Title: MAJOR DEPRESSION AND SURVIVAL IN PEOPLE WITH CANCER

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ABSTRACT

Objective

The question of whether depression is associated with worse survival in people with cancer remains unanswered because of methodological criticism of the published research on the topic. We aimed to study the association in a large methodologically robust study.

Methods

We analysed data on 20,582 patients with breast, colorectal, gynaecological, lung and prostate cancers who had attended cancer outpatient clinics in Scotland, UK. Patients had completed two-stage screening for major depression as part of their cancer care. These data on depression status were linked to demographic, cancer and subsequent mortality data from national databases. We estimated the association of major depression with survival for each cancer using Cox regression. We adjusted for potential confounders and interactions between potentially time-varying confounders and the interval between cancer diagnosis and depression screening, and used multiple imputation for missing depression and confounder data. We pooled the cancer-specific results using fixed-effects meta-analysis.

Results

Major depression was associated with worse survival for all cancers, with similar adjusted hazard ratios: breast cancer (HR 1.42, 95% CI 1.15-1.75), colorectal cancer (HR 1.47, 95% CI 1.11-1.94), gynaecological cancer (HR 1.36, 95% CI 1.08-1.71), lung cancer (HR 1.39, 95% CI 1.24-1.56), prostate cancer (HR 1.76, 95% CI 1.08-2.85). The pooled hazard ratio was 1.41

(95% CI 1.29-1.54, p<0.001, I^2=0%). These findings were not materially different when we only considered the deaths (90%) that were attributed to cancer.

Conclusions

Major depression is associated with worse survival in patients with common cancers. The mechanisms of this association and the clinical implications require further study.

Key words

Depression; Cancer; Neoplasms; Survival; Mortality; Cohort

Abbreviations

NHS = National Health Service; HADS = Hospital Anxiety and Depression Scale; SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; NRS = National Records of Scotland; SMCFCS = substantive model compatible fully conditional specification; HR = hazard ratio; CI = confidence interval

INTRODUCTION

The question of whether depression is associated with worse survival in people with cancer remains unanswered. Whilst many relevant studies have been published (1-23), their methods have been have been criticised (24-26). The methodological limitations described include: (a) the use of small unrepresentative samples of patients; (b) poorly defined cancer diagnoses, including often a reliance on self-report; (c) frequently an inadequate determination of depression status, often using questionnaire scores rather than a diagnostic interview; (d) incomplete follow-up of participants to determine their survival; (e) a lack of data on cause of death; (f) inadequate statistical methods; and (g) a failure to adequately control for the factors that may confound an association between major depression and survival, including cancer severity and demographic factors such as social deprivation (24-26).

We had the opportunity to address the question in a methodologically robust study by analysing prospectively collected data from a large cohort of patients with common cancers (breast, colorectal, gynaecological, lung and prostate cancers) who had completed systematic screening for major depression as part of their cancer care and for whom we also had data on subsequent deaths. Our aim was therefore to investigate the association between major depression and subsequent survival in patients with common cancers.

METHODS

Study design and patients

We analysed data from patients who had attended the outpatient clinics of the Edinburgh, Glasgow and Dundee National Health Service (NHS) cancer centres in Scotland, UK, and participated in screening for major depression as part of their cancer care. Each of these publically funded cancer centres provides a full range of diagnostic and treatment services through teaching hospitals and outreach clinics. Together the three centres serve a geographically defined area of approximately four million people and provide specialist care for the vast majority of patients who have been diagnosed with cancer in this region.

We included a patient's data in this analysis if: (a) they had attended an outpatient oncology consultation in a central or outreach cancer clinic between May 12, 2008 and August 24 2011; (b) they had participated in the routine major depression screening programme that operated in these clinics; (c) they had given consent for their relevant clinical data to be used for research; (d) we could obtain their matched demographic and clinical data from the Scottish National Cancer Registry; and (e) they had a primary breast, colorectal, gynaecological, lung or prostate cancer. We chose these cancers because they are the most common, they often form the basis for multidisciplinary cancer care (therefore the association between major depression and survival in each group is clinically useful) and the number of patients with each cancer was sufficient to estimate this association with acceptable accuracy.

Measures

Major depression

Screening for major depression was carried out as part of usual clinical care; 80% of patients attending the relevant cancer clinics completed depression screening (the main reason that patients did not complete screening was that their oncology appointment had begun before they could do so). The screening used a conventional two-stage procedure to ensure efficiency of the diagnostic process; this procedure is described in detail in previous publications (27, 28). In brief, the first stage of screening used the Hospital Anxiety and Depression Scale (HADS) self-rated questionnaire to identify those patients who required a diagnostic interview (those with a HADS total score ≥15) (29, 30). In the second stage, patients with a high score on the HADS were assessed using the depression section of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID) to determine whether they met criteria for major depression (31, 32). Interviews were carried out over the telephone to the patient's home usually within several days of clinic attendance; telephone SCID interviews have good agreement with face-to-face interviews (33). Telephone interviews were audio-recorded with patients' permission.

