du Personnel des Industries Électrique et Gazière). We also acknowledge the Population-based Cohorts Research Platform Team (INSERM, Unit 1018), who were responsible for management of the GAZEL database.

Conflict of interest: none declared.

REFERENCES

1. Shekelle RB, Raynor WJ Jr, Ostfeld AM, et al. Psychological depression and 17-year risk of death from cancer. *Psychosom Med*. 1981;43(2):117–125.
2. Persky VW, Kempthorne-Rawson J, Shekell RB. Personality and risk of cancer: a 20-year follow-up of the Western Electric Study. *Psychosom Med*. 1987;49(5):435–449.
3. Hahn RC, Petitti DB. Minnesota Multiphasic Personality Inventory-rated depression and the incidence of breast cancer. *Cancer*. 1988;61(4):845–848.
4. Kaplan GA, Reynolds P. Depression and cancer mortality and morbidity: prospective evidence from the Alameda County Study. *J Behav Med*. 1988;11(1):1–13.
5. Zonderman A, Costa P, McCrae R. Depression as a risk for cancer morbidity and mortality in a nationally representative sample. *JAMA*. 1989;262(9):1191–1195.
6. Nyklícek I, Louwman WJ, Van Nierop PW, et al. Depression and the lower risk for breast cancer development in middle-aged women: a prospective study. *Psychol Med*. 2003; 33(6):1111–1117.
7. McGee R, Williams S, Elwood M. Depression and the development of cancer: a meta-analysis. *Soc Sci Med*. 1994; 38(1):187–192.
8. Penninx BW, Guralnik JM, Pahor M, et al. Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst*. 1998;90(24):1888–1893.
9. Oerlemans ME, van den Akker M, Schuurman AG, et al. A meta-analysis on depression and subsequent cancer risk. *Clin Pract Epidemiol Ment Health*. 2007;3:29.
10. Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol*. 2008;5(8):466–475.
11. Coyne JC, Ranchor AV, Palmer SC. Meta-analysis of stress-related factors in cancer [letter]. *Nat Rev Clin Oncol*. 2010; 7(5):1–2.
12. Ustün TB, Ayuso-Mateos JL, Chatterji S, et al. Global burden of depressive disorders in the year 2000. *Br J Psychiatry*. 2004;184:386–392.
13. Institut National du Cancer. *La Situation du Cancer en France en 2011*. Boulogne-Billancourt, France: Institut National du Cancer; 2011.
14. Goldberg M, Leclerc A, Bonenfant S, et al. Cohort profile: the GAZEL Cohort Study. *Int J Epidemiol*. 2007;36(1):32–39.
15. Melchior M, Ferrie JE, Alexanderson K, et al. Does sickness absence due to psychiatric disorder predict cause-specific mortality? A 16-year follow-up of the GAZEL occupational cohort study. *Am J Epidemiol*. 2010;172(6):700–707.
16. Ferrie JE, Vahtera J, Kivimäki M, et al. Diagnosis-specific sickness absence and all-cause mortality in the GAZEL Study. *J Epidemiol Community Health*. 2009;63(1):50–55.
17. Marmot M, Feeney A, Shipley M, et al. Sickness absence as a measure of health status and functioning: from the UK Whitehall II Study. *J Epidemiol Community Health*. 1995; 49(2):124–130.
18. Kivimäki M, Head J, Ferrie JE, et al. Sickness absence as a global measure of health: evidence from mortality in the Whitehall II Prospective Cohort Study. *BMJ*. 2003; 327(7411):364.
19. World Health Organization. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Ninth Revision*. Geneva, Switzerland: World Health Organization; 1977.
20. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
21. Fuhrer R, Rouillon F. La version française de l'échelle CES-D [Center for Epidemiologic Studies-Depression scale]. Description et traduction de l'échelle d'autovalutation. *Psychiatry Psychobiol*. 1989;4(3):163–166.
22. MacCallum RC, Zhang S, Preacher KJ, et al. On the practice of dichotomization of quantitative variables. *Psychol Methods*. 2002;7(1):19–40.
23. Chevalier A, Goldberg M, Godard C, et al. Cancer incidence among active male workers at Electricite de France-Gaz de France. *Rev Epidemiol Sante Publique*. 1996;44(1):25–36.
24. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems. Tenth Revision*. Geneva, Switzerland: World Health Organization; 1993.
25. Lemogne C, Niedhammer I, Khlat M, et al. Gender differences in the association between depressive mood and mortality: a 12-year follow-up population-based study. *J Affect Disord*. 2012;136(3):267–275.
26. Abgrall-Barbry G, Lemogne C, Lamarque D, et al. Depressive mood and subsequent cancer diagnosis in patients undergoing a colonoscopy. *Psychosomatics*. 2012; 53(4):356–362.
27. Dalton SO, Mellemkjaer L, Olsen JH, et al. Depression and cancer risk: a register-based study of patients hospitalized with affective disorders. *Am J Epidemiol*. 2002;155(12):1088–1095.
28. Friedman GD. Psychiatrically-diagnosed depression and subsequent cancer. *Cancer Epidemiol Biomarkers Prev*. 1994;3(1):11–13.
29. Melchior M, Ferrie JE, Alexanderson K, et al. Using sickness absence records to predict future depression in a working population: prospective findings from the GAZEL cohort. *Am J Public Health*. 2009;99(8):1417–1422.