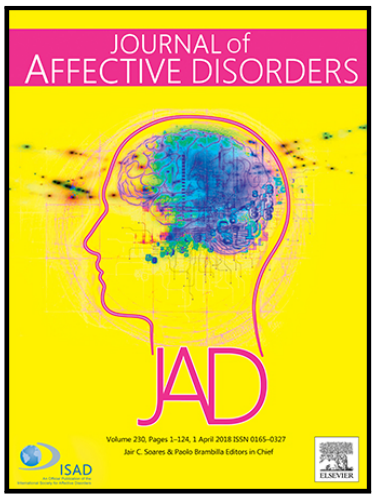

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Wentian Lu , Hynek Pikhart , Anne Peasey , Ruzena Kubinova , Alexandra Pitman , Martin Bobak

PII: S0165-0327(20)32467-8
DOI: https://doi.org/10.1016/j.jad.2020.06.070
Reference: JAD 12192

To appear in: *Journal of Affective Disorders*

Received date: 16 April 2020
Revised date: 22 May 2020
Accepted date: 23 June 2020

Please cite this article as: Wentian Lu , Hynek Pikhart , Anne Peasey , Ruzena Kubinova , Alexandra Pitman , Martin Bobak , Risk of depressive symptoms before and after the first hospitalisation for cancer: evidence from a 16-year cohort study in the Czech Republic, *Journal of Affective Disorders* (2020), doi: https://doi.org/10.1016/j.jad.2020.06.070

Highlights

- The risk of depressive symptoms starts increasing five years prior to the first hospitalisation for cancer.
- This may be due to pre-diagnosis neuropsychiatric or biopsychosocial processes.
- This excess risk continued for up to 7.5 years after hospitalisation.
- Cancer is an independent risk factor for depressive symptoms.
- Early psychological assessment for patients diagnosed with cancer is needed.

Research paper

Risk of depressive symptoms before and after the first hospitalisation for cancer: evidence from a 16-year cohort study in the Czech Republic

Wentian Lu[1*], Hynek Pikhart[1], Anne Peasey[1], Ruzena Kubinova[2], Alexandra Pitman[3,4], Martin Bobak[1]

[1]Research Department of Epidemiology and Public Health, University College London, London, United Kingdom.

[2]Centre for Environmental Health Monitoring, National Institute of Public Health, Prague, Czech Republic

[3]UCL Division of Psychiatry, University College London, London, United Kingdom

[4]Camden and Islington NHS Foundation Trust, London, United Kingdom

[*]Corresponding author. Central and Eastern European Health Research Group, Research Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 7HB, United Kingdom. Email: wentian.lu.14@ucl.ac.uk

Abstract

Background Whether depression risk starts increasing before cancer diagnosis, and whether cancer is an independent risk factor for depression, remain unclear. We aimed to quantify the risk of

depressive symptoms before and after the first hospitalisation for cancer (as a proxy for cancer diagnosis) among patients with cancer.

Methods We linked cohort data with national hospitalisation records in the Czech Republic. We followed 1056 incident cancer cases for up to 15 years before and 15 years after the first hospitalisation for cancer. Depressive symptoms were measured using the Centre for Epidemiological Studies-Depression (CES-D) scale. We used multilevel ordered logistic regression to assess the relationship between follow-up years (pre- and post-hospitalisation) and depressive symptoms among incident cancer cases. Propensity Score Matching was employed to match each case with a cancer-free control, to test the independent effect of cancer on depressive symptoms over time.

Results Per one year of follow-up (whether pre- or post- hospitalisation) was associated with 1.07 (1.05–1.10) times more likely to have high severity of depressive symptoms among patients with cancer. The probability of having high severity of depressive symptoms increased from 25% at five years before hospitalisation to 33% at 7.5 years after hospitalisation. In parallel analyses among matched cancer-free controls, the risk of depressive symptoms had no significant changes during follow-up.

Limitations Stratified analyses based on cancer types and stages of malignancy were infeasible.

Conclusions The excess risk of depressive symptoms was apparent five years prior to the first hospitalisation for cancer. Using cancer-free matched controls, we confirmed that cancer was an independent predictor of depressive symptoms.