In order to ensure the validity and reliability of the diagnosis of major depression, the following procedures were used: (a) Interviewers (psychology graduates and nurses) received four weeks' training from consultation-liaison psychiatrists with expertise in the use of the SCID. (b) Interviewers had to complete at least 20 satisfactory interviews which resulted in accurate diagnoses (that is, 100% inter-rater reliability between interviewer and psychiatrist) before conducting interviews independently. (c) The psychiatrists provided

ongoing individual and group supervision of interviewers informed by regular review of at least 10% of interviews.

The diagnosis of major depression was made using the standard inclusive approach (all relevant symptoms counted towards the diagnosis of depression without attempting to establish whether they should be attributed to depression or to cancer); this is the most reliable method and has been found to not significantly overestimate depression in the medically ill (34). To minimise the misdiagnosis of adjustment disorder as a depressive disorder, major depression was only diagnosed if the patient described relevant symptoms of at least four weeks' duration. If they reported symptoms between two weeks (the usual minimum duration required for a diagnosis of major depression) and four weeks, the patient was re-interviewed two weeks later. We classified patients as 'depressed' if they met criteria for major depression at the diagnostic interview.

Demographic and cancer data

We obtained data on patients' demographic and cancer characteristics from the NHS Scotland Cancer Registry. The Registry systematically collects information from hospitals throughout Scotland for all recorded cases of cancer. The data included sex, date of cancer diagnosis (the date on which the cancer was first diagnosed whether by histopathological, radiological or other clinical methods), age at cancer diagnosis, social deprivation score (calculated using the Scottish Index of Multiple Deprivation, which provides a relative measure of deprivation, based on area of residence at the time of cancer diagnosis; see appendix for details), primary cancer (see appendix for details) and initial cancer treatment objective (curative or palliative). We used cancer treatment objective as a proxy for cancer

severity because it could be applied across all the cancers studied, whereas staging systems differ between and within the five common cancers.

Mortality data

We obtained data on the date and recorded cause of death of each patient from the National Records of Scotland (NRS) database.

Data linkage

To ensure data security and confidentiality the dataset of patients' depression status was sent to the Information Services Division of NHS Scotland for linkage using unique patient identification numbers (Community Health Index numbers) and dates of birth. All identifying data were then removed in a one-way linkage to produce the anonymised dataset that was used for analysis. The study was approved by the South East Scotland Research Ethics Committee, the NHS Scotland Caldicott Guardian Forum and the NHS Scotland Privacy Advisory Committee.

Statistical analyses

For each patient, we calculated the time to their death from the date they attended the cancer clinic and took part in depression screening. If a patient had attended the cancer clinic and participated in depression screening more than once during the study period, we used the data relating to the earliest of their clinic attendances. In the primary analysis, we considered deaths from all causes, censoring patients who had left Scotland (at their date of emigration) and patients who were not known to have died or to have emigrated at the latest date on which data were available (April 30, 2012). We also censored one patient

whose mortality status was unknown on April 30, 2012 at their last known appointment date. In a secondary analysis, we considered only deaths attributed to cancer, additionally censoring non-cancer deaths at the date of death.

We used Cox proportional hazards models to estimate the effect of major depression on survival from the time of depression screening for each of the primary cancers (breast, colorectal, gynaecological, lung, and prostate). We assigned patients who had multiple primary cancers according to the cancer diagnosis that most closely preceded the clinic appointment (11 patients who were given two different cancer diagnoses on the same day were included in the analyses of both cancers).

The models adjusted for the following potential confounders: sex, age at cancer diagnosis, social deprivation score, initial cancer treatment objective and the interval between cancer diagnosis and depression screening. Full details of the statistical models are given in the online appendix. In brief, we modelled the confounding effects of the continuous variables using fractional polynomials, using the method described by Benner in order to allow for non-linear effects (35).

A further refinement was made because age at cancer diagnosis, social deprivation score and initial cancer treatment objective were measured at the time of patients' cancer diagnoses, and it is likely that the magnitude of their confounding effects on survival may change according to the time interval between cancer diagnosis and depression screening. To allow for this possibility the models also included interactions between the fractional polynomial terms for this time interval and initial cancer treatment objective, and between

the fractional polynomial terms for this time interval and the fractional polynomial terms for age at cancer diagnosis and social deprivation score respectively.

We used multiple imputation to deal with missing data on initial cancer treatment objective (2,606 patients) and on depression status (1,081 patients who had a high HADS score at stage one of depression screening but did not undergo a diagnostic interview, mainly because they declined or could not be contacted). The propensity for data to be missing was associated with both the HADS score and with subsequent survival. To attempt to reduce potential bias in our estimates we imputed these data using the substantive model compatible fully conditional specification (SMCFCS) method in order to properly account for interactions and non-linear effects (36). For each cancer we performed 20 imputations, fitted the Cox regression models on each imputed dataset and combined the coefficients using Rubin's rules (see appendix for further details) (37).

We pooled the combined log hazard ratios for each cancer using the inverse variance method in a fixed-effects meta-analysis (as noted above, eleven patients were included in the analysis of two separate cancers but this number is small relative to the cohort size and the impact of this on the pooled result is negligible). We also conducted a sensitivity meta-analysis omitting lung cancer. We did this because patients with lung cancer had: a much worse prognosis than those with the other cancers, as expected (38); a substantially shorter average time interval between cancer diagnosis and depression screening; and the most missing (and therefore imputed) depression data.

All analyses were carried out in R version 3.5.1 using the packages “mfp”, “smcfcs” and “mitools” (35, 36, 39, 40).

RESULTS

We included data from 20,582 patients in the analysis (see Table 1 for a description of their characteristics). 6,099 patients died (from all causes) during the period of follow-up. Most of the deaths (more than 90%) were recorded as being due to cancer (see online appendix for details of the primary causes of death).

[Table 1 about here]

In our primary analysis (Figure 1, panel A) where we considered all-cause mortality, major depression was associated with worse survival in all five cancers (p ranged from 4.0×10^{-8} for patients with lung cancer to 2.2×10^{-2} for patients with prostate cancer). The hazard ratios comparing the survival of patients with a diagnosis of major depression with that of patients who did not have major depression were similar for all five cancers: breast cancer (HR 1.42, 95% CI 1.15, 1.75), colorectal cancer (HR 1.47, 95% CI 1.11, 1.94), gynaecological cancer (HR 1.36, 95% CI 1.08, 1.71), lung cancer (HR 1.39, 95% CI 1.24, 1.56) and prostate cancer (HR 1.76, 95% CI 1.08, 2.85)(see Table 2 for all parameter estimates from these models). There was no evidence of heterogeneity in these estimates (I^2=0%). The estimated hazard ratio pooled for all cancers was 1.41 (95% CI 1.29, 1.54, p<0.001) and was similar when we omitted lung cancer (HR 1.43, 95% CI 1.26, 1.63).

[Figure 1 about here] [Table 2 about here]

The results of a secondary analysis (Figure 1, panel B) which considered only deaths attributed to cancer (censoring follow-up at the time of death for deaths from other causes) were not materially different. For this analysis the estimated hazard ratio pooled for all cancers was 1.38 (95% CI 1.26, 1.51, $p<0.001$).

DISCUSSION

We addressed the question of whether comorbid major depression is associated with worse subsequent survival in a methodologically robust study of a large cohort of patients with breast, colorectal, gynaecological, lung or prostate cancer. We found that the survival of patients with major depression was worse than that of patients who did not have major depression. This association of major depression with worse survival remained even when a number of potential confounders were adjusted for. Notably, the observed association was of a similar magnitude for all of the cancers studied and our findings were not materially different when we omitted lung cancer from the meta-analysis or when we only considered the deaths that were attributed to cancer.

Our estimated hazard ratio of 1.41 might be considered small to medium in magnitude (41). It is interpretable as a 41% increase in the mortality rate throughout follow-up for patients with major depression compared with the mortality rate for those without major depression. The prevalence of major depression in our cohort varied by cancer from five to 13 percent, which is similar to that reported by a systematic review of interview-based studies of cancer outpatients (42). This means that this increase in mortality rate affects a modest but significant number of patients.

The previous literature on the association of depression with worse subsequent survival in people with cancer has been subject to methodological criticism. Whilst two published meta-analyses of the literature (22, 23), concluded that depression does predict worse survival, these conclusions have been disputed (24 , 26, 43). More recent studies have failed

to resolve the dispute as some found depression to be associated with worse survival (1-6, 8, 10-16, 19-21) and others did not (7 , 9 , 17, 18). A recent overview concluded that the inherent methodological limitations prevented any clear conclusions from being drawn (25).

We had the opportunity to address this question in a robust study that was able to address the methodological critiques of the published literature listed in the introduction. The strengths of our study were: (a) it used data on a large representative sample of patients with common cancers attending cancer centres that served geographically defined areas; (b) the diagnosis of major depression was made by diagnostic interview; (c) cancer diagnosis and severity assessment was made by oncologists; (d) there was almost complete follow-up using individually linked national registry data, including data on cause of death; and (e) the analysis addressed missing data and controlled for most potential confounders, including not only age and sex but also social deprivation (determined by the patient's address) and initial cancer severity (determined by recorded treatment objective).

Our study also had limitations however. These were: (a) uncertain generalisability to other populations (such as patients attending different healthcare settings and patients diagnosed with cancer many years ago who no longer attend clinics); (b) incomplete patient participation in the screening programme that determined depression status, although participation was high at 80 percent; (c) missing data on depression status and on initial cancer treatment objective which we addressed with multiple imputation; (d) the assessment for major depression occurring at varying intervals after initial cancer diagnosis, which we allowed for in our analysis; (e) lack of information on the time-course of depression either prior to or subsequent to the depression diagnostic assessment; (f)

availability of data on deaths for a mean of only two years after depression assessment; (g) potentially inadequate adjustment for all confounders. In particular we had to rely on initial treatment objective as a measure of cancer severity. We were also unable to control for other medical comorbidities that may have affected survival, although almost all patient deaths were attributed to cancer and the findings were similar when we considered only deaths from cancer. In summary, despite its limitations, this study was able to address most of the limitations of previous research on the topic and consequently provides strong support for the hypothesised association between major depression and worse subsequent survival of patients with common cancers.