Key words: Cancer, depression, hospitalisation, Czech Republic

Introduction

There is evidence that the prevalence of mental disorders among patients with cancer is higher than that among the general population, and that survival rates among patients with cancer and co-morbid anxiety or depression are significantly lower than those for the general population (Batty et

al., 2017; Kisely et al., 2013; Pitman et al., 2018; Zhu et al., 2017). Clinically, depression in patients with cancer tends to be under-recognised, with depressive symptoms such as anorexia, weight loss, fatigue and insomnia often attributed to the somatic effects of cancer rather than depression (Lloyd-Williams, 2000). The World Health Organization (WHO) suggests that the risk of mental disorders in patients with cancers is routinely overlooked and should be better understood (World Health Organization, 2017).

Previous work has shown an excess risk of mental disorders (Dalton et al., 2009; Lu et al., 2016; Mallet et al., 2018; Suppli et al., 2014), and of suicide (Henson et al., 2018), after cancer diagnosis, with risks more marked in cancers with poor prognosis. For example, a population-based study in England indicated that patients with mesothelioma had the highest suicide risk among all patients after cancer diagnosis (Henson et al., 2018). A Danish registry-based study found a general pattern of an increased risk of depression in the first year after cancer diagnosis, with decreasing but still significant excess risk in subsequent years for most types of cancer (Dalton et al., 2009). A recent study reported that the risk of mental disorders after cancer diagnosis in the US was significantly higher among patients with a prior history of mental disorders compared with those without psychiatric histories (Mallet et al., 2018). A Swedish registry-based study suggested that risk of mental disorders both before and after cancer diagnosis increased to a greater extent among patients with cancers of poor prognosis (i.e. lung and colorectal cancers) compared with patients with other cancers (i.e. breast cancer) (Lu et al., 2016). Generally risk of depression and anxiety applies at all points in the cancer trajectory, whether in curative or palliative treatment (Burgess et al., 2005; Fallowfield et al., 1990; Mitchell et al., 2011).

The onset of depression in relation to cancer diagnosis requires careful study, as it provides clues as to the aetiology of depression in the cancer context, including the putative effect of cancer-related inflammation on mental disorders (Messay et al., 2012). Previous work has shown that the excess risk of depression is apparent in the year before cancer diagnosis, corresponding with the period of cancer diagnostic workup (Lu et al., 2016). This suggests that direct neuropsychiatric effects may be involved even before an awareness of cancer diagnosis, at which point predominant explanations for depression or anxiety involve biopsychosocial processes (Pitman et al., 2018). The majority of work describing the association between cancer and depression derives from high-income countries, including the United States (US), England, Denmark, Australia and Sweden (Batty et al., 2017;

Burgess et al., 2005; Dalton et al., 2009; Fallowfield et al., 1990; Henson et al., 2018; Kisely et al., 2013; Lu et al., 2016; Suppli et al., 2014; Zhu et al., 2017). However, the generalisability of these findings to more recent years or among other populations is questionable.

To address the research gap, our 16-year longitudinal study aimed to assess the risk of depressive symptoms before and after the first hospitalisation for cancer (as a proxy for cancer diagnosis) in the Czech Republic. We investigated whether and when depressive symptoms occur before the first hospitalisation for cancer. We also used matched controls to evaluate the independent effect of cancer on depressive symptoms.

Methods

Data

Data were from the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study – Czech cohort, a prospective cohort study of a representative sample of 8857 individuals (response rate: 82%) aged 45–69 years at baseline in the Czech Republic (Peasey et al., 2006). Random samples stratified by gender and five-year age groups were selected from population registers. Written informed consent was obtained from all participants. The study received ethical approval from the ethics committee at University College London, UK (99/0081). We used data from baseline wave (2002–2005), wave 2 (2006–2008) and follow-up postal surveys in 2009, 2012, 2013, 2016 and 2017. The information on cancer diagnosis was obtained from the national hospitalisation records (2001–2017) of all participants, which contain information on, for example, dates of admission and discharge, ICD codes of primary, operation and other diagnosis, and whether being hospitalised for the first time for each diagnosis. We included 1056 (473 women) incident cancer cases (2003–2017) (Supplementary Figure S1), who were matched with population-based controls (matching ratio: 1:1) using Propensity Score Matching (PSM) (Rosenbaum and Rubin, 1983). Figure 1 illustrates the detailed procedure of sample selection.