Why might there be an association between major depression and subsequent survival? One clinically important possible explanation is that depression has a negative *causal* influence on cancer prognosis, for example by reducing patients' adherence to anticancer treatment or by directly influencing the progression of their cancer (21, 44, 45). Whilst this explanation is a tantalising one, with potentially important implications for practice, it must be regarded with some caution. In particular, we should note that there is currently little good evidence that treating comorbid major depression in patients with cancer improves their survival (46).

Another possible explanation is that people who are dying from cancer are more likely to be depressed as a result and the association reflects reverse causation; that is dying from cancer causes depression. However, this is an unlikely explanation of the findings of this, and other studies, in which there was a substantial interval between the diagnosis of major depression and subsequent death.

Yet another possible explanation is that there are common factors that lead both to the development of major depression and to worse survival. Such factors might include biological processes such as inflammation, immunological activity and the effect of stress on physiological systems, as well as behavioural factors known to be risk factors for both depression and cancer such as low physical inactivity and high alcohol intake (47).

In conclusion, this study of a large prospectively assessed cohort of cancer patients adds weight to the accumulating but disputed evidence that major depression is associated with the worse subsequent survival of patients with common cancers. The mechanisms underlying this association remain unknown and clearly require further investigation. Importantly, we do not currently have good evidence that treating comorbid depression in patients with cancer lengthens their life. However, we do have evidence that treating depression in patients with cancer improves the quality of their lives (48). Whilst more research into the effect of treating depression on survival is needed, we already have sufficient evidence to justify the identification and active treatment of depression in people suffering from cancer.

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Table 1. Demographics, depression status and survival of patients included in the analysis.

	Breast cancer	Colorectal cancer	Gynaecological cancer	Lung cancer	Prostate cancer
Total	8679[a]	2807[a]	3052[a]	4476[a]	1579[a]
Sex					
Female	8679 (100%)	1191 (42%)	3052 (100%)	2113 (47%)	0 (0%)
Male	0 (0%)	1616 (58%)	0 (0%)	2363 (53%)	1579 (100%)
Age at cancer diagnosis [median years, IQR]	58 [49, 66]	65 [58, 72]	61 [51, 69]	68 [61, 74]	67 [62, 72]
SIMD score quintile [b]					
1	1488 (17%)	521 (19%)	648 (21%)	1507 (34%)	271 (17%)
2	1591 (18%)	555 (20%)	657 (22%)	1085 (24%)	258 (16%)
3	1584 (18%)	504 (18%)	580 (19%)	714 (16%)	266 (17%)
4	1669 (19%)	498 (18%)	572 (19%)	571 (13%)	345 (22%)
5	2346 (27%)	728 (26%)	595 (19%)	599 (13%)	439 (28%)
Missing	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Initial cancer treatment objective					
Curative	6702 (77%)	1998 (71%)	2093 (69%)	1145 (26%)	660 (42%)
Palliative	479 (6%)	572 (20%)	552 (18%)	3132 (70%)	653 (41%)
Missing	1498 (17%)	237 (8%)	407 (13%)	199 (4%)	266 (17%)
Time interval between cancer diagnosis & depression screening [median years, IQR]	2.0 [0.4, 5.2]	1.0 [0.3, 2.5]	1.0 [0.4, 3.0]	0.3 [0.1, 0.9]	2.0 [0.8, 4.5]
Major depression status					
Pre-imputation					
No major depression	7699 (89%)	2547 (91%)	2654 (87%)	3613 (81%)	1456 (92%)
Major depression	665 (8%)	140 (5%)	273 (9%)	412 (9%)	63 (4%)
Depression status missing	315 (4%)	120 (4%)	125 (4%)	451 (10%)	60 (4%)
Post-imputation [c]					
No major depression	91%	94%	89%	87%	95%
Major depression	9%	6%	11%	13%	5%
Time from depression screening to death or censoring [median years, IQR]	2.3 [1.6, 3.0]	1.8 [1.2, 2.7]	1.9 [1.2, 2.7]	0.8 [0.4, 1.5]	2.2 [1.7, 3.1]
Died during study period	1036 (12%)	876 (31%)	865 (28%)	3029 (68%)	299 (19%)
Died of cancer during study period	912 (11%)	813 (29%)	816 (27%)	2799 (63%)	257 (16%)

Data are n (%) unless stated otherwise. [a]11 patients are included in this table twice because they were diagnosed with more than one primary cancer on the same day: 3 had breast & gynaecological cancers, 3 had colorectal & gynaecological cancers, 2 had breast & lung cancers, 1 had breast & colorectal cancers, 1 had colorectal & lung cancers, 1 had colorectal & prostate cancers. [b] Scottish Index of Multiple Deprivation quintile score: 1=most deprived, 5=least deprived. [c] mean after 20 imputations.

Table 2: Parameter estimates from the primary analysis models

Parameter	Hazard Ratio	95% CI	p-value
Breast cancer			
Major depression diagnosis	**1.42**	**1.15, 1.75**	**0.001**
Years between cancer diagnosis and depression screening[a]	0.96	0.46, 1.99	0.905
Age at cancer diagnosis[b]	0.28	0.19, 0.41	<0.001
Age at cancer diagnosis[b] squared	1.13	1.10, 1.17	<0.001
SIMD[b]	1.09	1.05, 1.14	<0.001
Therapy intent (palliative v curative)	7.80	6.57, 9.26	<0.001
Years between cancer diagnosis and depression screening[a] × Age at cancer diagnosis[b]	1.17	0.91, 1.52	0.218
Years between cancer diagnosis and depression screening[a] × Age at cancer diagnosis[b] squared	0.98	0.96, 1.01	0.157
Years between cancer diagnosis and depression screening[a] × SIMD[b]	1.02	0.99, 1.05	0.123
Years between cancer diagnosis and depression screening[a] × therapy intent (palliative v curative)	0.74	0.65, 0.84	<0.001
Colorectal cancer			
Major depression diagnosis	**1.47**	**1.11, 1.94**	**0.007**
Years between cancer diagnosis and depression screening[c]	1.06	0.88, 1.27	0.553
Age at cancer diagnosis[b]	1.14	1.06, 1.24	<0.001
Sex (male v female)	1.13	0.98, 1.29	0.087
SIMD[b]	1.02	0.97, 1.08	0.378
Therapy intent (palliative v curative)	7.39	6.10, 8.94	<0.001
Years between cancer diagnosis and depression screening[c] × Age at cancer diagnosis[b]	1.00	0.98, 1.03	0.793
Years between cancer diagnosis and depression screening[c] × SIMD[b]	1.01	0.99, 1.03	0.444
Years between cancer diagnosis and depression screening[c] × therapy intent (palliative v curative)	0.79	0.71, 0.87	<0.001
Gynaecological cancer			
Major depression diagnosis	**1.36**	**1.08, 1.71**	**0.010**
Years between cancer diagnosis and depression screening[d]	1.00	0.95, 1.06	0.896
Years between cancer diagnosis and depression screening[e]	1.00	0.98, 1.02	0.997
Age at cancer diagnosis[b]	1.18	1.11, 1.26	<0.001
SIMD[b]	1.04	0.99, 1.09	0.148
Therapy intent (palliative v curative)	5.03	4.14, 6.11	<0.001
Years between cancer diagnosis and depression screening[d] × Age at cancer diagnosis[b]	1.00	0.99, 1.01	0.794
Years between cancer diagnosis and depression screening[e] × Age at cancer diagnosis[b]	1.00	1.00, 1.00	0.761
Years between cancer diagnosis and depression screening[d] × SIMD[b]	1.00	0.99, 1.01	0.487

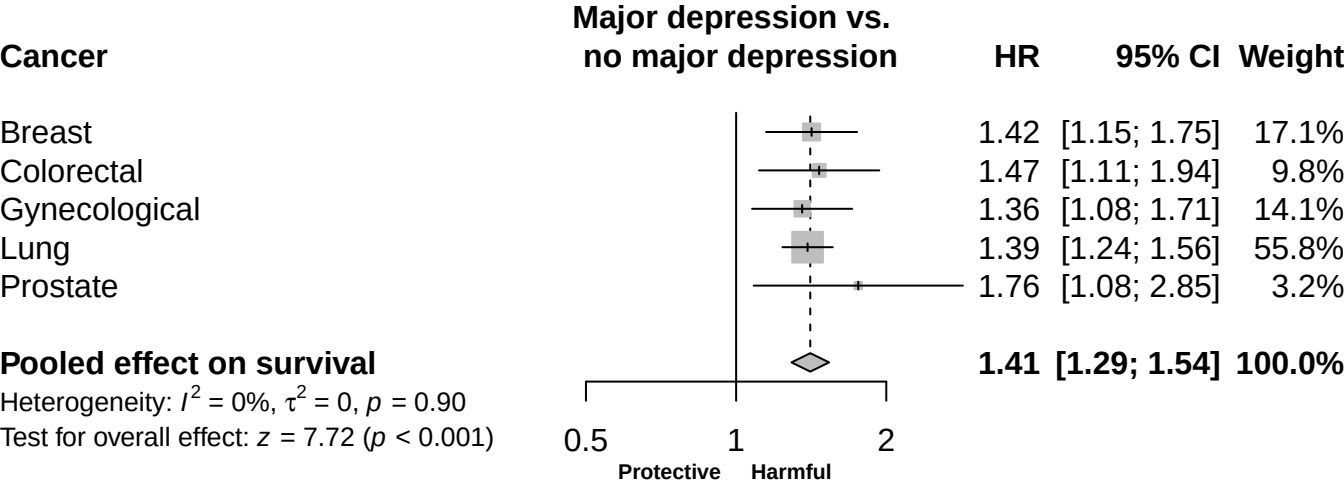
Years between cancer diagnosis and depression screening[e] × SIMD[b]	1.00	1.00, 1.00	0.407
Years between cancer diagnosis and depression screening[d] × therapy intent (palliative v curative)	0.96	0.88, 1.03	0.252
Years between cancer diagnosis and depression screening[e] × therapy intent (palliative v curative)	1.01	0.98, 1.05	0.425
Lung cancer			
Major depression diagnosis	**1.39**	**1.24, 1.56**	**<0.001**
Years between cancer diagnosis and depression screening[a]	0.81	0.62, 1.06	0.133
Age at cancer diagnosis[b]	1.09	1.04, 1.15	<0.001
Sex (male v female)	1.13	1.05, 1.21	0.001
SIMD[b]	1.02	1.00, 1.05	0.075
Therapy intent (palliative v curative)	2.16	1.93, 2.41	<0.001
Years between cancer diagnosis and depression screening[a] × Age at cancer diagnosis[b]	1.03	1.00, 1.08	0.078
Years between cancer diagnosis and depression screening[a] × SIMD[b]	1.00	0.98, 1.02	0.819
Years between cancer diagnosis and depression screening[a] × therapy intent (palliative v curative)	0.69	0.63, 0.75	<0.001
Prostate cancer			
Major depression diagnosis	**1.76**	**1.08, 2.85**	**0.022**
Years between cancer diagnosis and depression screening[c]	0.76	0.47, 1.22	0.254
Age at cancer diagnosis[b] cubed	0.93	0.89, 0.97	0.001
Age at cancer diagnosis[b] cubed × $\log_e$(age at cancer diagnosis[b])	1.03	1.01, 1.05	<0.001
SIMD[b]	1.17	1.06, 1.30	0.003
Therapy intent (palliative v curative)	3.11	2.01, 4.82	<0.001
Years between cancer diagnosis and depression screening[c] × age at cancer diagnosis[b] cubed	1.01	1.00, 1.02	0.080
Years between cancer diagnosis and depression screening[c] × age at cancer diagnosis[b] cubed × $\log_e$(age at cancer diagnosis[b])	1.01	1.00, 1.02	0.080
Years between cancer diagnosis and depression screening[c] × SIMD[b]	0.98	0.96, 1.00	0.027
Years between cancer diagnosis and depression screening[c] × therapy intent (palliative v curative)	0.98	0.90, 1.06	0.551