Variables

Depressive symptoms

Depressive symptoms were measured using the Centre for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977), and used as a time-varying outcome. The format of the CES-D scale used at

baseline (CES-D-20; original 20-item measure, 4-category response) differed at Wave 2 (2006–2008), the 2009 postal surveys (CES-D-10; 10-item measure, Boston scale; 2-category response), and the 2012–2017 postal surveys (CES-D-10; 10-item measure, Andresen scale; 4-category response) (Kohout et al., 1993; Mohebbi et al., 2018). Cronbach's alpha values were all above 0.70, indicating acceptable reliability (Heale and Twycross, 2015). To maintain the integrity of the scale, up to four, one and one missing items, respectively, were allowed for calculating the sum scores based on original, Boston and Andresen scales. We substituted the mean values for missing items then summed all items (Kohout et al., 1993). For comparability of results over time, we organised sum scores into tertiles based on the entire sample size. High severity of depressive symptoms was defined as the highest tertile of CES-D scores.

Incident cancer cases

We identified incident cancer cases in cancer-free individuals at baseline, measured as the first ever hospitalisation for any cancer (ICD-10: C00–C97) recorded on the national hospitalisation register during follow-up (as a proxy for cancer diagnosis), on a date later than the dates of baseline interview. Supplementary Figure S1 and Figure S2 illustrate the numbers of incident cancer cases (2003–2017), and the numbers of each type of cancer, respectively.

Follow-up years

We calculated each participant's number of years of follow-up using the date of depressive symptom measurement in each wave of data collection minus the date of the first hospitalisation for any cancer. The date of the first cancer hospitalisation (a proxy for diagnostic year) was set at zero. Negative and positive values designated pre-hospitalised (-15.0 to -0.1) and post-hospitalised (0.1 to 15.0) years. Supplementary Figure S3 shows a normal distribution of follow-up years.

Confounders

We selected confounders based on previous evidence (Batty et al., 2017; Bortolato et al., 2017; Burgess et al., 2005; World Health Organization, 2017): baseline gender; age; marital status; education; smoking; alcohol use; fruit consumption; vegetable consumption; weekly hours of physical activity; diagnosed cardiovascular disease (CVD), diabetes and chronic respiratory diseases; and Body Mass Index.

Statistical methods

We conducted univariate analysis of baseline relationships between confounders and depressive symptoms. We used multilevel ordered logistic regression to assess the longitudinal relationship between follow-up years and depressive symptoms among incident cancer cases, allowing for random intercepts. Multilevel modelling can handle attrition and wave non-response (which allows us to include incident cancer cases who died during the post-diagnostic period), unequal time spaces, and the inclusion of time-varying and between-individual covariates that are either continuous or discrete measures (Curran et al., 2010).

A time-cohort model (repeat follow-up year model controlling for baseline age group) was estimated with full adjustment. We included year as a linear, quadratic, and a cubic term, to detect non-linear effects. We predicted the overall average probability of being in the highest tertile of CES-D scores in each year, considering both fixed and random effects based on this model. We fitted curves using kernel-weighted local polynomial smoothing to explore non-linear effects of follow-up years, allowing the data to "speak for themselves" by fitting the response to a polynomial form of the regressor via locally weighted least squares (Gasser and Müller, 1979). We produced curves within a thirty-year range (15 pre-hospitalised years and 15 post-hospitalised years).

To test the independent effect of cancer on depressive symptoms over time, we used PSM to match each incident cancer case with a cancer-free participant based on similar propensity scores obtained from a logistic regression model adjusting for all aforementioned confounders (Rosenbaum and Rubin, 1983). The nearest neighbour matching was used (calliper bound=0.04, mean bias=1.8%) (Rubin, 1973). As a result, the observed baseline characteristics became very similar between incident cancer cases and those of cancer-free controls (Supplementary Table S1). In order to compare risk of depressive symptoms before and after a hypothetical non-cancer diagnosis date in cancer-free controls, each control was allocated a non-exposure data, which was the date of the first cancer hospitalisation of his or her matched treated participant. We assessed the unadjusted relationships between follow-up years and depressive symptoms in both groups. We also predicted the overall probabilities of being in the highest tertile of CES-D scores after year=0 in both groups.

We conducted a *post hoc* analysis to confirm whether the risk of depressive symptoms did indeed increase in the five years prior to the first cancer hospitalisation. For this, we applied fully-adjusted piecewise regression with three segments separated by two "knots" (at year -5 and 0) (Ryan and Porth, 2007), to quantify the slope changes of the probability of being in the highest tertile of CES-D scores. Three independent variables were included in piecewise regression, reflecting three segments: '6–15 years before hospitalisation' '1–4 years before hospitalisation' and '1–15 years after hospitalisation'.