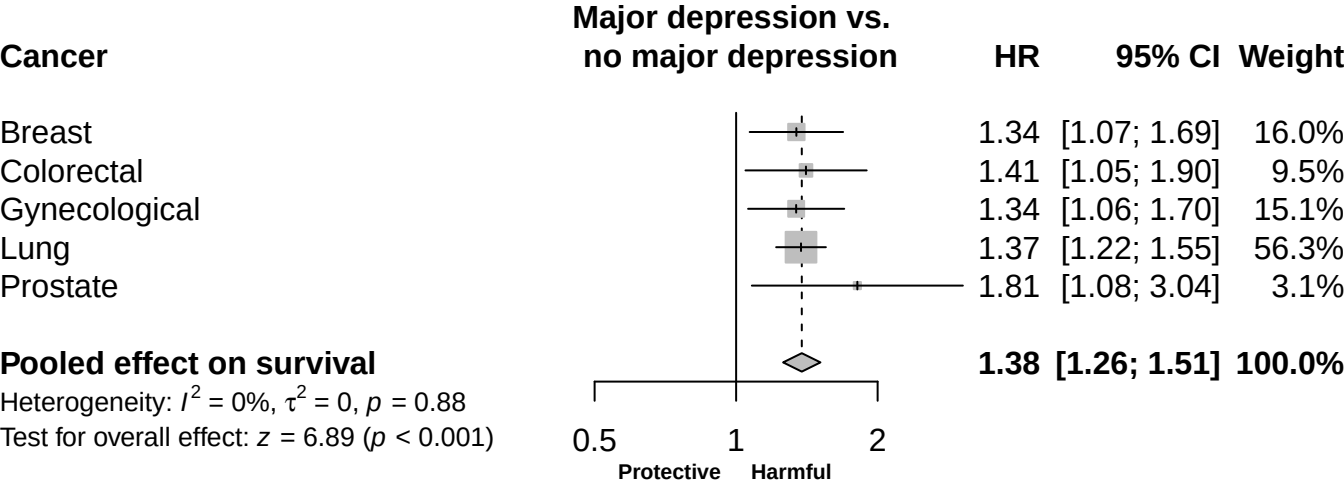
The hazard ratios of primary importance (shown in bold) relate to the comparison between those patients with and without major depression. The hazard ratios for other variables and interactions between pairs of such variables are for (sometimes) transformed covariates that make up the fractional polynomial model used for covariate adjustment. The transformations are [a]$\log_e$ (X+0.1); [b]X/10; [c] X+0.1; [d](X+0.1)^2 and [e]([X+0.1]^2)×$\log_e$[X+0.1].

Figure 1. Association of major depression with survival: estimated hazard ratios (95% confidence intervals)

Panel A: Deaths from all-causes

Panel B: Deaths from cancer


Cancer
Major depression vs. no major depression
HR
95% CI
Weight
Breast
1.42 [1.15; 1.75] 17.1%
Colorectal
1.47 [1.11; 1.94] 9.8%
Gynecological
1.36 [1.08; 1.71] 14.1%
Lung
1.39 [1.24; 1.56] 55.8%
Prostate
1.76 [1.08; 2.85] 3.2%
Pooled effect on survival
1.41 [1.29; 1.54] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.90
Test for overall effect: z = 7.72 (p < 0.001)
0.5
1
2
Protective
Harmful


Cancer
Major depression vs. no major depression
HR
95% CI
Weight
Breast
1.34
[1.07; 1.69]
16.0%
Colorectal
1.41
[1.05; 1.90]
9.5%
Gynecological
1.34
[1.06; 1.70]
15.1%
Lung
1.37
[1.22; 1.55]
56.3%
Prostate
1.81
[1.08; 3.04]
3.1%
Pooled effect on survival
1.38
[1.26; 1.51]
100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88
Test for overall effect: z = 6.89 (p < 0.001)
0.5
1
2
Protective
Harmful

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Major depression and survival in people with cancer.

Social deprivation scores

Social deprivation was calculated using the Scottish Index of Multiple Deprivation (SIMD) 2009. The SIMD divides Scotland into 6,505 small geographical areas or divisions (data zones) and ranks these from the most deprived (ranked 1) to the least deprived (ranked 6,505).

Reference
Office of the Chief Statistician. Scottish Index of Multiple Deprivation 2009 Technical Report: Scottish Government; 2011.

Cancer groupings

Grouping	ICD-10 codes*	Diagnoses
Breast	C500	Malignant neoplasm of nipple and areola
	C501	Malignant neoplasm of central portion of breast
	C502	Malignant neoplasm of upper-inner quadrant of breast
	C503	Malignant neoplasm of lower-inner quadrant of breast
	C504	Malignant neoplasm of upper-outer quadrant of breast
	C505	Malignant neoplasm of lower-outer quadrant of breast
	C506	Malignant neoplasm of axillary tail of breast
	C508	Malignant neoplasm, overlapping lesion of breast
	C509	Malignant neoplasm of breast, unspecified
Lung	C340	Malignant neoplasm of main bronchus
	C341	Malignant neoplasm of upper lobe, bronchus or lung
	C342	Malignant neoplasm of middle lobe, bronchus or lung
	C343	Malignant neoplasm of lower lobe, bronchus or lung
	C348	Malignant neoplasm of overlap les of bronchus & lung
	C349	Malignant neoplasm of bronchus or lung, unspecified
	C450	Mesothelioma of pleura
	C451	Mesothelioma of peritoneum
	C452	Mesothelioma of pericardium
	C457	Mesothelioma of other sites
	C459	Mesothelioma, unspecified
Colorectal	C182	Malignant neoplasm of ascending colon
	C183	Malignant neoplasm of hepatic flexure
	C184	Malignant neoplasm of transverse colon
	C185	Malignant neoplasm of splenic flexure
	C186	Malignant neoplasm of descending colon
	C187	Malignant neoplasm of sigmoid colon
	C188	Malignant neoplasm overlapping lesion of colon
	C189	Malignant neoplasm of colon, unspecified
	C19X	Malignant neoplasm of rectosigmoid junction
	C20X	Malignant neoplasm of rectum
Gynaecological	C481	Malignant neoplasm of specified parts of peritoneum
	C482	Malignant neoplasm of peritoneum, unspecified
	C510	Malignant neoplasm of labium majus
	C511	Malignant neoplasm of labium minus
	C512	Malignant neoplasm of clitoris
	C518	Malignant neoplasm of overlapping lesion of vulva
	C519	Malignant neoplasm of vulva, unspecified
	C52X	Malignant neoplasm of vagina
	C530	Malignant neoplasm of endocervix
	C531	Malignant neoplasm of exocervix
	C538	Malignant neoplasm, overlapping lesion of cervix uteri
	C539	Malignant neoplasm of cervix uteri, unspecified
	C540	Malignant neoplasm of isthmus uteri

	C541	Malignant neoplasm of endometrium
	C542	Malignant neoplasm of myometrium
	C543	Malignant neoplasm of fundus uteri
	C548	Malignant neoplasm overlapping lesion of corpus uteri
	C549	Malignant neoplasm of corpus uteri, unspecified
	C55X	Malignant neoplasm of uterus, part unspecified
	C56X	Malignant neoplasm of ovary
	C570	Malignant neoplasm of fallopian tube
	C571	Malignant neoplasm of broad ligament
	C572	Malignant neoplasm of round ligament
	C573	Malignant neoplasm of parametrium
	C574	Malignant neoplasm of uterine adnexa, unspecified
	C577	Malignant neoplasm of other specified female genital organs
	C578	Malignant neoplasm, overlapping lesion female genital organs
	C579	Malignant neoplasm of female genital organ, unspecified
	C763	Malignant neoplasm of pelvis
Prostate	C61X	Malignant neoplasm of prostate

*International Classification of Diseases 10th edition

Transformation of confounders

To more precisely control for confounding, we transformed three adjustment variables with continuous values (interval between cancer diagnosis and depression screening, age at cancer diagnosis and social deprivation score) separately in each cancer group so that their relationships with the outcome in the Cox regression models (the log hazards of death) were optimally specified.