Sensitivity analyses

We compared baseline characteristics between the analysed (N=1056) and excluded incident cancer cases (N=181), to explore whether missing data were likely to bias findings. We also employed another harmonisation strategy – converting the CES-D sum scores into z-scores (mean [S.D.] =0 [1]) and re-run the fully-adjusted model using the continuous z-scores, which helps predict the overall changes of depressive symptoms over time, and make further comparison with other samples.

All analyses were performed using Stata SE 15 (StataCorp, 2017), with a p-value threshold of <0.05 for statistical significance.

Results

Baseline sample characteristics

Table 1 presents baseline sample characteristics among incident cancer cases. Over half (55%) this sample were men. Participants were mainly aged between 50 and 69 years, married or cohabiting, and had vocational or secondary education at baseline. Around 30% of participants were current smokers. Around 15% of participants consumed alcohol more than 5 times per week. Participants consumed a mean of 3.48 (S.D. = 3.52) and 3.13 (S.D. = 2.25) portions of fruit and vegetable per day, respectively. The mean hours spent on physical activity per week were 13.49, but with wide variation (S.D. = 12.50). The majority of the participants were diagnosed with diabetes, CVD, or chronic respiratory diseases, and 45% and 34% were pre-obese and obese, respectively.

Our sample contained more than twenty types of cancer. The sample sizes of different types of cancer were diverse (Supplementary Figure S2). For example, there were 102, 118 and 141 incident cases of lung (C33, C34), breast (C50) and prostate (C61) cancers, respectively; whereas there were only 3, 23, 18 incident cases of oesophagus (C15), stomach (C16) and brain cancers, respectively.

Supplementary Table S2 shows the univariate relationships between confounders and depressive symptoms among incident cancer cases. Participants who were female, unmarried, diagnosed with cardiovascular or chronic respiratory diseases, or had vocational or primary education or below, were more likely to have depressive symptoms at baseline than those who were male, married, diagnosed without cardiovascular or chronic respiratory diseases, or who had a university degree. However, compared with non-alcohol consumers, alcohol consumers were less likely to have depressive symptoms at baseline.

Association between follow-up years and depressive symptoms

Table 2 shows the results of our fully-adjusted model describing the association between follow-up years and depressive symptoms among incident cancer cases. After controlling for covariates, years of follow-up were positively associated with severity of depressive symptoms. For each year of observation, patients with cancer were 1.07 (95%CI: 1.05–1.10) times more likely to be in the highest tertile of CES-D scores (whether pre- or post-diagnosis). We also found significant quadratic and cubic effects of year, suggesting a non-linear effect of year on depressive symptoms.

Figure 2 illustrates the predicted probability of being in the highest tertile of CES-D scores during follow-up among incident cancer cases, with year=0 as a proxy for cancer diagnosis. Overall, although the change in probability between two subsequent years was small, the cubic shape of the curve was statistically significant (Table 2, 0.9997, 95%CI: 0.9994–0.9999). The probability was around 25% at five years before hospitalisation, and increased to around 32% at five years after hospitalisation. Thereafter, the probability continued increasing at a slower rate until its highest point (around 33%) at 7.5 years after hospitalisation. The predicted values prior to 10 years pre-hospitalisation or after 10 years post-hospitalisation were dispersed, due to the small sample size for those followed-up for more than 10 years before or after hospitalisation (Supplementary Figure S3).

Table 4 Changes of the probability of being in the highest tertile of CES-D scores at 6-15 and 1-4 years before hospitalisations, and 1-15 years after hospitalisation

Probabilities	Slope (change per year)	95%CIs	P-values
6-15 years before hospitalisation	-0.06	(-0.10 to -0.02)	0.007
1-4 years before hospitalisation	0.11	(0.07 to 0.15)	<0.001
Change (between 6-15 years and 1-4 years before hospitalisation)	0.12	(0.07 to 0.18)	<0.001
1-15 years after hospitalisation	0.07	(0.01 to 0.13)	0.024
Change (between 1-4 years before hospitalisation and 1-15 years after hospitalisation)	-0.05	(-0.12 to 0.03)	0.250

CES-D: Centre for Epidemiological Studies-Depression; 95%CI: 95% Confidence Interval