We searched for sets of fractional polynomial terms that would do this on the complete case data, but there is some evidence that this may not find the correct terms even if the data are missing at random (Morris et al 2015). However, the full model specification, including the polynomial terms, is necessary for the SMCFCS imputation (see below); as well we need the correctly imputed datasets to find the optimal polynomial terms. Pragmatically, we restricted the identification of the polynomials to the complete cases since it is likely that the SMCFCS imputation will be better specified with some possibly sub-optimal polynomials rather than none.

Full model specification

Our full Cox proportional model specification was as follows for subject *i* at follow-up time *t*.

$$h_i(t) = h_0(\mathrm{t}) * \exp\Big(\beta_1 x_{MD_i} + \beta_2 x_{sex_i} + \beta_3 x_{ther_i} + \boldsymbol{\gamma_1^T g_1}(\boldsymbol{x_{CD_i}}) + \boldsymbol{\gamma_2^T g_2}(\boldsymbol{x_{age_i}}) + \boldsymbol{\gamma_3^T g_3}(\boldsymbol{x_{SIMD_i}}) + \boldsymbol{\delta_1^T g_1}(\boldsymbol{x_{CD_i}}) * x_{ther_i} + \boldsymbol{\delta_2^T g_1}(\boldsymbol{x_{CD_i}}) * \boldsymbol{g_2}(\boldsymbol{x_{age_i}}) + \boldsymbol{\delta_3^T g_1}(\boldsymbol{x_{CD_i}}) * \boldsymbol{g_3}(\boldsymbol{x_{SIMD_i}})\Big)$$

Here x_{MD_i} is a binary covariate indicating major depression, x_{sex_i} is a binary covariate indicating sex, x_{ther_i} is a binary covariate indicating whether treatment was curative or palliative, x_{age_i} is age at cancer diagnosis, x_{SIMD_i} is social deprivation score and x_{CD_i} is the time interval between cancer diagnosis and depression screening. $\boldsymbol{\gamma^T}$ and $\boldsymbol{\delta^T}$ are vectors of regression coefficients and each function $\boldsymbol{g}$ is a set of fractional polynomial transformations for the variable indicated. The coefficient of main interest is β_1, the effect on survival of comparing major depression (MD) with no depression. We believe this specification controls confounding to the best of our ability given the size of the dataset, the data available to us and the differing time points at which they were collected.

Handling of missing data

We imputed missing data using the substantive model compatible fully conditional specification (SMCFCS) method, an extension of the more common fully conditional specification (FCS). This method imputes missing data across multiple covariates using an imputation model that is fully compatible with our substantive (intended) analysis model. For our study this may be more appropriate than FCS because we have specified non-linear and interaction effects in our regression model, which cannot be completely specified in FCS

imputation. The imputation models were specified with the substantive model variables plus extra variables that, over and above those in the substantive model both (1) predict the values of the missing data and (2) predict the probability of these data being missing. We determined this using logistic regression on the complete data where the outcome is the variable in question (1) or a 0/1 indicator of its missingness (2). We added to the imputation model those variables that were statistically significant at the 5% level for both. We included HADS anxiety score, HADS depression score, and tumour grade and/or clinical stage marker (as available) for each cancer type where there was evidence that these were associated with both survival and missingness. We did not include any of these extra variables in the substantive models for survival since we wanted to use a common set of covariates throughout in order to make the cancer-specific results comparable.

References

Bartlett J. SMCFCS: Multiple Imputation of Covariates by Substantive Model Compatible Fully Conditional Specification. https://CRAN.R-project.org/package=smcfcs2016.

Morris TP, White IR, Carpenter JR, Stanworth SJ, Royston P. Combining fractional polynomial model building with multiple imputation. Stat Med. 2015 Nov 10; 34(25): 3298–3317.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley; 1987.

Primary causes of death of patients included in the analysis.

Total number of deaths	**6099**
Cancer	**5581 (91.5%)**
Lung	2794
Breast	842
Gynaecological	790
Colorectal	691
Prostate	226
Other cancer	238
Circulatory	**226 (3.7%)**
Ischaemic heart disease (including acute myocardial infarction)	113
Aortic aneurysm	12
Cardiac arrhythmia	8
Cerebrovascular disease	62
Heart failure	6
Other	25
Respiratory	**95 (1.6%)**
Chronic obstructive airways disease	56
Respiratory infection	27
Interstitial pulmonary disease	6
Other	6
Gastro-intestinal	**47 (0.8%)**
Infection (non-respiratory)	**24 (3.4%)**
Injury, poisoning and external causes	**21 (0.3%)**
Fall	10
Fracture	3
Poisoning (accidental)	4
Road traffic accident	1
Drowning (undetermined intent)	1
Shooting (intentional self-harm)	1
Exposure to excessive cold	1
Neurological	**15 (0.2%)**
Renal	**13 (0.2%)**
Haematological	**12 (0.2%)**
Hepatic, pancreatic or biliary	**12 (0.2%)**
Endocrine, nutritional or metabolic	**9 (0.1%)**
Mental and behavioural	**8 (0.1%)**
Dementia	7
Alcohol dependence	1
Other	**4 (0.1%)**
Unknown	**32 (0.5%)**